09 November 2023
EMA/570477/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Talzenna

International non-proprietary name: talazoparib

Procedure No. EMEA/H/C/004674/X/0015/G

Note

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

Table of contents

List of abbreviations

Term	Definition
1L	first-line
ACTH	Adrenocorticotropic hormone
ADP	adenosine diphosphate
ADR	adverse drug reaction
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
AML	acute myeloid leukemia
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
ATM	ataxia-telangiectasia mutated
ATR	ataxia telangiectasia and Rad3 related
BICR	blinded independent central review
BID	twice a day
BMI	body mass index
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory – Short Form
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
CDK12	cyclin-dependent kinase 12
CHEK2	checkpoint kinase 2
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran–Mantel–Haenszel test
COVID-19	coronavirus disease 2019
CLcr	creatine clearance
CL/F	oral clearance
C_{max}	maximum plasma concentration
CMC	Chemistry, Manufacturing, and Controls
CO	clinical overview
CQ	customized query
CR	complete response
CRF	case report form
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
CSR	Clinical Study Report
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
C_{trough}	lowest plasma concentration before scheduled dose
DDI	drug-drug interaction
DDR	DNA damage response
DOR	duration of response
E	event

Term	Definition
ECOG	Easter Cooperative Oncology Group
E-DMC	external data-monitoring committee
eGFR	estimated Glomerular Filtration Rate
ENZA	enzalutamide
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Cancer Questionnaire 30
EORTC QLQ-PR25	EORTC Quality of Life Questionnaire Prostate 25
EQ-5D-5L	EuroQol-5 Dimensions- 5 Levels
E-R	exposure response
EU	European Union
FANCA	Fanconi anemia, complementation group A
FDA	Food and Drug Administration
GBR	Great Britain
GHS	Global Health Status
GnRH	gonadotropin-releasing hormone
GR	geographic region
HER/HER2	Human epidermal growth factor receptor
HR	hazard ratio
HRR	homologous recombination repair
HRR12	homologous recombination repair – core genes/mutations
HRRm	homologous recombination repair mutation/mutated
HTG	HTG Molecular Diagnostics, Inc.
iAP	integrated analysis plan
ibPFS	imaging-based progression-free survival
INV	investigator
ITT	intent-to-treat
IWRS	Interactive Web Response System
K-M	Kaplan Meier
M0	Cancer has not spread to other parts of the body
M1	Cancer has spread to other parts of the body
max	maximum
mCRPC	metastatic castration-resistant prostate cancer
MDRD	Modification of Diet in Renal Disease
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	metastatic hormone-sensitive prostate cancer
min	minimum
MLH1	MutL homolog 1
MRE11A	meiotic recombination 11A
N	number of participants
NBN	nibrin
NCI	National Cancer Institute
NE	not estimable (used interchangeably with NR)
NHT	novel hormonal therapy
NR	not reached (used interchangeably with NE)
NSAE	non-serious adverse event
OAEI	other event of special interest
OBP	Oncology Biomarker Panel
OCRDC	Oracle Clinical Remote Data Capture
OESI	other events of special interest

Term	Definition
OR	objective response
ORR	objective response rate
OS	overall survival
PALB2	Partner and Localizer of Breast Cancer 2
PARP	poly ADP-ribose polymerase
PC	prostate cancer
PCWG3	Prostate Cancer Working Group (bone disease)
PD	progressive disease
PFS	progression-free survival
PFS2	PFS on next line therapy
P-gp	p-glycoprotein
PI	prescribing information
PK	pharmacokinetic(s)
PLAC/PBO	placebo/placebo
PO	by mouth
PopPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
PSA	prostate-specific antigen
Pt/PT	participant
QD	once daily
QoL	quality of life
QXW	every x weeks
RAD51C	DNA repair protein RAD51 homolog 1 Paralog C
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	rest of the world
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	stable disease
SDTM	Study Data Tabulation Model
SE	study entry
SM	site of metastasis
SMQ	standardized MedDRA query
SOC	System Organ Class
TALA	talazoparib
TMB	tumor mutational burden
TTD	time to deterioration
ULN	upper limit of normal
US	United States
VTE	venous thrombotic event
WBC	white blood cell

1. Background information on the procedure

1.1. Submission of the dossier

Pfizer Europe MA EEIG submitted on 1 February 2023 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
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	II

Extension application for Talzenna to introduce a new strength of 0.1 mg hard capsules, grouped with a type II variation (C.I.6.a) in order to extend indication for Talzenna in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), based on final results from study C3441021 (TALAPRO-2) as well as supplemental data from study C3441006 (TALAPRO-1). Study C3441021 (TALAPRO-2) is a randomized, double-blind, placebo-controlled, phase 3 study of talazoparib in combination with enzalutamide in mCRPC, while study C3441006 (TALAPRO-1) is a phase 2, open-label, response rate study of talazoparib in men with DNA repair defects and mCRPC who previously received taxane-based chemotherapy and progressed on at least one novel hormonal agent. As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.5, 4.7, 4.8, 5.1, 5.2, 6.1, 6.5, 8 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0130/2021 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The MAH received Scientific advice from the CHMP on the development for the indication from the CHMP on 14 September 2017 (EMEA/H/SA/2545/5/2017/II), 26 April 2019 (EMEA/H/SA/2545/5/FU/1/2019/II) and 13 October 2022 (EMA/SA/0000099644). The Scientific advice pertained to clinical and quality aspects.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Hrefna Gudmundsdottir

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Ana Sofia Diniz Martins

The application was received by the EMA on	1 February 2023
The procedure started on	23 February 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 May 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 May 2023
The CHMP Co-Rapporteur's Assessment Report was circulated to all CHMP and PRAC members on	26 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 June 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 June 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	7 August 2023
The CHMP Rapporteur circulated the CHMP Rapporteurs Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	12 September 2023
The PRAC Rapporteur circulated the PRAC Rapporteurs Assessment Report on the responses to the List of Questions to all PRAC and CHMP members on	15 September 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2023
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the MAH on	12 October 2023
The MAH submitted the responses to the CHMP List of Outstanding	16 October 2023

Issues on	
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	25 October 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Talzenna on	09 November 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The sought indication is:

Talzenna is indicated in combination with enzalutamide for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC).

The approved indication is:

Talzenna is indicated in combination with enzalutamide for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC), in whom chemotherapy is not indicated.

2.1.2. Epidemiology

Prostate cancer is the second leading cause of cancer death in men globally and the most common cancer in men in Europe, with an age-standardised rate of 30.7 per 100.000 world-wide (Ferlay *et al.*, 2021), and an estimated 335,510 new cases and 69,940 deaths in Europe 2020 (American Cancer Society 2021, Siegel et al 2021, ECIS 2020)

Prostate cancer typically progresses through a series of characteristic clinical states that represent both the natural history of the disease and response to treatment. Initially, prostate cancer is hormone-sensitive and responds well to treatment but may evolve over time to become hormone-insensitive and more difficult to treat. (Scher HI et al, Urology. 2000).

2.1.3. Biologic features

The prostate contains a pseudostratified epithelium, consisting of terminally differentiated luminal, basal, and neuroendocrine epithelial cells. A definitive cell of origin for prostate cancer is not known, but malignant transformation of the prostate follows a multistep process, starting as prostatic intraepithelial neoplasia, followed by localised prostate cancer, which in turn is followed by advanced prostate adenocarcinoma with local invasion, and eventually culminating in metastatic prostate cancer. (A de la Taille et al, Nature 2002)

Approximately 20% of all prostate cancers harbour mutations in homologous recombination repair (HRR) genes, either germline (inheritable) or somatic (constitutional, non-inheritable), of which mutations in *BRCA2*, *ATM,* and *CHEK2* are the most common. HRR genes are crucial for repair of DNA double-strand breaks. (Abida et al 2017, Armenia et al 2018, Chung et al 2019, Mateo et al 2015, Robinson et al 2015). A mutation in *e.g.*, the *BRCA2* gene is a risk factor associated with early onset of disease, high risk of metastases and a worse prognosis.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Prostate cancer is a heterogenous disease, with a median age at onset around 70 years of age. Prostate cancer is rarely diagnosed in men <50 years of age. The relative 5-year overall survival (OS) for prostate cancer in general is approximately 85%, but the prognosis drops rapidly upon development of metastases, resulting in a relative 5-year OS of 31% in the metastatic setting. (American Cancer Society 2021, Siegel 2021)

Early prostate cancer is often asymptomatic, whilst advanced prostate cancer may cause problems urinating, nocturia, and haematuria as well as bone and back pain (indicating risk of bone metastases).

Early during tumour evolution, prostate cancers need normal levels of androgens to survive. These tumours are referred to as androgen-dependent or hormone-sensitive and are sensitive to treatments that decrease androgen levels or block androgen activity (androgen deprivation therapy; ADT). Eventually, tumours might progress from hormone sensitive to castration-resistant prostate cancer (CRPC), defined as tumour progression despite castrate levels of testosterone (<50 ng/dL). Approximately 10-20% of prostate cancer is castration resistant, which is considered an advanced disease stage that is difficult to treat. The median survival of men with metastatic CRPC (mCRCP) is approximately 18 months. (Oncology Times. New Non-Metastatic, Castration-Resistant Prostate Cancer Treatment. Oncology Times. 2018;40(6):17)

2.1.5. Management

The treatment goal for patients with mCRPC is to prolong overall and progression free survival and alleviate tumour associated symptoms while minimising treatment related morbidity.

Despite its resistance against Androgen Deprivation Therapy (ADT), CRPC continues to rely on the androgen receptor-driven transcriptional program, and ADT is normally part of the treatment also for CRPC. Hence, both androgen receptor (AR) inhibitors (*e.g.*, bicalutamide, enzalutamide) and androgen synthesis inhibitors (abiraterone) are used to treat mCRPC and show a benefit in terms of PSA and symptomatic responses, although the level of scientific evidence varies. The side-effects include hypertension (all ADTs) and hypokalaemia, oedema, and cardiac events (abiraterone). ADTs for treatment of mCRPC are recommended by both the European ESMO guidelines and American NCCN guidelines.

According to both European and American treatment guidelines, taxane-containing chemotherapy (docetaxel, cabazitaxel) is an established treatment of mCRPC too, with prolonged OS demonstrated in phase III trials. The side-effects are, however, more pronounced compared with ADT, and include myelosuppression, febrile neutropenia, alopecia, peripheral neuropathy, and peripheral oedema.

For palliation of symptomatic bone metastases, local radiation therapy can be used. Furthermore, the bone-targeted alpha-emitter radium-223 has been shown to increase both OS and the time to first symptomatic skeletal event compared with placebo in men with progressive, bone-predominant, symptomatic mCRPC. Due

to the increased risk of fractures, radium-223 is, however, in Europe restricted to patients who have received at least two lines of systemic therapies (or are ineligible to these).

There is no optimal sequence or combination of the above-mentioned treatment modalities. Normally, the treatment decisions are based on disease distribution and aggressiveness, previous treatments, comorbidities, and patient preferences.

Recently, two PARP inhibitors, olaparib and niraparib were approved in Europe for the treatment of men with mCRPC. Olaparib is approved for the treatment of mCRPC in patients with BRCA mutations who had progressed after prior treatment with enzalutamide or AAP and in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated. Niraparib is approved as fixed dose combination with abiraterone and in combination with prednisone or prednisolone, for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) and BRCA1/2 mutations in whom chemotherapy is not clinically indicated.

2.2. About the product

Talazoparib is an oral inhibitor of the poly-ADP ribose polymerase (PARP) enzymes 1 and 2, which are involved in DNA damage response signalling pathways such as DNA repair, gene transcription, and cell death. By inhibiting the catalytic effect of PARP1/2 and by preventing the PARP proteins from dissociating from the DNA, DNA repair, replication, and transcription is inhibited. Cancer cells that already harbour DNA repair deficiencies, *e.g.*, HRR gene mutations, have to rely on other DNA repair mechanisms such as *e.g.*, the more error-prone non-homologous end-joining and are thus sensitive to PARP inhibitors that interfere with DNA repair. Single-agent therapy with talazoparib 1 mg QD is currently approved as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments (see section 5.1). Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy or be considered unsuitable for endocrine-based therapy.

Enzalutamide is an oral, second-generation Androgen Receptor (AR) inhibitor that competitively inhibits binding of androgens to the AR.

The Applicant has submitted a grouped application. to seek approval for a new indication (type II variation) of oral combination treatment with talazoparib 0.5 mg QD + enzalutamide 160 mg QD in metastatic Castration Resistant Prostate Cancer (mCRPC) regardless of HRR-mutation status and extension with a new capsule strength (0.1 mg) for dose reduction measures. The reason for the lower dose of talazoparib in mCRPC compared to the previous approved dose in breast cancer is a drug-drug interaction between talazoparib and enzalutamide, leading to increased talazoparib exposure.

The Proof of concept for the efficacy of talazoparib in patients with mCRPC and HRR deficiencies in a heavily pre-treated patient population was established in study 1006. This is an open-label, phase II study with talazoparib monotherapy in patients with mCRPC.

The rational of combining talazoparib with the AR signaling inhibitor is based on research on nonclinical models and clinical studies (phase III PROpel study and phase III MAGNITUDE study). AR signalling inhibition with *e.g.*, enzalutamide suppresses the expression of HRR genes, including the *BRCA* genes, leading to sensitivity to PARP inhibitors. PARP1 activity has also been shown to be required for maximal AR function and thus inhibiting PARP is expected to reduce AR signalling and increase sensitivity to ADT. Hence, according to

the Applicant, there is a mechanistic rationale for treatment of mCRPC with a PARP inhibitor + ADT independent of HRR gene mutational status. (Rao A et al, Cancers (Basel). 2022;14(3):801.).

The primary claim for treatment of mCRPC with talazoparib + enzalutamide, regardless of HRR gene mutation status, is based on the pivotal study C3441021 (`Study 1021´).

The MAH received Scientific advice from the CHMP on the development for the indication from the CHMP:

- 14 September 2017 (EMEA/H/SA/2545/5/2017/II), regarding the planned development program in prostate cancer including a single-agent phase II study and a randomised phase III study of combination therapy with novel hormonal therapy in patients with mCRPC.
- 26 April 2019 (EMEA/H/SA/2545/5/FU/1/2019/II) the Applicant sought advice on their clinical development program and provided supportive documentation, including a proposed revised phase III study design.
- 13 October 2022 (EMA/SA/0000099644). The Scientific advice pertained to development of new strength.

2.3. Quality aspects

2.3.1. Introduction

Talzenna is currently available as an immediate release hard capsule in two strengths 0.25 mg and 1 mg. In this Line Extension application a new strength of 0.1 mg is introduced.

The finished product is presented as an immediate release capsule for oral administration containing 0.1 mg of talazoparib as active substance.

Other ingredients are:

capsule content: silicified microcrystalline cellulose (sMCC) (microcrystalline cellulose and silicone dioxide);

capsule shell: hypromellose (HPMC), titanium dioxide (E171);

printing ink: shellac (E904), propylene glycol (E1520), ammonium hydroxide (E527), black iron oxide (E172), potassium hydroxide (E525).

The product is available in high-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat induction seal liner, as described in the SmPC (section 6.5).

2.3.2. Active Substance

No new documentation for the active substance (AS) talazoparib has been submitted for this application. The AS has been assessed in connection with the central procedure EMEA/H/C/4674 for Talzenna 0.25 mg and 1 mg capsules applications and is applicable in the new strength; this is acceptable.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product (FP) is available as immediate release hard capsule for oral administration, measuring approximately 14.30 mm x 5.32 mm with a white cap (printed with "Pfizer" in black) and a white body (printed with "TLZ 0.1" in black).

Talazoparib is approved as an immediate release capsule for oral administration at 0.25 mg and 1 mg strengths. The additional 0.1 mg capsule strength is being introduced to allow for dosing flexibility according to the indication.

The formulation of all strengths of Talzanna is comprised of a binary mixture of conventional pharmaceutical excipients combined with the AS. A conventional dry blending and encapsulation manufacturing process is utilized to manufacture the capsules. The three different strengths (two approved and the new one) have the same capsule content weight while differ in the quantity of the AS which is compensated by the diluent silicified microcrystalline cellulose (sMCC).

The same two grades of the same excipient sMCC, is used for the new strengths 0.1 mg capsules as with the approved strengths. The same type (HPMC) and size (#4) of pre-printed capsules are used for 0.1 mg as with the approved 0.25 mg, with different colors to differentiate the strengths.

The AS has already been assessed in connection with central procedure EMEA/H/C/4674 for strength 0.25 mg and 1 mg capsules.

No changes in the quality attributes of talazoparib AS is required for the manufacture of talazoparib additional strength.

The development for talazoparib capsules 0.1 mg formulation is based on the following principles:

1. Leverage the clinical (0.1 mg, 0.25 mg and 1 mg) and commercial formulation and process knowledge acquired during the development of the approved 0.25 mg and 1 mg strength capsules.
2. No changes in the formulation components (aside from the colour of the capsule shell used for strength differentiation
3. No changes to the manufacturing process.

Formulation and process development studies for the manufacturing aspects of talazoparib capsules have been described in the initial registration dossier, all of which are applicable to the development of the 0.1 mg capsules. The sections also described all clinical formulations used during the development of the 0.25 mg and 1 mg capsules. In addition, the 0.1 mg has been manufactured and used in the clinical study C3441021 and the same formulation is proposed as the commercial formulation, except for the capsule color and imprints.
Several development batches of 0.1 mg capsules were manufactured according to the approved manufacturing process for the 0.25 and 1 mg capsule strengths and at the current manufacturing site. Three validation batches were then manufactured to confirm the formulation and process. The manufacture of all batches was carried out using the same manufacturing process (equipment, scale, operating conditions) which is already approved as part of the initial dossier.

AS and excipient risks were previously identified during formulation development of the 0.25 and 1 mg capsules, based on prior knowledge and experience with the formulation development and the relevant information is contained in the initial dossier, for the 0.25 and 1 mg capsules. Since all talazoparib capsules strengths are manufactured using the same process, the results of the risk assessments and development studies for the 0.25 mg and 1 mg are directly applicable to the formulation of all other strengths.

The approved dissolution test method for the authorised 0.25 mg and 1 mg capsules is appropriate for the 0.1 mg capsules for the reasons outlined below:

- Talazoparib capsules are immediate release (IR) formulation employing simple dry blends of AS and silicified microcrystalline cellulose in same size HPMC capsules. All product strengths 0.25 mg and 1 mg (approved) and 0.1 mg (proposed) have approximately the same amount of excipient per capsule but have different AS loading.
- The solubility of talazoparib tosylate has been characterised over the physiological pH range at 37 °C and sink conditions are achieved over the entire range for all capsule strengths. Extensive dissolution method development was carried out for the approved 0.25 mg and 1 mg strengths to determine that a surfactant was required to aid AS dispersion and produce a robust, discriminating dissolution method.

The appropriateness of the approved dissolution test conditions for the talazoparib 0.25 and 1 mg strengths was described in initial registration dossier.

Dissolution profiles of the new 0.1 mg capsule strengths of talazoparib capsules were generated to confirm the appropriateness of the approved dissolution method. Complete release was achieved using the approved dissolution method and all batches met the acceptance criteria of Q=80% in 30 minutes.

The currently approved manufacturing process for the talazoparib 0.25 mg and 1 mg capsules is adequate for the manufacture of the new talazoparib 0.1 mg capsule strength. The pharmaceutical development has adequately been described.

The 0.1 mg strength capsules are packaged in are high-density polyethylene (HDPE) bottles and polypropylene (PP) closures with heat induction (HIS) seal liners , which complies with the relevant Eu and Ph. Eur. requirements.

2.3.3.2. Manufacture of the product and process controls

The approved manufacturing site for the 0.25 and 1 mg capsules is also the manufacturing site for the 0.1 mg capsules.

The approved manufacturing process used to manufacture the authorised strengths is also used for 0.1 mg, capsules.
Talazoparib immediate release capsules are manufactured by a standard manufacturing process which includes dry mixing/blending and encapsulation using commonly available equipment in the pharmaceutical industry. The proposed batch size of the finished product has been clearly defined.

Process validation data for 3 commercial scale batches were provided. Based on validation data and experience gained on manufacturing of Talzenna 0.25 mg and 1 mg, it is considered that the manufacture is sufficiently robust to provide assurance that the process produces the finished product (Talzenna 0.1 mg capsules) of consistent quality, complying with the designated specification.

2.3.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC , UV), assay (HPLC), degradation products (HPLC), dissolution (Ph.Eur.), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.) and microbial limits (Ph. Eur.).

The rationale for the specification and associated analytical test procedures for talazoparib 0.1 mg capsules has been presented. The specifications used for the control of talazoparib capsules were selected on the basis of the available manufacturing and testing experience, manufacturing process capabilities, regulatory guidance, scientific knowledge, and the stability characteristics. All specifications are aligned with those currently approved for talazoparib 0.25 mg and 1 mg capsules.

The specifications for talazoparib 0.1 mg capsules are considered adequately justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The information regarding the reference standards used is also satisfactory.

Batch analysis data were provided for 19 batches of the 0.1 mg strength manufactured at the proposed site. All results were within the proposed specifications and demonstrate consistency of the manufacturing process.

2.3.3.4. Stability of the product

Stability data from 3 commercial scale batches of finished product manufactured by the proposed site, stored for up to 24 months under both long-term storage conditions of 25 °C / 60% RH and intermediate condition 30 °C / 75% RH, and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, dissolution, microbial quality (TAMC and TYMC) and water content. No significant changes were observed in any of the monitored parameters through 24 months at both long-term storage conditions of 25°C/60%RH and intermediate condition 30 °C / 75% RH, and through 6 months of storage at the accelerated storage condition of 40 °C / 75% RH compared to the initial values.

A photostability study was carried out on one batch according to the ICH Guideline Q1B on Photostability Testing of New Drug Substances and Products. No trends were detected in appearance, dissolution or water content. In unprotected samples (open dish) total degradation products increased when compared to dark the control. It is therefore concluded that when packaged in the proposed HDPE bottles, 0.1 mg talazoparib capsules are stable to light and no additional packaging or labeling is required.

In-use stability studies were conducted for capsules in an open dish on one batch of 0.1 mg talazoparib capsules. Samples were stored in an open dish at 30°C/75%RH for 45 days and were tested after 45 days for appearance, assay, degradation products, dissolution and water content. No significant changes were observed in appearance, assay and dissolution. A slight increase in the levels of degradation products was observed. The levels of two specified impurities increased but both remained within specification as did the total degradation products. The water content also increased but remained within specification. Since all tested parameters met the acceptance criteria an in-use label restriction is not required.

Based on the overall stability data the proposed shelf life of the finished product of 3 years without special storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

2.3.3.5. Adventitious agents

No materials of human or animal origin are used in the manufacture of the finished product.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

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

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendations for future quality development

None.

2.4. Non-clinical aspects

2.4.1. Introduction

Talazoparib is a PARP inhibitor, which exerts it cytotoxic effect on cancer cells by two mechanisms: 1) inhibition of PARP catalytic activity and 2) PARP trapping, whereby PARP protein bound to a PARPi does not readily dissociate from a DNA lesion, thus preventing DNA repair, replication, and transcription, and ultimately leads to apoptosis and/or cell death. Enzalutamide is an AR inhibitor, which was rationally designed to block the AR signalling pathway and to be devoid of agonist activity.

2.4.2. Pharmacology

No new non-clinical pharmacology studies have been submitted for this procedure which is acceptable.

2.4.3. Pharmacokinetics

The nonclinical Pharmacokinetic (PK) and Toxicokinetic (TK) of talazoparib in combination with enzalutamide have not been investigated. This is acceptable.

2.4.4. Toxicology

No new toxicological studies have been submitted for the present procedure. However, a non-clinical overview has been provided.

2.4.5. Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): talazoparib			
CAS-number: 1373431-65-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		N/A	Not a potential PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	Default: 0.005	µg/L	< 0.01 threshold
Other concerns (e.g. chemical class)			Clastogenic Embryotoxic Teratogenic
Calculation of PEC $_{surfacewater}$,– mCRPC	Default: 0.005	µg/L	< 0.01 threshold
Calculation of Total PEC $_{surfacewater}$	Default: 0.005	µg/L	< 0.01 threshold

2.4.6. Discussion on non-clinical aspects

No new non-clinical pharmacology studies have been submitted and this is acceptable. A scientific rationale has been provided to justify the combination clinical study. This rationale is based on scientific literature. It is agreed that the data indicate increased anti-tumor potential by combined pharmacological action of talazoparib and enzalutamide combination in mCRPC patients.

No new toxicological studies have been submitted for the present procedure. However, a non-clinical overview has been provided. The toxicity profiles of talazoparib and enzalutamide were individually assessed extensively in a series of nonclinical studies in the documents of the original Market Authorizations. Therein, a discussion about the potential relevance of pre-existing non-clinical information for the new proposed line extension alterations, including the drugs respective toxicology and their interaction potential, was included. The MAH summarises that the dose limiting hematolymphopoietic toxicity observed in non-clinical species with talazoparib and the mild decreases in the red blood cell parameters seen with enzalutamide have been translated in patients. Therefore, patients should be carefully monitored for any potential additive hematologic toxicity due to the combination treatment.

Both substances have been sufficiently characterized in toxicity studies separately and according to current standards. As both pharmaceuticals are being regarded as late-stage entities *(ICH guideline M3(R2) EMA/CPMP/ICH/286/1995)*, together with the fact that combinations of pharmaceuticals are intended to treat patients with advanced cancer *(ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals EMA/CHMP/ICH/646107/2008)*, combination toxicology studies investigating the safety are not warranted.

In conclusion, combination genotoxicity, safety pharmacology, carcinogenicity or repeat dose toxicity studies are not needed to support marketing since the individual agents have been tested according to current standards.

Based on data presented Talazoparib PEC $_{surfacewater}$ value is below the action limit of 0.01 μg/L and is not a PBT substance as log K_{ow} does not exceed 4.5. Therefore, talazoparib is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

The lack of non-clinical talazoparib/enzalutamide combination studies evaluating PD, PK and toxicity is acceptable, and the addition of a new indication for talazoparib does not pose a risk to the environment.

The non-clinical evidence available for talazoparib supports the new indication.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Study	Description	Status
C3441021 (TALAPRO-2)	Pivotal, Phase 3, international, two-part study enrolling participants with mCRPC where no systemic cancer treatments have been initiated after documentation of the CRPC state. **Part 1:** open-label and non-randomized and evaluated the safety, tolerability, and PK of talazoparib in combination with enzalutamide **Part 2:** randomized, double-blind, and placebo-controlled evaluating the efficacy and safety of talazoparib in combination with enzalutamide compared with placebo in combination with enzalutamide; Part 2 enrolled 2 cohorts (Cohort 1: all-comers population; Cohort 2: HRR deficient population). *Only results from Cohort 1 are included in this submission*	Part 1 completed Part 2 ongoing; Study Start: 8 Aug 2017 Part 1 and Part 2 Cohort 1: Data cutoff date: 16 Aug 2022 Cohort 2: blinded, ongoing
C3441006 (TALAPRO-1)	Phase 2, international, open-label, soft tissue response rate study of talazoparib to evaluate the efficacy and safety of talazoparib monotherapy in adult male subjects with mCPRC with HRR deficiencies whose disease has previously progressed on NHT:enzalutamide and/or abiraterone acetate, given for the treatment of mCRPC and who were previously treated with taxane based chemotherapy for metastatic disease.	Completed Study Start: 04 Jul 2017 Data cutoff date: 04 Sep 2020.

2.5.2. Clinical pharmacology

This application concerns the extension of Talzenna (talazoparib) Marketing Authorisation to add a new strength of 0.1 mg hard capsules, and to extend Talzenna indication in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC).

2.5.2.1. Pharmacokinetics

Methods

Bioanalysis

Plasma concentrations of talazoparib, enzalutamide and its metabolite N-desmethyl-enzalutamide were determined with LC-MS/MS methods.

Non-compartmental analysis

Standard methods were used in the non-compartmental analysis.

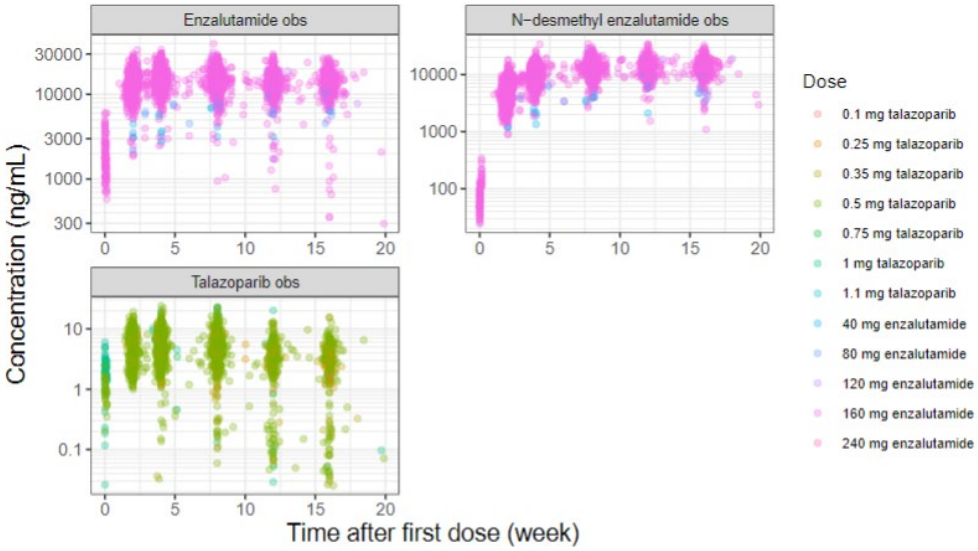
Statistical analysis

For each study, talazoparib (and enzalutamide and N-desmethyl enzalutamide where relevant) plasma concentrations and PK parameter values were summarized by descriptive statistics including number of observations, arithmetic mean, SD, geometric mean, %CV, geometric %CV, median, minimum, and maximum.

Population PK

The objective of the population PK analysis was to develop an integrated analysis for talazoparib in combination with enzalutamide, identify potential covariates that have impact on exposure, evaluate effect of enzalutamide dose reduction on talazoparib exposure and provide post-hoc predictions from the final population PK model to be used to generate individual exposure metrics for efficacy and safety exposure-response analyses. Data from Part 1 and Part 2 Cohort 1 of Study C3441021 were included in the model building process.

Figure 1. Observed Plasma Enzalutamide, N-desmethyl enzalutamide and Talazoparib Concentrations Versus Time Stratified by the Actual First Dose Patient Received on Log Scale



Enzalutamide model

Data from all patients in both arms were used in the analysis as talazoparib did not impact the pharmacokinetic (PK) of either enzalutamide or n-desmethyl enzalutamide as indicated by the similar trough concentration prior to dose (Ctrough) observed across treatment arms by visit. The final model was a 2-compartment model with age effect on CL/F and Vc/F and body weight effect on CL/F and Vc/F. It included effects of BWT and AGE on CL/F and Vc/F (Table 3).

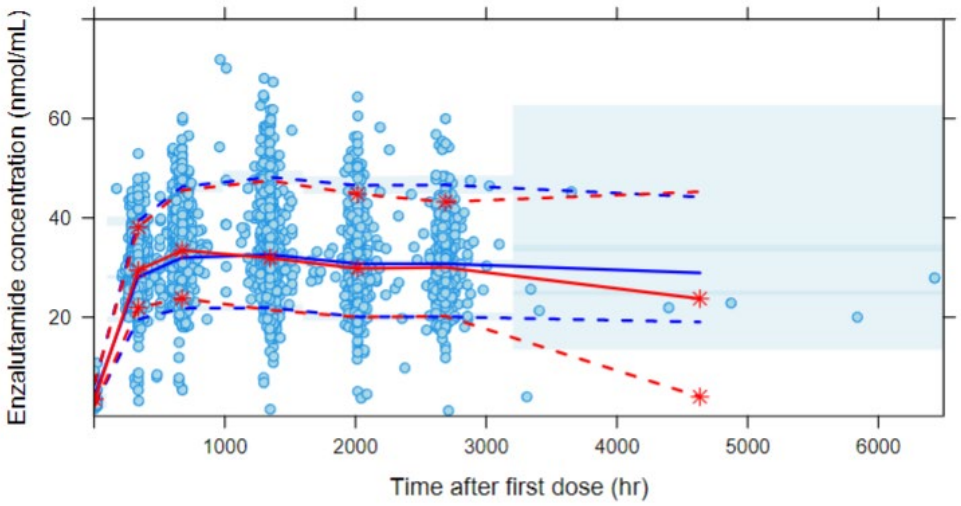
Table 1. Enzalutamide Final Model Pharmacokinetics Parameters Summary

Parameter	Estimate	SE	RSE (%)	CV (%)	Shrinkage (%)
$\theta_{CL/F}$ (L/hr)	0.425	0.003	0.74	-	-
$\theta_{V_c/F}$ (L)	25.293	2.862	11.31	-	-
$\theta_{Q/F}$ (L/hr)	20.644	1.505	7.29	-	-
$\theta_{V_p/F}$ (L)	45.928	2.836	6.17	-	-
θ_{k_a} (hr^{-1})	3.431	0.475	13.85	-	-
θ_{F_1} (Fixed)	1.000	-	-	-	-
Thetarized Sigma	0.145	0.010	6.86	-	8.99
Age effect on $\theta_{CL/F}$	-0.003	0.001	27.53	-	-
Body weight effect on $\theta_{CL/F}$	0.549	0.035	6.42	-	-
Age effect on $\theta_{V_c/F}$	1.223	0.271	22.17	-	-
Body weight effect on $\theta_{V_c/F}$	3.495	0.279	7.99	-	-
$\omega^2_{CL/F}$	0.037	0.002	6.02	19.32	4.82
$\omega_{V_c/F}\omega_{CL/F}$	-0.015	0.010	65.35	12.17	-
$\omega^2_{V_c/F}$	0.350	0.102	29.19	59.18	39.53
OFV	-14587.871	-	-	-	-

Repository artifact ID FI-35194490. Line 1 substituted.

CV=approximate percent coefficient of variation calculated as $\sqrt{\omega^2} \cdot 100\%$; IIV=inter-individual variability; CL/F=apparent clearance; F_1=enzalutamide relative bioavailability; k_a=first order absorption rate constant; Q/F=apparent inter-compartmental clearance; Vc/F=apparent central volume of distribution; Vp/F=apparent

Figure 2. Prediction- and Variance-Corrected Visual Predictive Check with Final Enzalutamide Model: Linear



Observed concentration data points, represented by blue scatter points. The red lines represent the median (solid line), 5th percentile (lower dash line) and 95th percentile (upper dash line) of the observed data. The median, 5th percentile and 95th percentile of simulated concentration values are presented by blue lines. 95% confidence intervals for simulated median and each percentile are shown by light blue shaded areas. hr=hour

N-desmethyl Enzalutamide model

There were no prior models for n-desmethyl enzalutamide available in the literature. Enzalutamide parameters were fixed to Empirical Bayes Estimates (EBEs) to develop a population PK model for n-

desmethyl enzalutamide. The fraction of enzalutamide converted to n-desmethyl metabolite, Fmet, was fixed to 0.634 based on a physiologically based PK model for enzalutamide. It resulted in a better fit compared to assuming equal central volumes for both parent and metabolite to overcome the unidentifiability issue. Same covariates as for enzalutamide were tested for the metabolite in a stepwise manner. The final model for n-desmethyl enzalutamide was a two-compartment model that included the effect of BWT on CL and Vc. It included the effect of BWT on CL and Vc (Table 4).

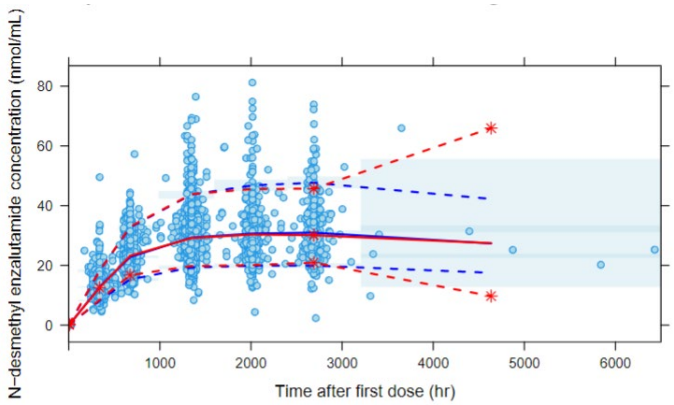
Table 2. N-desmethyl Enzalutamide Final Model Pharmacokinetics Parameters Summary

Parameter	Estimate	SE	RSE (%)	CV (%)	Shrinkage (%)
θ_{CL} (L/hr)	0.286	0.003	0.89	-	-
θ_{V_c} (L)	44.944	4.189	9.32	-	-
θ_{Q} (L/hr)	9.443	1.349	14.28	-	-
θ_{V_p} (L)	52.373	3.788	7.23	-	-
$\theta_{F_{met}}$ (Fixed)	0.634	-	-	-	-
Effect of body weight on θ_{CL}	0.006	0.001	9.42	-	-
Effect of body weight on θ_{V_c}	0.027	0.001	2.52	-	-
Thetarized σ	0.125	0.007	5.20	-	11.65
ω^2_{CL}	0.057	0.004	6.84	23.83	5.36
$\omega_{V_c}\omega_{CL}$	0.006	0.006	91.42	7.93	-
$\omega^2_{V_c}$	0.342	0.052	15.18	58.44	14.75
OFV	-15331.931	-	-	-	-

Repository artifact ID FI-36040052. Line 1 substituted.

CV=approximate percent coefficient of variation calculated as $\sqrt{\omega^2} \cdot 100\%$; IIV=inter-individual variability; CL=clearance; F=bioavailability; Q=inter-compartmental clearance; Vc=central volume of distribution; F_{met}=fraction enzalutamide that is biotransformed into n-desmethyl active metabolite; Vp=peripheral volume of distribution; hr=hour; L=liter; OFV=objective function value; (R)SE=(relative) standard error; ω^2=variance of the IIV.

Figure 3. Prediction- and Variance-Corrected Visual Predictive Check with Final N-desmethyl Enzalutamide Model: Linear



Observed concentration data points, represented by blue scatter points. The red lines represent the median (solid line), 5th percentile (lower dash line) and 95th percentile (upper dash line) of the observed data. The median, 5th percentile and 95th percentile of simulated concentration values are presented by blue lines. 95% confidence intervals for simulated median and each percentile are shown by light blue shaded areas. hr=hour

Talazoparib model

Enzalutamide and its metabolite PK parameters were fixed to EBEs to develop a population PK model for talazoparib. A linear relationship was assumed for CL/F of talazoparib as a function of enzalutamide and n-desmethyl enzalutamide (Pgp-inhibitors) concentrations. This was implemented in the model by considering talazoparib CL/F to be dependent on the plasma concentrations of enzalutamide (Ce) and its n-desmethyl metabolite (Cn) via a linear relationship:

$$\theta_{CL/F} = \theta_{CL_0/F} \cdot [1 - \theta_{slope} \cdot (C_e + C_n)] \quad (1)$$

with θCL0/F representing the intercept, or apparent baseline talazoparib clearance, and θslope representing the slope of linear relationship. Enzalutamide and n-desmethyl metabolite were considered similar in terms of their potency.

The final model for talazoparib included the effect of BCCL on CL0/F via a power model (Table 5). shows the prediction- and variance-corrected Visual Predictive Check plot.

Table 3. Talazoparib Final Model Pharmacokinetics Parameters Summary

Parameter	Estimate	SE	RSE (%)	CV (%)	Shrinkage (%)
$\theta_{CL_0/F}$ (L/hr)	5.078	0.197	3.887	-	-
$\theta_{V_c/F}$ (L)	14.389	0.066	0.462	-	-
$\theta_{V_p/F}$ (L)	382.135	18.094	4.735	-	-
$\theta_{Q/F}$ (L/hr)	15.568	0.008	0.053	-	-
θ_{F_6} (Fixed)	1.000	-	-	-	-
θ_{k_a} (hr^{-1})	0.157	1.11E-04	0.071	-	-
θ_{slope} (mL/ng)	6.58E-06	1.22E-06	18.514	-	-
Thetarized σ	0.354	0.013	3.676	-	8.50
BCCL effect on $\theta_{CL_0/F}$	0.455	0.051	11.111	-	-
$\omega^2_{CL_0/F}$	0.073	0.007	10.207	26.984	10.20
$\omega^2_{V_c/F}$	2.582	0.319	12.364	160.674	46.81
OFV	-2097.146	-	-	-	-

Repository artifact ID FI-36149791. Line 1 substituted.

BCCL=baseline creatinine clearance; CV=approximate percent coefficient of variation calculated as $\sqrt{\omega^2} \cdot 100\%$; IIV=inter-individual variability; CL_0/F=talazoparib apparent base clearance; F_6=talazoparib relative bioavailability; k_a=first order absorption rate constant; Q/F=apparent inter-compartmental clearance; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution; hr=hour; L=liter; OFV=objective function value; (R)SE=(relative) standard error; ω^2=variance of the IIV; θ_{slope}=slope of linear relationship in Equation 1 to account for the effect of enzalutamide and its metabolite on CL/F of talazoparib.

Figure 4. Prediction- and Variance-Corrected Visual Predictive Check with Final Talazoparib Model: Linear

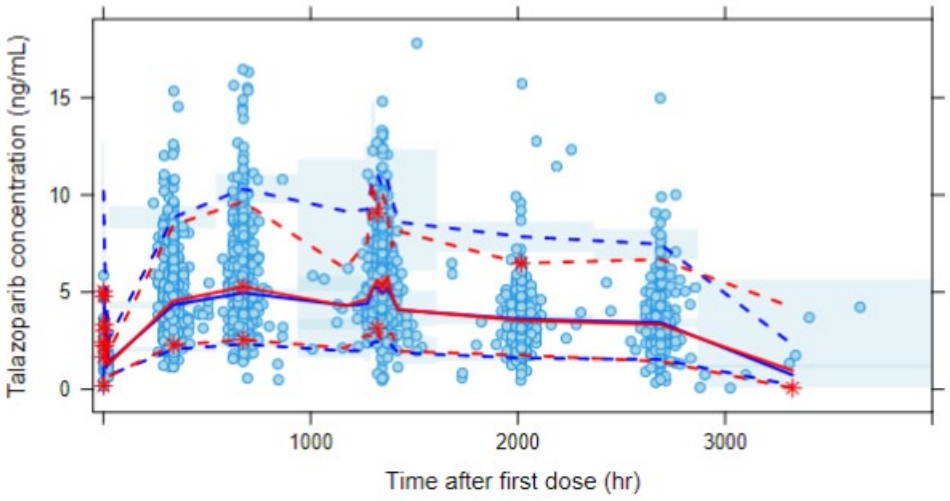


Table 6 shows patients with normal renal function who received 120 and 80 mg enzalutamide with 0.5 talazoparib dose experienced 5.8% and 10.99% reductions in steady state AUC0-24, respectively, relative to patients who received 160 mg enzalutamide. Based on these results, a dose reduction for enzalutamide does not require a dose modification for talazoparib as the magnitude of reduction in exposure measures for talazoparib was not considered clinically significant when enzalutamide dose was reduced.

Table 4. Effect of Enzalutamide Dose Reduction on Talazoparib Exposure for Patients Randomized to 0.5 mg Talazoparib Dose and BCCL=90 mL/min

Exposure measure	0.50/160 mg talazoparib/enzalutamide	0.50/120 mg talazoparib/enzalutamide	0.50/80 mg talazoparib/enzalutamide
SS AUC0-24 (ng*hr/mL)	120.80	113.79 (-5.8)	107.53 (-10.99)
SS Cmin (ng/mL)	3.91	3.64 (-6.91)	3.39 (-13.3)
SS Cmax (ng/mL)	6.93	6.62 (-4.47)	6.34 (-8.51)

Repository artifact ID FI-36158603. Line 1 substituted.
Note: values in parentheses represent percent reduction in exposure measure from 0.50/160 mg talazoparib/enzalutamide. BWT and AGE were considered at the median values of population, i.e., BWT=80.1 kg and AGE=71 years.
BCCL=baseline creatinine clearance; mL=milliliter; SS AUC0-24=area under the concentration-time curve for 24 hours at steady state; SS Cmin=minimum concentration at steady state; SS Cmax=maximum concentration at steady state.

Absorption

Proposed new strength of 0.1 mg

Talazoparib capsules are commercially available in two strengths, 0.25 mg and 1 mg. The proposed additional 0.1 mg capsule will have the same qualitative formulation and will be distinguished by the capsule shell color and imprint. The 0.1 mg strength has been used for dose reductions in study 1021 (TALAPRO-2). No bioequivalence study or in vitro dissolution data comparing the different strengths has been provided.

Study 1021 (TALAPRO-2)

Study 1021 was a Phase 3, international, two-part study enrolling participants with mCRPC.

Study 1021, Part 1, Dose finding (nr of patients =19) was open-label and non-randomized with the primary objective to assess the safety, tolerability, and PK of talazoparib in combination with enzalutamide and to determine the dosing regimen for the randomized Phase 3 portion of the Study (Part 2). In Part 1, rich PK blood sampling was applied.

The first participants enrolled into Part 1 initially received talazoparib 1 mg QD in combination with enzalutamide, based on the monotherapy dose used for breast cancer patients. Enzalutamide was administered at the labelled mCRPC dose of 160 mg QD.

Safety data from the initial 13 participants enrolled to Part 1 showed higher than expected Grade 3 haematological toxicities likely due to an observed ~2-fold increase in talazoparib exposure with the combination regimen when compared to historical monotherapy PK data.

Talazoparib dose was reduced from 1 mg QD to 0.5 mg QD for participants continuing to receive talazoparib in combination with enzalutamide in Part 1, and a further 6 participants were enrolled at this lower starting dose. Part 1 data indicated that reducing the talazoparib dose to 0.5 mg QD in combination with enzalutamide was expected to account for the observed DDI and maintain similar talazoparib exposure to that achieved with 1 mg QD monotherapy with an acceptable safety profile.

In general, enzalutamide and N-desmethyl enzalutamide following single and/or multiple doses of enzalutamide were similar across the talazoparib 1 mg and 0.5 mg QD dosing cohorts.

Table 5. Summary of Plasma Talazoparib, Enzalutamide, and N-Desmethyl Enzalutamide Pharmacokinetic Parameters by Dose Level Following Administration of Single Doses (Week 1) (Study C3441021 Part 1 PK Evaluable Population)

		PK Parameter Summary Statistics[a]		
Analyte	**Dose Level**	**AUC_τ[b]**	**C_{max}**	**T_{max}**
Talazoparib	Units	(ng•hr/mL)	(ng/mL)	(hr)
	Tala 1.0 mg + Enza	12, 46.38 (38)	13, 3.39 (52)	13, 2.10 (1.0-24.0)
	Tala 0.5 mg + Enza	6, 17.85 (26)	6, 1.60 (30)	6, 1.51 (1.0-4.0)
Enzalutamide	Units	(µg•hr/mL)	(µg/mL)	(hr)
	Tala 1.0 mg + Enza	11, 33.32 (33)	13, 3.57 (27)	13, 1.00 (1.0-2.0)
	Tala 0.5 mg + Enza	6, 31.59 (38)	6, 3.62 (43)	6, 1.00 (1.0-2.0)
N-Desmethyl Enzalutamide	Units	(µg•hr/mL)	(µg/mL)	(hr)
	Tala 1.0 mg + Enza	11, 2.458 (30)	13, 0.147 (40)	13, 24.0 (5.6-24.4)
	Tala 0.5 mg + Enza	6, 2.834 (40)	6, 0.197 (48)	6, 23.1 (22.0-24.1)

Data source: Study C3441021 CSR Appendix Tables 14.4.5.1.a, 14.4.5.2.a, and 14.4.5.3.a.
PK parameters are defined in Table 2.
Abbreviations: D = day; Enza = enzalutamide; n = number of patients for whom PK parameters were evaluable; NC = not calculated; Tala = talazoparib.
a. n, Geometric mean (geometric %CV) is shown for all PK parameters except n, median (range) for T_{max}.
b. $AUC_\tau = AUC_{24}$.

Table 6. Summary of Plasma Talazoparib, Enzalutamide, and N-Desmethyl Enzalutamide Pharmacokinetic Parameters by Dose Level Following Administration of Multiple Daily Doses (Week 9) (Study C3441021 Part 1 PK Evaluable Population)

		PK Parameter Summary Statistics[a]				
Analyte	**Dose Level**	**AUC_τ[b]**	**C_{max}**	**T_{max}**	**C_{trough}**	**CL/F**
Talazoparib	Units	(ng•hr/mL)	(ng/mL)	(hr)	(ng/mL)	(L/hr)
	Tala 1.0 mg	3, 277.9	3, 15.72	3, 5.05	3, 8.74	3, 3.60
	+ Enza QD	(52)	(38)	(4.0-5.5)	(40)	(52)
	Tala 0.5 mg	5, 133.9	5, 8.74	5, 1.95	4, 4.57	5, 3.74
	+ Enza QD	(22)	(25)	(1.0-4.0)	(53)	(22)
Enzalutamide	Units	(µg•hr/mL)	(µg/mL)	(hr)	(µg/mL)	(L/hr)
	Tala 1.0 mg	6, 251.0	6, 12.1	6, 1.05	10, 11.4	6, 0.64
	+ Enza QD	(13)	(15)	(1.0-2.0)	(21)	(13)
	Tala 0.5 mg	6, 211.4	6, 11.7	6, 1.00	6, 9.36	6, 0.76
	+ Enza QD	(20)	(28)	(0.9-2.0)	(25)	(20)
N-Desmethyl	Units	(µg•hr/mL)	(µg/mL)	(hr)	(µg/mL)	(L/hr)
Enzalutamide	Tala 1.0 mg	6, 221.4	6, 10.1	6, 0.00	10, 11.6	NC
	+ Enza QD	(17)	(17)	(0.0-0.0)	(23)	
	Tala 0.5 mg	6, 239.2	6, 11.5	6, 13.8	6, 11.2	NC
	+ Enza QD	(25)	(27)	(0.0-24.4)	(27)	

PK parameters are defined in Table 2.
Abbreviations: D = day; Enza = enzalutamide; n = number of patients for whom PK parameters were evaluable; NC = not calculated; Tala = talazoparib.
a. n, Geometric mean (geometric %CV) is shown for all PK parameters except n, median (range) for T_{max}.
b. $AUC_\tau = AUC_{24}$.

Study 1021, Part 2 was, randomized 1:1, (n=1018, n=395 included in the PK analysis of combination therapy) double-blinded, placebo-controlled study evaluating the efficacy and safety of talazoparib in combination with enzalutamide compared with placebo in combination with enzalutamide with mCRPC. In Part 2, PK sampling was sparse and occurred at Weeks 3, 5, 9, 13 and 17.

Participants with normal renal function or with mild renal impairment received a talazoparib starting dose of 0.5 mg QD in combination with enzalutamide 160 mg QD, whereas participants with moderate renal impairment received a talazoparib starting dose of 0.35 mg QD in combination with enzalutamide 160 mg QD.

Table 7. Summary of Plasma Talazoparib, Enzalutamide, and N-Desmethyl Enzalutamide Ctrough by Treatment, Dose Level, and Visit Following Administration of Multiple Daily Doses (Study C3441021 Part 2 Cohort 1 PK Evaluable Population)

		Plasma C_{trough} Summary Statistics[a]				
Analyte	**Dose Level**	**Week 3**	**Week 5**	**Week 9**	**Week 13**	**Week 17**
Talazoparib (ng/mL)	Tala 0.5 mg + Enza QD	310, 3.13 (47)	261, 3.56 (50)	218, 3.68 (45)	161, 3.40 (45)	124, 3.29 (48)
	Tala 0.35 mg + Enza QD[b]	35, 3.28 (43)	30, 3.79 (52)	24, 3.63 (32)	19, 3.69 (33)	11, 4.06 (33)
Enzalutamide (µg/mL)	Tala + Enza 160 mg QD	352, 12.3 (31)	323, 14.5 (28)	296, 14.0 (26)	252, 13.9 (26)	224, 13.9 (23)
	Plb + Enza 160 mg QD	351, 12.3 (28)	319, 14.6 (26)	301, 14.0 (27)	265, 13.8 (25)	254, 13.6 (31)
N-Desmethyl Enzalutamide (µg/mL)	Tala + Enza 160 mg QD	352, 5.44 (42)	323, 10.5 (34)	296, 13.2 (29)	252, 13.2 (26)	224, 13.5 (27)
	Plb + Enza 160 mg QD	351, 5.45 (40)	319, 10.6 (31)	301, 13.8 (27)	265, 14.0 (25)	254, 13.8 (29)

Abbreviations: Enza = enzalutamide; n = number of patients for whom PK parameters were evaluable; Plb = placebo; Tala = talazoparib.

a. n, Geometric mean (geometric %CV) is shown for all PK parameters.

b. In Part 2 of Study C3441021, participants with moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2 by the MDRD equation) at screening were enrolled at a talazoparib starting dose of 0.35 mg QD.

Study 1006

Study 1006 was an open-label, Phase 2, international, open-label, soft tissue response rate study of talazoparib to evaluate the efficacy and safety of talazoparib monotherapy in adult male participants with mCRPC with HRR deficiencies (n=128). Participants received talazoparib 1 mg QD orally. If participants were determined to have moderate renal impairment at screening (eGFR: 30-59 mL/min/1.73 m2 per central laboratory) then the talazoparib starting dose was reduced to 0.75 mg QD orally. Sparse PK samples were collected for talazoparib.

Distribution

No new data have been submitted with this application.

Elimination

In study 1021 part 1, the talazoparib geometric mean CL/F ranged from 3.60 to 3.74 L/hr across tested dose levels.

Dose proportionality and time dependencies

When talazoparib was dosed in combination with 160 mg enzalutamide QD the mean (C_{max}), mean AUC_{tau}, and mean C_{trough} for talazoparib following multiple doses increased in a dose-proportional manner across the tested talazoparib doses of 0.5 mg QD to 1.0 mg QD.

When administered daily in combination with enzalutamide 160 mg QD, talazoparib generally achieved steady-state exposures at or before the Week 9 visit, as indicated by the similar geometric mean C_{trough} values from this visit and all proceeding visits.

Special populations

Impaired renal function

The results from a previously conducted dedicated clinical renal impairment study formed the basis for dose recommendations for subjects with renal impairment given talazoparib monotherapy. The talazoparib total exposure (AUC0-24) after multiple talazoparib once daily doses increased by 92% and 169% in patients with moderate and severe renal impairment, respectively, relative to patients with normal renal function. The mCRPC study included 152 patients with mild renal impairment, 72 patients with moderate renal impairment, and only 2 patients with severe renal impairment. A popPK analysis of the effect of renal function on talazoparib exposure (AUC) showed that mild and moderate renal impairment participants had 9% and 37% higher AUC compared to that of participants with normal renal function. Due to the limited number of severe renal impairment participants (only 2 participants), the impact of severe renal impairment on CL0/F cannot be concluded and dose recommendations are based on the dedicated monotherapy RI study.

Impaired Hepatic function

The information of the impact of hepatic impairment on the combination treatment talazoparib and enzalutamide is currently lacking.

A dedicated hepatic impairment study with talazoparib monotherapy indicated that mild, moderate (total bilirubin >1.5 to 3.0 × ULN and any AST), or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST) had no significant impact on the PK of talazoparib (Population Modelling Assessment Report-1052). A popPK analysis was performed using data from 412 mCRPC participants treated with talazoparib in combination with enzalutamide that included 40 participants had mild hepatic impairment.

Gender

Sex has been shown to have no clinically relevant effect on the PK of talazoparib, enzalutamide or N-desmethyl enzalutamide.

Race

A previously conducted population PK analysis using data from 490 patients with cancer who received talazoparib 1 mg daily as monotherapy, where 41 patients were Asian and 449 patients were Non-Asian (361 White, 16 Black, 9 Others, and 63 Not reported), found that talazoparib CL/F was higher in Asian patients compared to Non-Asian patients, leading to 19% lower exposure (AUC) in Asian patients.

Weight

A previously conducted population PK analysis using data from 490 patients with cancer who received talazoparib 1 mg daily as monotherapy concluded no clinically relevant effect of body weight (ranging from 35.7 kg to 162 kg) on the PK of talazoparib.

Body weight (ranging from 45 to 178 kg) was found to be a significant covariate on the PK of enzalutamide (on CL/F and Vc/F) and its metabolite (on CL/F and Vc/F) N-desmethyl enzalutamide in the population PK models that included data from the mCPRP study 1021 (enzalutamide and talazoparib combination treatment) including 811 subjects.

Age

A previously conducted population PK analysis using data from 490 patients with cancer who received talazoparib 1 mg daily as monotherapy concluded no clinically relevant effect of age (ranging from 18 to 88 years) on the PK of talazoparib.

Table 8. Summary of Number of Subjects Contributing to Talazoparib Pharmacokinetic Data by Age Group in Clinical Studies

Study	Treatment	N	Age (Yrs)			
			<65 n (%)	65-74 n (%)	75-84 n (%)	>85 n (%)
MDV3800-06 (C3441006) TALAPRO-1	Monotherapy	98	30 (30.61%)	46 (46.94%)	22 (22.45%)	0
C3441021 Part 1	Enzalutamide Combination	19	3 (15.79%)	12 (63.16%)	4 (21.05%)	0
C3441021 Part 2 Cohort 1	Enzalutamide Combination	393	77 (19.59%)	184 (46.82%)	118 (30.03%)	14 (3.56%)

Pharmacokinetic interaction studies

For this application, study 1021 investigated the interaction between enzalutamide and talazoparib (see section on absorption for details). Talazoparib exposure was increased approximately 2-fold when dosed in combination with enzalutamide, likely due to the inhibition of P-gp by enzalutamide and its active metabolite N-desmethyl enzalutamide.

2.5.2.2. Pharmacodynamics

Relationship between plasma concentration and effect

Data from Study C3441021 (Phase 3 study, Part 1 and Cohort 1 of Part 2) was included in the analyses of exposure-efficacy and exposure-safety.

Relationship between exposure and efficacy

The objectives of the population exposure-efficacy analysis were to characterize the relationship between talazoparib exposure and Radiographic Progression-Free Survival (rPFS) in patients with metastatic castration-resistant prostate cancer regardless of deoxyribonucleic acid (DNA) damage repair (DDR) status and to identify potential prognostic factors (covariates) for efficacy.

A time-varying exposure metric, Cavg,t, was used in the analysis to account for dose modifications over time due to reasons other than the safety and the impact of enzalutamide and its n-desmethyl metabolite on talazoparib exposure over time. The results of the analyses showed that higher talazoparib exposure was associated with longer rPFS. In addition to the exposure metric other covariates were identified to be significantly correlated with rPFS. Longer rPFS was associated with lower Baseline Lactate Dehydrogenase, lower Baseline Alkaline Phosphatase, higher Baseline Lymphocytes, No Measurable Disease (vs Presence of Measurable Disease) and Disease Site (Any visceral vs Lymph node only).

Relationship between exposure and safety

The objectives of this population exposure-safety analysis were to characterize the relationship between talazoparib exposure and selected safety endpoints including Grade 3 and higher anemia, neutropenia, and thrombocytopenia from Study C3441021 in patients with metastatic castration-resistant prostate cancer

(mCRPC) and to identify potential prognostic factors (covariates) for selected safety endpoints. Anemia, neutropenia and thrombocytopenia are the most common Grade 3 or higher AEs leading to dose reductions or interruptions.

Higher talazoparib exposure was associated with a higher risk of Grade 3 or higher anemia, thrombocytopenia, or neutropenia. A summary of all key covariates from final models for all safety endpoints is presented in Table 11.

Table 9. Summary of Key Covariates from Final Models for Safety Endpoints

Safety Endpoint	Cavg,t Significant?	Higher Risk Associated With
Anemia	Yes (Cavg,t)	Lower baseline hemoglobin Lower baseline body weight Higher baseline lactate dehydrogenase
Thrombocytopenia	Yes (Cavg,t)	Lower baseline hemoglobin
Neutropenia	Yes (LogCavg,t)	Lower baseline absolute neutrophil count Lower baseline body weight Lower baseline hemoglobin

2.5.3. Discussion on clinical pharmacology

Methods

Talazoparib: The methods for analysing talazoparib were previously validated and found acceptable. Long term freezer stability was shown for a period covering the storage time for study samples. Incurred sample re-analysis was performed with acceptable results.

Enzaluatmide: The Methods for analysing enzalutamide and its metabolite N-desmethyl-enzalutamide were in general adequately validated. Long term freezer stability was shown for a period covering the storage time for study samples. Incurred sample re-analysis was performed with acceptable results.

Absorption

Proposed new strength of 0.1 mg

Talazoparib capsules are commercially available in two strengths, 0.25 mg and 1 mg. For this application an additional strength of 0.1 mg is proposed. The 0.1 mg strength has been used in study 1021, when dose reductions from 0.5 mg to 0.35 mg talazoparib have been required (using a 0.25 mg capsule and a 0.1 mg capsule). Forty-two participants received a reduced starting dose of talazoparib and 210 participants had at least one talazoparib dose reduction. Thus, there are clinical data with the 0.1 mg capsule in combination with the already approved strength, but no bioequivalence study has been performed and no dedicated PK-data for the 0.1 mg capsule only have been provided. Also, no in vitro dissolution data comparing the different strengths has been presented. Thus, there is no support that the 0.1 mg strength is interchangeable with other strengths and the intended use of the 0.1 mg strength is to support dose modifications (SmPC section 4.2).

Study 1021, part 1, dose finding

In study 1021 part 1, one of the primary objectives was to assess the pharmacokinetics of talazoparib in combination with enzalutamide and to determine the dosing regimen for the randomized Phase 3 portion of

the Study (Part 2). The starting dose of 1 mg talazoparib QD was the same dose as used in the approved breast cancer indication. Enzalutamide was administered at the labelled mCRPC dose of 160 mg QD. This combination therapy resulted in a ~2-fold increase in talazoparib exposure compared to historical monotherapy PK data. Safety data from the first 13 participants in Part 1 also showed higher than expected dose reductions and dosing interruptions due to Grade 3 hematological toxicities (anemia, thrombocytopenia and neutropenia).

It is previously known and stated in the SmPC's of the investigated products that enzalutamide is an inhibitor of P-gp and talazoparib is a substrate for P-pg. It its therefore likely that increase in talazoparib exposure is due to inhibition of P-gp by enzalutamide and its N-desmethyl metabolite in the intestine (increasing talazoparib bioavailability) and the renal tubules (reducing talazoparib elimination).

Following a repeated daily dosing of 1 mg talazoparib in monotherapy to breast cancer patients, mean (CV%) C_{trough} at steady state was 3.53 (61%) ng/mL. When 1 mg talazoparib was given in combination with 160 mg enzalutamide in mCRPC patients, this resulted in a mean (CV%) C_{trough} of 8.74 (40%) ng/mL. When the talazoparib dose was reduced to 0.5 mg QD in combination with enzalutamide 160 mg, mean (CV%) C_{trough} was 4.57 (53%) ng/mL and thus more comparable to monotherapy $C_{trough.}$

The reduced dose of 0.5 mg talazoparib in combination with 160 mg enzalutamide was chosen as new dose for part 2 of study.

Enzalutamide was tested at one strength, 160 mg and in combination with 0.5 mg or 1 mg talazoparib. The difference in dose of talazoparib did not seem to impact the exposure of enzalutamide and N-enzalutamide at the tested dose.

Study 1021, part 2

The results from part 1 of study 1021 were confirmed in part 2. The selected doses were 0.5 mg QD for patients with normal renal function or mild renal impairment and 0.35 mg for patients with moderate renal impairment in combination with 160 mg enzalutamide.

The steady-state exposure (C_{trough}) achieved after the dose reductions was 3.29-3.68 ng/mL and 3.63-4.06 ng/mL across week 9-17 for the 0.5 mg dose and 0.35 mg dose (for moderate RI), respectively. This is comparable to the talazoparib mean steady-state C_{trough} value reported from the pivotal Phase 3 Study EMBRACA (monotherapy in breast cancer) of 3.53 ng/mL. Thus, the dose reduction made for combination therapy achieved steady state exposure comparable to previously reported exposure for monotherapy. Exposure for patients with mild and moderate renal impairment was similar or slightly higher than for patients with normal renal function.

In general, coadministration of talazoparib did not seem to affect the exposures of enzalutamide and N-desmethyl enzalutamide (C_{trough}) and variability (geometric CV%).

Study 1006

Study 1006 was a phase II study with talazoparib as monotherapy. Patients with normal renal function and with mild renal impairment received a dose of 1 mg QD. For participants with moderate renal impairment the dose was reduced to 0.75 mg QD orally.

C_{trough} across week 5 to 13 was generally higher in participants with moderate renal impairment compared to normal renal function or mild renal impairment.

Distribution

No new data has been submitted which is acceptable.

Elimination

Talazoparib geometric mean CL/F ranged from 4.8 to 5.53 L/h in monotherapy compared to combination with enzalutamide when CL/F was 3.60-3.74 L/h across tested dose levels. Thus, a decrease in clearance was seen for combination therapy.

Dose proportionality and time dependencies

Previous data show that talazoparib (monotherapy) exposure generally increased proportionally with dose across the range of 0.025 mg to 2 mg. When talazoparib was tested in combination with 160 mg enzalutamide a dose proportional increase in exposure was seen for the two tested dose levels of 0.5 mg and 1 mg.

According to the SmPC of enzalutamide, no major deviations from dose proportionality are observed over the dose range 40 to 160 mg. For the studies in this application, only the 160 mg dose of enzalutamide was tested.

Population PK

An enzalutamide model was developed based initially on a literature model. It was concluded that talazoparib does not have an impact on enzalutamide exposure, therefore, all data could be used in the model. The goodness-of-fit (GOF) plots show a relatively adequate description of data. Enzalutamide parameters were fixed to EBEs to develop a population PK model for n-desmethyl enzalutamide. The fraction metabolite was fixed to a value based on a previously developed PBPK model which is acceptable. The GOF plots for N-desmethyl enzalutamide do not show any major deviation, and the models' ability to capture the observed data appears reasonable based on the pvcVPC.

Enzalutamide and its metabolites PK parameters were fixed to EBEs to develop a population PK model for talazoparib. A linear relationship was assumed for CL/F of talazoparib as a function of enzalutamide and n-desmethyl enzalutamide (Pgp-inhibitors) concentrations. This was implemented in the model by considering talazoparib CL/F to be dependent on the plasma concentrations of enzalutamide (Ce) and its n-desmethyl metabolite (Cn) via a linear relationship. It is concluded that the model can adequately describe the PK of talazoparib, enzalutamide and n-desmethyl enzalutamide collected in mCRPC patients and be used to derive post-hoc exposures. However, out of 811 participants in the popPK dataset who received enzalutamide, 21 participants in the enzalutamide and talazoparib treatment arm had an enzalutamide only dose reduction that they remained on (i.e., excluding patients that reduced both enzalutamide and talazoparib, and excluding dosing holidays and dose increases beyond first dose). There is therefore too limited information on the impact of enzalutamide dose reductions on talazoparib exposure in this dataset. In addition, the study was not designed to answer this question and the sampling times are not optimized for this purpose. With the sparse sampling, the long time to steady-state and the complexity of the interaction, there is inherently a large uncertainty in the conclusion on the extent of impact of enzalutamide dose/exposure on the exposure of talazoparib. The predicted impact should be interpreted and used with caution.

Special populations

For talazoparib monotherapy treatment (starting dose of 1 mg), the dose recommendations for subjects with renal impairment (RI) were determined based on a dedicated renal impairment study with talazoparib monotherapy. The talazoparib total exposure (AUC0-24) after multiple talazoparib once daily doses increased

by 92% and 169% in patients with moderate and severe renal impairment, respectively, relative to patients with normal renal function. No RI study has been performed for the combination treatment of talazoparib and enzalutamide. Based on a population PK analysis that included 412 mCRPC patients who received talazoparib co-administered with enzalutamide, where 152 patients had mild renal impairment (60 mL/min ≤ CrCL < 90 mL/min) and 72 patients had moderate renal impairment (30 mL/min ≤ CrCL < 60 mL/min), talazoparib CL/F was decreased by 8% and 27%, corresponding to increases in AUC of 9% and 37% in patients with mild and moderate renal impairment respectively, compared to patients with normal renal function. No dose adjustment is necessary for patients with mild renal impairment. For patients with moderate renal impairment, the recommended dose of Talzenna is 0.35 mg once daily in combination with enzalutamide orally once daily. Only 2 subjects with severe renal impairment were included in the phase 3 study precluding a conclusion on the exposure in this patient population. The recommended dose reduction to 0.25 mg once daily in combination with enzalutamide once daily is therefore based on the dedicated monotherapy RI study. The PK of talazoparib has not been studied in patients requiring haemodialysis.

The MAH has only discussed the impact of HI on talazoparib for the combination treatment and has not accounted for impact of HI on enzalutamide and its active metabolite. There is very limited or no data on subjects with moderate and severe hepatic impairment give the combination treatment. The exposure of enzalutamide and its active metabolite increases in subjects with hepatic impairment (the sum of unbound enzalutamide plus the unbound active metabolite AUC in subjects with severe hepatic impairment increased by 34%). It is not clear that this increase in enzalutamide will not subsequently affect talazoparib's exposure. Due to the way the interaction between the substances were included in the population PK model it may not be show the true impact on talazoparib exposure. Given the increase in enzalutamide and N-desmethyl enzalutamide total exposure in subjects with severe HI, talazoparib in combination with enzalutamide is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C), as pharmacokinetics and safety has not been established in these patients.

Simulated steady state PK parameters showed a trend towards higher exposures of enzalutamide, N-desmethyl enzalutamide, and talazoparib at lower baseline body weights. The increases in drug exposures at lower baseline body weights were associated with corresponding increases in cytopenic all grade and Grade 3+ TEAEs, talazoparib dose interruptions and reductions, and need for blood transfusions relative to the higher baseline body weight group. However, the proposed dose modification guidelines are considered an effective approach for management of AEs and that it is not warranted with an up-front dose adjustment based on body weight.

Interactions

When talazoparib is co-administered with enzalutamide, exposure increases approximately 2-fold compared to monotherapy.

The increase in talazoparib exposure may be due to inhibition of P-gp by enzalutamide and its N-desmethyl metabolite in the intestine (increasing talazoparib bioavailability) and/or the renal tubules (reducing talazoparib elimination). It is likely that P-gp-inhibition effect of enzalutamide plays an important role in increasing the absorption and thereby the exposure of talazoparib. However, the effect of enzalutamide on talazoparib exposure is larger compared to P-gp inhibitor itraconazole indicating that other factors contribute to the interaction. Moreover, CL/F is decreased for the combination treatment compared to monotherapy suggesting renal P-gp-inhibition as well.

Previous DDI studies with talazoparib and multiple doses of P-gp inhibitor itraconazole increased total exposure AUC_{inf} and C_{max} by approximately 56 and 40%, respectively. The effect of co-administration of P-gp

inhibitors on talazoparib exposure when talazoparib is given in combination with enzalutamide has not been studied. Therefore, concomitant use of P-gp inhibitors during treatment with talazoparib should be avoided (see section 4.5).

Regarding enzalutamide, in vitro data indicate that enzalutamide may be an inhibitor of the efflux transporter P-gp. Also, a DDI study with probe P-gp substrate digoxin before and concomitantly with enzalutamide increased AUC and C_{max} by 33% and 17%, respectively.

2.5.4. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics of enzalutamide, N-desmethyl enzalutamide and talazoparib and their interactions have been adequately characterised.

2.5.5. Clinical efficacy

Throughout the assessment report, the terms homologous recombination repair (HRR) and DNA damage response (DDR) are used interchangeably.

An overall presentation of the clinical studies supporting the current application is presented below.

Table 10. Overview of relevant clinical studies

Study/ Protocol Number	Study Start/Data Cutoff Date/ Status	Study Design	Primary Endpoint Analysis	Treatment Dose/ Number of Participants
Pivotal Phase 3				
C3441021 TALAPRO-2	08 Aug 2017/ 16 Aug 2022/ Part 1: *Completed* Part 2: *Ongoing*	Phase 3, international, two-part study enrolling patients with mCRPC where no systemic cancer treatments have been initiated after documentation of the CRPC state. **Part 1:** open-label and non-randomized and evaluated the safety, tolerability, and PK of talazoparib in combination with enzalutamide **Part 2:** randomized, double-blind, and placebo-controlled, evaluating the efficacy and safety of talazoparib in combination with enzalutamide compared with placebo in combination with enzalutamide; Part 2 enrolled 2 cohorts	Part 1: (Open label) Occurrence of target safety events to determine starting dose of talazoparib when given in combination with enzalutamide during Part 2. Part 2: (Blinded) BICR assessed rPFS in participants with mCRPC. Cohort 1 all-comers population: the primary analysis will be completed after reaching 333 rPFS events based BICR assessment. Enrolment of approximately 750 mCRPC participants unselected for gene mutation status will be needed to observe the 333 events. *Cohort 2 is not included in this submission*	**Part 1** - talazoparib 0.5 mg – 1 mg with enzalutamide 160 mg QD **Part 2** - talazoparib or identical placebo at a starting dose of 0.5 mg QD in combination with enzalutamide 160 mg QD. • Moderate renal impairment at screening: (eGFR 30-59 mL/min/1.73 m^2) - talazoparib or identical placebo capsules at a reduced starting dose of 0.35 mg/day Approximately 1037 men (19 in Part 1 and 1018 in Part 2) with mCRPC were enrolled. **Part 1:** 19 participants were enrolled **Part 2:** • Cohort 1 - 805 mCRPC participants unselected for HRR status enrolled • Cohort 2 – 399 mCRPC participants, whose disease has HRR mutations likely to sensitize to PARP inhibition
Supplemental Phase 2				
C3441006 TALAPRO-1	04 Jul 2017/ 04 Sep 2020/ *Completed*	Phase 2, international, open-label, soft tissue response rate study of talazoparib to evaluate the efficacy and safety of talazoparib monotherapy in adult male subjects with mCRPC with HRR deficiencies whose disease has previously progressed on NHT: enzalutamide and/or abiraterone acetate, given for the treatment of mCRPC and who were previously treated with taxane based chemotherapy for metastatic disease.	Objective Response Rate (ORR), defined as the proportion of participants with a best overall soft tissue response of CR or PR per RECIST 1.1 by BICR assessment, in the HRR Deficient Measurable Disease population. The primary analysis was conducted when 100 participants completed at least 6 months of study treatment or were otherwise no longer being followed (eg withdrew consent, discontinued from the study, or died).	Talazoparib monotherapy, 1 mg QD, orally Moderate renal impairment at screening (eGFR: 30-59 mL/min/1.73 m^2 per central laboratory): starting and maximum dose was 0.75 mg QD As of data cutoff (04 Sep 2020): • 128 participants enrolled, 127 participants received study intervention (Safety Population) • HRR Deficient Measurable Disease Population, n=104

2.5.5.1. Dose response study(ies)

Part 1 (open label) of the pivotal study C3441021 (study 1021) was conducted to determine the starting dose of talazoparib administered in combination with enzalutamide. This was done due to a potential drug-drug interaction of talazoparib with Pgp drug transporters Enzalutamide is known to exhibit both Pgp induction and inhibition properties.

Talazoparib was evaluated at doses of 1.0 mg QD (n=13, approved dose) or 0.5 mg QD (n=6), in combination with 160 mg QD enzalutamide. Results indicated that talazoparib exposure was increased by enzalutamide; thus, the recommended starting dose of talazoparib for Study 1021 part 2 was reduced from 1 mg QD to 0.5 mg QD (see clinical pharmacology section).

Study Participants; Study 1021 part 1 enrolled 19 patients

Treatments: Talazoparib and enzalutamide were administered orally QD in the morning at fixed doses of 1 mg talazoparib and 160 mg enzalutamide. Talazoparib was provided as 0.25 mg and 0.1 mg hard capsules, and enzalutamide as gelatine capsules of 40 mg. Talazoparib and enzalutamide could be taken with or without food and was to be swallowed whole. Following a review of available PK and safety data from the 13 first enrolled patients, six additional patients were enrolled and received 0.5 mg talazoparib QD+ 160 mg enzalutamide QD. The evaluation of the data suggested that the lower talazoparib dose maintained talazoparib AUC_{tau} at levels similar to that obtained with 1 mg talazoparib QD, which is the approved monotherapy dose in breast cancer. Talazoparib capsules were provided by the sponsor and dispersed from the study sites to the patients. Enzalutamide capsules were sourced by the study sites to the patients.

Objectives: The primary objective of part 1 was to determine the starting dose of talazoparib when given in combination with enzalutamide to be used in part 2 (double-blind treatment period).

Outcomes/endpoints:

Primary endpoint: Target safety events (haematologic, non-haematologic, and liver toxicity).

Secondary endpoints were PK samples collected at week 1 and PK samples collected at weeks 5, 9, 13, and 17 at the same dose level without any dose modification for at least 14 days.

Exploratory endpoints: Circulating tumour cell (CTC) counts. Summary of the mean (standard deviation), median, and range of baseline and post baseline values and the number and percentage of patients with CTC count ≥ 5 vs. < 5 and CTC count > 0 vs. =0 per 7.5 mL.

Results

Participant flow

Part 1 *Enrolment:* Assessed for eligibility = 32; Randomised = 19

Allocation: Talazoparib + enzalutamide = 19

Follow-up: Discontinued due to AE = 5/19; Discontinued due to progressive disease = 4/19

Recruitment: *Study period*

Study initiation date: 08 Aug 2017

Data cut-off date: 16 Aug 2022 study 1021. Part 1 completed.

Baseline data: The median age of patients at inclusion in part 1 was 71.0 years. The median time since

diagnosis was 51.94 months. The majority of patients (63.2%) did not have any metastases at initial diagnosis but had Gleason score ≥8 (high-risk factor). Thus, 36.8% of the patients had de novo metastases. No data on HRR gene mutations were provided. HRR gene testing was optional for participants in part 1. For information about study treatment exposure, please refer to the safety assessment.

Numbers analysed: All 19 patients enrolled in part 1 received both talazoparib (1 mg or 0.5 mg) and enzalutamide. All patients that received at least one dose of study treatment (talazoparib or enzalutamide) were included in the **safety population**. All 19 patients (100.0%) met this criterion.

2.5.5.2. Main study

Pivotal study C3441021 (TALAPRO-2)

The pivotal study C3441021, hereafter referred to as study 1021, is a multicentre, phase III study consisting of two parts. As mentioned above Part 1 was an open-label, non-randomised dose finding part on patients with mCRPC to determine the starting dose of talazoparib for part 2.

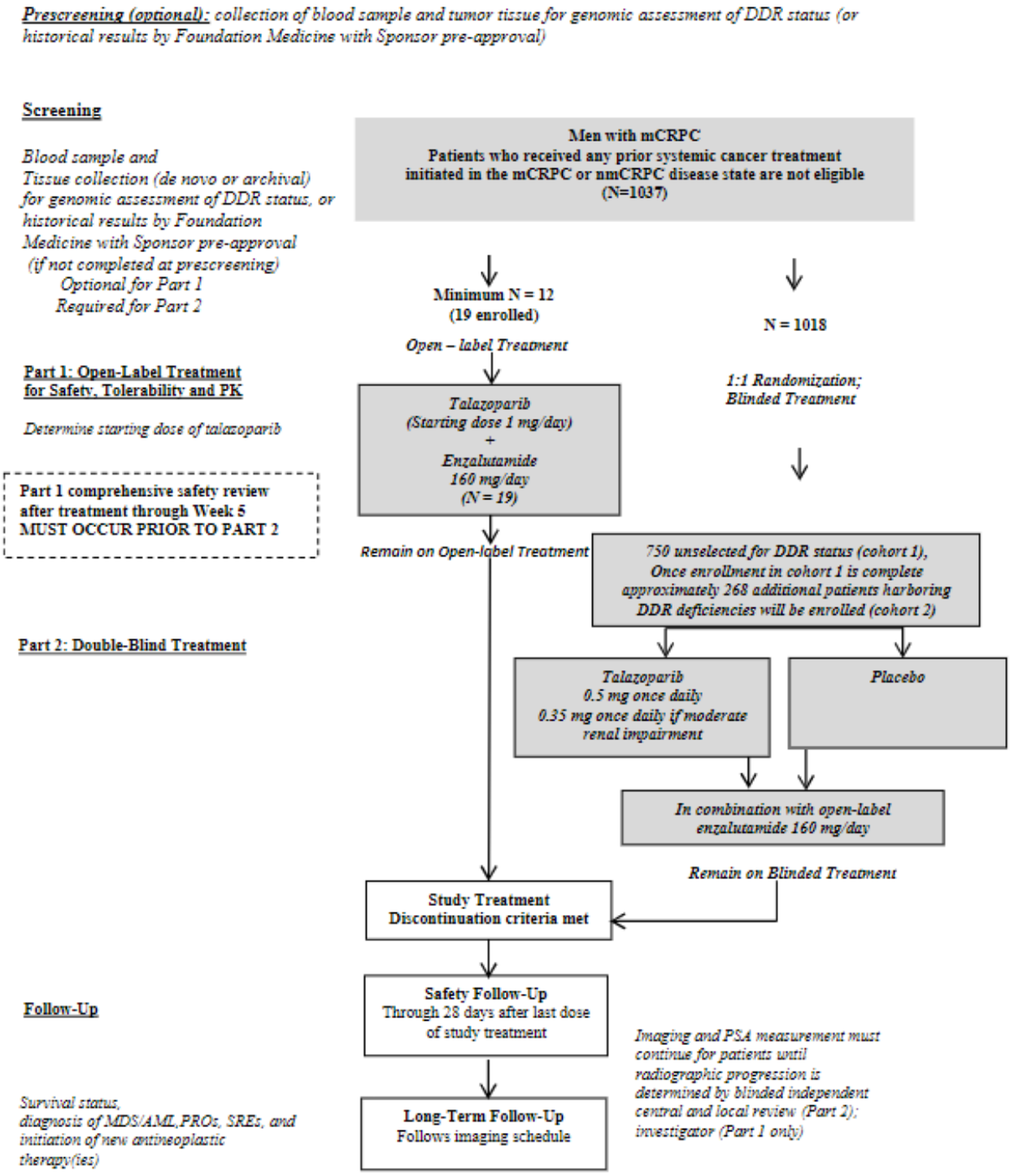
Part 2 was a randomised, double-blind, placebo-controlled study on patients with mCRPC and consisted of two cohorts.

Part 2 cohort 1 constitutes the basis for the current application. Patients with mCRPC unselected for HRR-mutation status were randomised 1:1 to either talazoparib 0.5 mg QD + enzalutamide 160 mg QD or placebo + enzalutamide 160 mg QD. Patients in cohort 1 were stratified for HRR-mutation status (deficient vs. non-deficient/unknown) and previous treatment with any Novel Home Therapy (NHT) or taxane-based chemotherapy.

Part 2 cohort 2 – HRR-deficient cohort: patients with mCRPC with known HRR-mutations. Analyses on this cohort will also include HRR-deficient patients enrolled in cohort 1. This part of the study is still ongoing and not formally part of the current application, but top line data are used to support the results in the HRR-deficient study population in cohort 1. Enrolment in part 2 cohort 2 started upon completed enrolment in cohort 1.

Data from part 2, cohort 1 have been blinded until the all-comers population meet the primary endpoint. As stated in the study protocol, blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code was absolutely essential for further management of the subject. In total, premature unblinding occurred in 20 (2.5%) cases, six in the talazoparib + enzalutamide arm and 14 in the placebo + enzalutamide arm. The reasons for premature unblinding were to allow the investigator to make future treatment decisions (14 cases) and due to subject safety concerns (six cases).

Figure 5. Study schematic



DDR status = HRR status
Source: Summary of Clinical Efficacy, Figure 1

HRR-mutation status

HRR deficiency was defined as a mutation in one or more of the following 12 genes: *ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2*, or *RAD51C* (also referred to as HRR12 or core genes/mutations). HRR-mutation status was analysed using the FoundationOne CDx or FoundationOne Liquid gene panels.

For patients enrolling in part 1, submission and testing of tumour tissue was optional.

Patients enrolled in part 2 were required to give consent during an optional pre-screening period or at screening to submit sufficient tumour tissue (de novo or archival tissue) for genomic assessment. A peripheral blood sample was collected and submitted for retrospective blood-based genomic assessment.

The patient HRR mutational status was considered unknown if the test failed due to either not meeting specified quality control metrics, or due to insufficient or inadequate blood or tumour tissue sample.

Methods

- **Study Participants**

Study 1021 part 2 enrolled 805 patients at 270 study sites across 26 countries around the world. In part 2, patients were stratified for i) previous treatment with NHT or taxane-based chemotherapy for CSPC and ii) HRR-mutation status (deficient vs. non-deficient/unknown). Prior abiraterone treatment for metastatic castration sensitive prostate cancer (mCSPC) was allowed.

The most important inclusion and exclusion criteria are listed below.

Selected key inclusion criteria

1. For enrolment into part 2 only (optional in part 1): assessment of HRR-mutation status by prospective analysis of blood (liquid biopsy), or tissue, or historical analysis of most recent tumour tissue per FoundationOne testing.
2. For enrolment into part 2 only (optional for part 1): consent to a saliva sample collection for retrospective sequencing of the same HRR genes tested on tumour tissue and blood.
3. Surgically or medically castrated, with serum testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening. Ongoing ADT with a gonadotropin-releasing hormone (GnRH) agonist or antagonist for participants who had not undergone bilateral orchiectomy must have been initiated at least 4 weeks before Day 1 (part 1) or randomisation (part 2) and must have continued throughout the study.
4. Metastatic disease in bone documented on bone scan or in soft tissue documented on CT/MRI scan. Measurable soft tissue disease was not required. (Adenopathy below the aortic bifurcation alone did not qualify).
5. Progressive disease at study entry in the setting of medical or surgical castration

Selected key exclusion criteria

1. Any prior systemic cancer treatment initiated in the nonmetastatic CRPC or mCRPC disease state. (ADT and first-generation anti-androgens received in the CRPC disease state were NOT exclusionary).
2. Participants whose only evidence of metastasis was adenopathy below the aortic bifurcation.

3. Prior treatment with second-generation AR inhibitors (enzalutamide, apalutamide, and darolutamide), a PARP inhibitor, cyclophosphamide, or mitoxantrone for prostate cancer.
4. Prior docetaxel for mCSPC was allowed if more than four weeks had elapsed from the last dose of docetaxel.
5. Current use of potent P-gp inhibitors within seven days prior to Day 1 (Part 1) or randomisation (part 2).

- **Treatments**

Part 2 talazoparib/placebo + enzalutamide randomised treatment

Talazoparib 0.5 mg or placebo capsules with identical appearance to each dosage strength of talazoparib capsules were administered orally together with enzalutamide 160 mg QD in the morning. Switching to evening dose was permitted after week 13 and week 17 visit. Talazoparib and enzalutamide could be taken with or without food and was to be swallowed whole. Talazoparib or placebo capsules and enzalutamide capsules were provided by the sponsor and dispersed from the study sites to the patients.

Treatment in both part 1 and 2 continued until radiographic progression (determined by local review in part 1 and by blinded independent central review [BICR] in part 2), intolerable toxicity, until the patient was no longer clinically benefitting, until the patient decided to discontinue treatment, or death. Study treatment post progression was allowed, regardless of radiographic progression, if the investigator considered that the patient was still deriving benefit from the treatment.

Part 2 randomised treatment

Primary objectives

- To demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging BICR-assessed rPFS in patients with mCRPC unselected for HRR status.
- To demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging BICR-assessed rPFS in patients with mCRPC harbouring HRR deficiencies.

Secondary objectives

- To demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging OS in patients with mCRPC unselected for HRR status.
- To demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging OS in patients with mCRPC harbouring HRR deficiencies.

Part 2 randomised treatment

Primary endpoint

- rPFS based on BICR between talazoparib + enzalutamide vs. talazoparib-matching placebo + enzalutamide. rPFS is defined as the time from the date of randomisation to first objective evidence of radiographic progression as assessed in soft tissue per RECIST 1.1 or in bone (upon subsequent confirmation) as per PCWG3 guidelines, or death due to any cause, whichever occurs first.

Selected secondary endpoints

- OS, defined as the time from randomisation to the date of death due to any cause.
- ORR, defined as the proportion of patients with measurable soft tissue disease at baseline with at best overall confirmed soft tissue response of complete response (CR) or partial response (PR) according to RECIST 1.1.
- Duration of response (DoR); duration of soft tissue response defined as the time from the date of the first soft tissue response to the first documented objective evidence of progression (in soft tissue per RECIST 1.1 or in bone per PCWG3 guidelines) or start of new antineoplastic therapy.
- Proportion of patients with PSA response >50%, defined as decline from baseline PSA (ng/mL) by at least 50%.
- Time to PSA progression, defined as the time from the date of randomisation to the date of the first PSA value demonstrating progression.

Other secondary endpoints were time to initiation of cytotoxic chemotherapy, time to initiation of antineoplastic therapy, time to first symptomatic skeletal event, investigator assessed PFS2, time to opiate use for prostate cancer pain, patient reported outcome (PRO) endpoints.

Other endpoints

- CTC endpoints for both the all-comers and HRR-deficient population
- Molecular profiling
- Concordance of HRR deficiency results

- **Sample size**

The sample size and power calculations for part 2 are based on the log-rank test. A selection of assumptions used to determine the sample size for the primary endpoint of radiographic PFS are presented here:

• Median rPFS was assumed to be 16 months for the control arm. The median rPFS for the test arm was assumed to be 23 months for patients with mCRPC unselected for HRR status and 25 months for the HRR-deficient population; this corresponds to a hazard ratio of 0.696 in the all-comers population and 0.64 in the HRR-deficient population, respectively under an exponential model assumption.

• Median OS for patients in the control arm was assumed to be 35 months (Beer et al, 2017) and the median OS for patients in the test arm was assumed to be 46.7 months in both the all-comers and HRR-deficient populations; this corresponds to a HR of 0.75 under the exponential model assumption.

• Approximately 15% of the all-comers population will harbour HRR deficiencies.

Initially, approximately 750 patients were to be enrolled regardless of HRR mutation status (cohort 1). Once enrolment was complete in the all-comers population, additional patients with HRR-deficient disease would have been enrolled (cohort 2) until there were approximately 380 patients with HRR-deficient mCRPC across cohorts 1 and 2. Analysis on the HRR-deficient population included patients with HRR-deficient mCRPC enrolled in cohorts 1 and 2.

For the primary comparison of rPFS in the all-comers population, 333 rPFS events based on BICR assessment would provide 85% power to detect a HR of 0.696 using a 1-sided stratified log rank test at a significance level of 0.0125 and an interim analysis for futility using a Lan-DeMets β–spending function to determine the futility boundary. It was estimated that 750 mCRPC patients unselected for mutation status would be needed to observe the 333 events.

For the primary comparison of rPFS in the HRR-deficient population, 224 rPFS events based on BICR assessment would provide 85% power to detect a HR of 0.64 using a 1-sided stratified log rank test at a significance level of 0.0125 and two interim analyses using a Lan DeMets α–spending function and a Lan DeMets β-spending function to determine the non-binding boundaries and preserve the overall error rate. It was estimated that 380 HRR-deficient patients would be needed to observe the 224 events.

For OS in the all-comers population, 438 OS events would provide 78% power to detect a HR of 0.75 using a 1-sided log rank test at a significance level of 0.0125 and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries.

The study would be underpowered for OS in the HRR-deficient population; however, if H_{02} (rPFS in the HRR-deficient population) was rejected then H_{04} (OS in the HRR-deficient population) would be tested. The final analysis for OS in the HRR-deficient population would occur at the time of the final analysis of OS in the all-comers population. It was estimated that 173 OS events in the HRR-deficient population would have occurred at this time, providing 36% power to detect a HR of 0.75 using a 1-sided log rank test at a significance level of 0.0125.

- **Randomisation and Blinding (masking)**

Randomisation

Participants were centrally assigned to talazoparib or placebo (1:1 randomisation), based on the following stratification factors:

1) Previous treatment with any novel hormonal therapy (NHT) or taxane-based chemotherapy (yes/no)
2) HRR mutational status (deficient vs. non-deficient/unknown).
    - In the case of a test failure due to not meeting specified quality control metrics, or insufficient or inadequate blood or tumour tissue sample, the patient HRR mutational status would be considered unknown.
    - If results from blood and tumour tissue samples were both available prior to randomisation, a positive result from either would be considered HRR-deficient.

The stratification factors were to be specified by the investigator and recorded in the Interactive Web Response System (IWRS) before randomisation. The stratified analysis of the primary efficacy endpoint was based on the stratification information recorded in IWRS.

Blinding (masking)

The study (part 2) was participant and investigator blinded to talazoparib or matching placebo; enzalutamide was open label.

According to the CSR, the sponsor was to be unblinded to the all-comers population if the e-DMC notifies the sponsor that the final analysis of rPFS in the all-comers population met the primary endpoint. Otherwise, the

sponsor would remain blinded to the all-comers population until the unblinding of the HRR-deficient population at the end of the study.

The study part 2 was designed as double-blinded to talazoparib or matching placebo.

While study part 2 was planned to be double blinded throughout the study period, it is obvious that the study is double-blind only up to the timepoint of the interim analysis in the CSR (based on the data cut-off from 16 August 2022), *i.e.*, analyses presented in this report.

- **Statistical methods**

Analysis populations

Intent-to-Treat population: All patients randomised to double-blind study treatment in part 2 regardless of whether or not treatment was administered.

Safety Population: All patients who received at least one dose of study treatment (talazoparib/placebo or enzalutamide) in part 2 and was based on the actual treatment received.

All-comers population includes patients unselected for HRR status enrolled in Cohort 1.

DDR-deficient population includes patients with HRR deficiencies enrolled in Cohorts 1 and Cohort 2.

Hypotheses

The following statistical hypotheses were tested to address the primary objectives:

H_{01}: $HR_{rPFS} \geq 1$ vs. H_{11}: $HR_{rPFS} < 1$

H_{02}: $HR_{rPFS+} \geq 1$ vs. H_{12}: $HR_{rPFS+} < 1$

where HR_{rPFS} and HR_{rPFS+} are the hazard ratios (talazoparib in combination with enzalutamide vs. placebo in combination with enzalutamide) of rPFS based on BICR assessment in the all-comers population and in the HRR-deficient population, respectively. In addition, the following statistical hypotheses were to be tested to address the key secondary objectives:

H_{03}: $HR_{OS} \geq 1$ vs. H_{13}: $HR_{OS} < 1$

H_{04}: $HR_{OS+} \geq 1$ vs. H_{14}: $HR_{OS+} < 1$

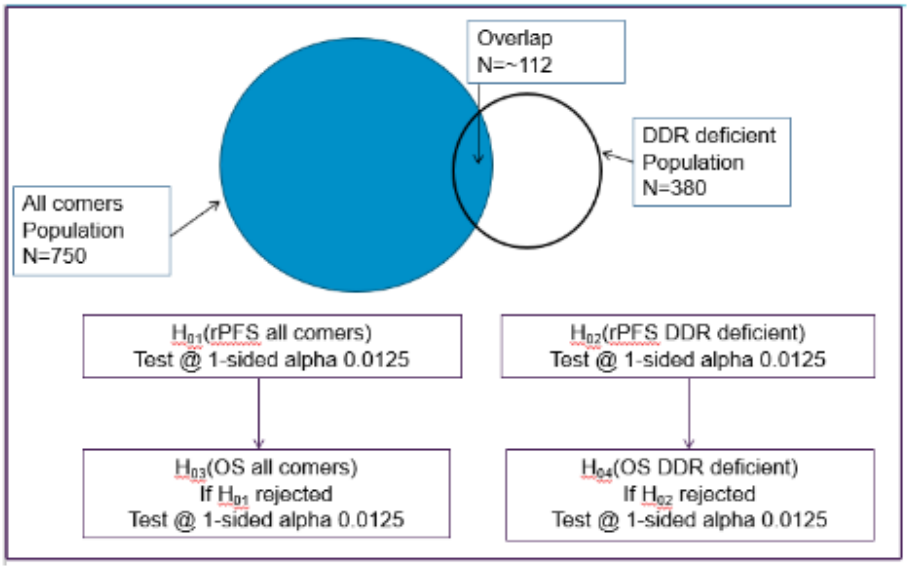
where HR_{OS} and HR_{OS+} are the hazard ratios (talazoparib in combination with enzalutamide vs. placebo in combination with enzalutamide) of OS in the all-comers and HRR-deficient populations, respectively.

Multiplicity

Alpha was split equally (1-side 0.0125) between H_{01} and H_{02} to maintain the overall type-I error at or below 1-sided 0.025. The study was considered positive if at least one of the null hypotheses was rejected. To

further preserve the overall alpha, a hierarchical stepwise gatekeeping testing procedure were to be used to test OS. Specifically, H_{03} would be tested only if H_{01} was rejected and H_{04} would be tested only if H_{02} was rejected.

Figure 6. Study populations and hypotheses



DDR-deficient = HRR-deficient
Source: Statistical Analysis Plan, Figure 1

Methods of primary analysis

The primary efficacy analysis compared rPFS based on BICR between talazoparib in combination with enzalutamide vs. talazoparib-matching placebo in combination with enzalutamide and was performed using one-sided stratified log-rank test for the allcomers and HRR-deficient populations respectively (subsets of the ITT population).

The stratified hazard ratio (talazoparib in combination with enzalutamide/control) and the associated 95% CI were estimated using a Cox proportional hazards model. Ties were handled using the Breslow method. Both one-sided and two-sided p-values are provided in summary tables.

The primary stratified analysis was based on the stratification information recorded in IWRS. A secondary stratified analysis based on HRR mutational status derived from clinical database was also performed.

Censoring rules for rPFS

1) The patient was censored on the date of the last adequate tumour assessment on or before the data cut-off date if the patient did not have radiographic progression and did not die.

2) The patient was censored on the date of last adequate tumour assessment prior to the start of new antineoplastic therapy, if the patient started a new antineoplastic therapy prior to radiographic progression, or death.

3) The patient was censored on randomisation date, if the patient did not have baseline, or postbaseline tumour assessments.

4) The patient was censored on the date of the last adequate tumour assessment without evidence of disease progression prior to missed tumour assessments, if the patient missed 2 or more scheduled tumour assessments immediately prior to radiographic progression, or death.

Sensitivity analyses

The following sensitivity analyses were performed separately for the all-comers and HRR-deficient populations to explore the robustness of each primary analysis result.

1) Radiographic PFS counting all progression and deaths as events regardless of missing assessments or timing of the event (*i.e.*, not censoring due to the start of a new antineoplastic therapy prior to event or due to missed assessments) based on BICR and investigator assessments.

2) Radiographic PFS counting study treatment discontinuation, start of a new antineoplastic therapy, and occurrence of a symptomatic skeletal event as additional events based on BICR and investigator assessments. Censoring was similar to that described for the primary analysis, except for the following:

- Radiographic progression, death, discontinuation of study treatment (both treatment components), start of a new anti-cancer therapy, and a symptomatic skeletal event were all considered as events. rPFS was calculated as the time interval from the date of randomization to the date of radiographic progression, death, discontinuation of study treatment (both treatment components), start of a new anti-cancer therapy, or a symptomatic skeletal event, whichever occurs first.

3) Radiographic PFS by assigning the dates of censoring and events only at scheduled assessment dates based on BICR and investigator assessments:

- If a radiographic progression occurred within 7-day window of its scheduled assessment time, it was assigned the scheduled assessment date. If a radiographic progression occurred outside the 7-day window and between 2 scheduled assessments, the date of the later planned assessment was assigned as the radiographic progression date (*e.g.*, if a radiographic progression occurs between weeks 25 and 37, it will be assigned to week 37).

- In the event of death, the event date was not adjusted.

In addition, to assess the impact of COVID-19, sensitivity analyses of rPFS may be performed if COVID-19 related death is reported in at least 10 patients in the study.

Methods of Secondary analysis

OS was analysed by the similar methods as the primary endpoint rPFS. ORR and proportion of patients with PSA response ≥50% was analysed using Cochran-Mantel-Haenszel test.

Kaplan-Meier curves were used to estimate the time-to-event endpoints. The 50th percentile of Kaplan-Meier estimates was used to estimate the median duration of each endpoint. A 2-sided 95% CI based on the Brookmeyer-Crowley method was provided for this estimate. In addition, the event-free rate and 95% CI at 12 months, 24 months, and 36 months for each treatment arm were presented.

Planned analysis timepoints
Table 11. Summary of Analysis Timepoints

	Analysis Cut off Trigger	Analysis	
		Population	Hypothesis Tested
Analysis 1	167 (50% event fraction) rPFS events in the all-comers population	All-comers	Futility for rPFS
		DDR-deficient	No analysis
Analysis 2	333 rPFS events in the all-comers population	All-comers	Final rPFS
			IA OS
		DDR-deficient	Futility for rPFS
Analysis 3	157 (70% event fraction) rPFS events in the DDR-deficient population	All-comers	No analysis
		DDR-deficient	IA rPFS IA OS
Analysis 4	224 rPFS events in the DDR-deficient population	DDR-deficient	Final rPFS Final OS
	438 OS events in the all-comers population	All-comers	Final OS

Analyses conducted

On May 24, 2021, the e-DMC conducted unblinded efficacy review at the preplanned interim analysis (Analysis 1). e-DMC concluded that the study did not cross the futility boundary in Cohort 1 and recommended that the study continue. The blinding was maintained for the applicant.

Following e-DMC review of the Analysis 2 (cut-off date 16 August 2022), the Sponsor was informed that the study met its primary endpoint and was unblinded to these data. The Applicant's blinding for Cohort 2 was maintained.

Upon e-DMC review of the Analysis 3 (cut-off date 3 October 2022), Cohort 2 met its primary endpoint since the results crossed the prespecified efficacy boundary for rPFS (i.e., O'Brien-Fleming efficacy boundary of p-value ≤0.0038 one-sided, which was adjusted based on the 170 rPFS events in this population at the data cut-off). Subsequently, the Applicant was unblinded to all study data. This analysis became final analysis for rPFS in HRR-deficient population.

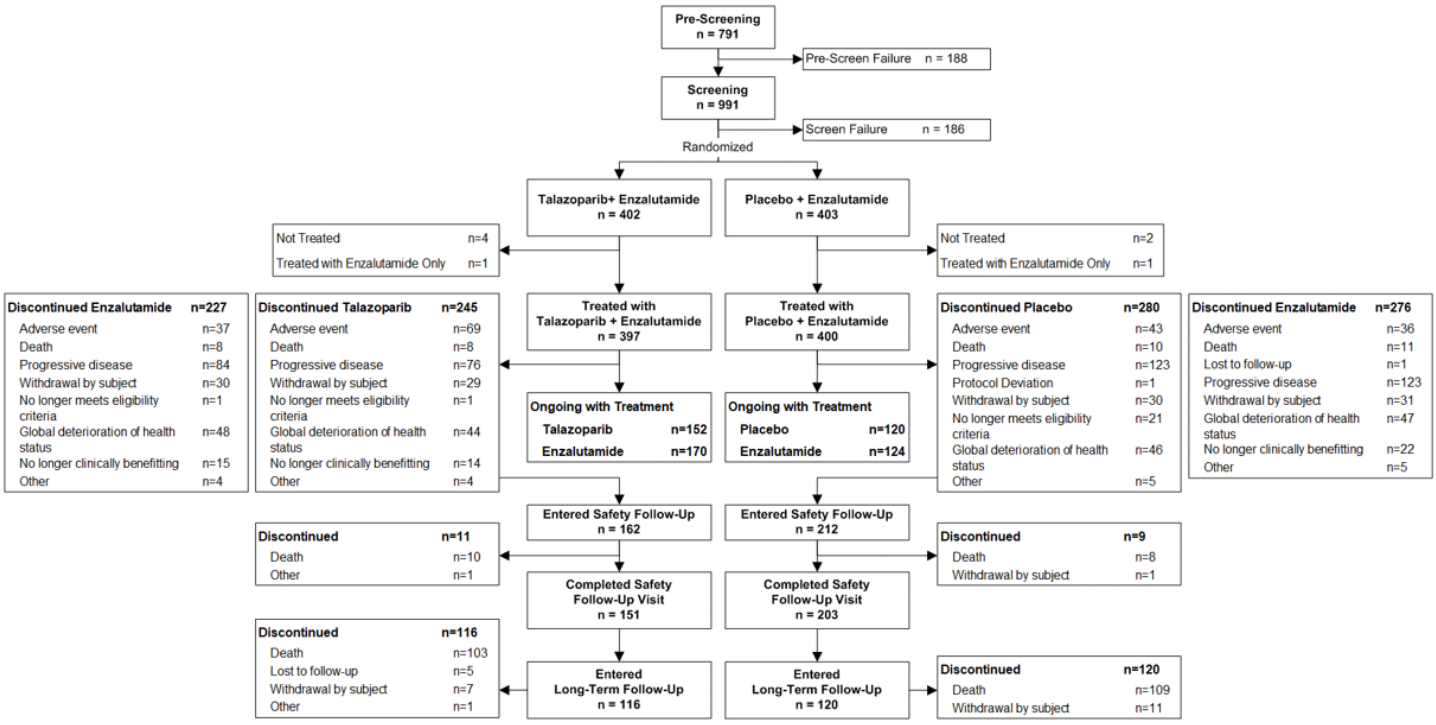
SAP management

The Statistical Analysis Plan (SAP) was based on the Protocol Amendment 8. The final (current) SAP version was dated 1 July 2022, prior to the primary analysis in all-comers. Major changes in the SAP development occurred in version 2 and version 5 and concerned increased sample sizes.

Results

Part 2 randomised treatment

Participant Disposition – Study 1021 Part 2, Cohort 1 (all-comers population)



- part 2 cohort 1 (ongoing)
- part 2 cohort 2 is still ongoing (immature data, not part of the present application)

The submitted CSR presented the results of the primary analysis with DCO of 16 Aug 2022 at which, according to the statistical analysis methods plan, approximately 333 rPFS events were observed. At the same time, a futility interim analysis of the HRR-deficient population was performed.

Study centres

The study was conducted at 287 sites in the following 26 countries: Argentina (1), Australia (2), Belgium (3), Brazil (4), Canada (5), Chile (6), China (7), Czech Republic (8), Finland (9), France (10), Germany (11), Hungary (12), Israel (13), Italy (14), Japan (15), Republic of Korea (16), New Zealand (17), Norway (18), Peru (19), Poland (20), Portugal (21), South Africa (22), Spain (23), Sweden (24), United Kingdom 25), and United States (26).

- **Conduct of the study**

Table 12. Selected key features of each amendment

Document	Version date	Summary of changes and rationale
Original protocol	28 July 2017	
Amendment 1	30 March 2018	• Abiraterone treatment arm removed from both part 1 and 2, sample size updated accordingly • Clarification on assessment of safety and PK data for confirmation of talazoparib starting dose (part 2)

Amendment 2	30 October 2018	• Inclusion of patients without HRR-deficiencies or with unknown mutation status • Specification of talazoparib dose in combination with enzalutamide in part 2 (HRR-deficient patients) • Update/clarification of inclusion criteria 4, 13, and 14 • Update/clarification of exclusion criteria 1, 5, 16, 18, and 21 • Clarification of end of treatment requirements • Clarification of HRR deficiency and unknown HRR status • Update of data analysis and statistical methods (part 2)
Amendment 3	12 March 2019	• Update/clarification regarding allowable additional treatment (post progression) • Updated discontinuation requirements
Amendment 4	22 July 2019	• Increased patient size: Number of patients in part 2 increased from 860 to 1018 Cohort 1 changed from 560 to 750 patients Cohort 2 changed from 300 to 268 patients • Change in number of study sites from 200 to 270 • Estimated overlap between HRR-deficient and all comers population changed from approximately 85-140 to approximately 112 • Clarification of when specific blood tests should be collected • Clarification of randomisation criteria • Clarification of exclusion criteria 1, 3, 4, 5, 6, 7, 8, 9, and 16
Amendment 5	28 October 2019	• Changes specific for South African study sites: Update regarding HIV testing
Amendment 6	26 February 2020	• Introduce the use of liquid biopsies for assessment of tumour HRR status at pre-screening or screening • New exploratory endpoint: concordance of HRR results between liquid and tumour tissue biopsies • Update/clarification of inclusion criteria 4, 5, and 8 • Update/clarification of exclusion criteria 1 and 15 • Clarification that skeletal events should continue in long-term follow up
Amendment 7	18 September 2020	• Introduce an extension cohort to ensure at least 113 mCRPC patients are randomised in China (additional patients randomised to the extension cohort not included in analysis of primary and secondary endpoints)
Amendment 8	17 June 2021	• Update analysis trigger of IA1 (futility analysis only) for the HRR-deficient cohort • Introduce a second IA for efficacy for the HRR-deficient cohort • Added an IA for futility in the HRR-deficient population at the final rPFS analysis for all comers • Updated the definition of PFS2

Baseline data

Part 2 cohort 1

Table 13. Baseline characteristics – ITT part 2, cohort 1 (all-comers population)

	TALAZOPARIB + ENZALUTAMIDE (N=402)	PLACEBO + ENZALUTAMIDE (N=403)	Total (N=805)
Age (Years) n (%):			
Age < 65	79 (19.7)	94 (23.3)	173 (21.5)
Age 65 - < 75	188 (46.8)	175 (43.4)	363 (45.1)
Age >= 75	135 (33.6)	134 (33.3)	269 (33.4)
Unspecified	0	0	0
n	402	403	805
Median	71.00	71.00	71.00
Mean	70.92	70.35	70.63
Std Dev	7.99	8.19	8.09
Range(min,max)	(41, 90)	(36, 91)	(36, 91)
Geographical Region n (%)			
North America	59 (14.7)	63 (15.6)	122 (15.2)
European Union/GBR	150 (37.3)	155 (38.5)	305 (37.9)
Asia	124 (30.8)	117 (29.0)	241 (29.9)
Rest of the world	69 (17.2)	68 (16.9)	137 (17.0)
Race n (%)			
White	243 (60.4)	255 (63.3)	498 (61.9)
Black or African American	11 (2.7)	5 (1.2)	16 (2.0)
Asian	127 (31.6)	120 (29.8)	247 (30.7)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	2 (0.5)	1 (0.2)	3 (0.4)
Not Reported	19 (4.7)	21 (5.2)	40 (5.0)
Unknown	0	0	0
Multiracial	0	1 (0.2)	1 (0.1)
Not Collected Due To Local Data Privacy Laws	0	0	0
NA	0	0	0
Ethnicity n (%)			
Hispanic or Latino Or of Spanish Origin	39 (9.7)	46 (11.4)	85 (10.6)
Not Hispanic or Latino Or of Spanish Origin	341 (84.8)	327 (81.1)	668 (83.0)
Unknown	0	0	0
Not Reported	22 (5.5)	30 (7.4)	52 (6.5)
Weight at Baseline (kg)			
n	402	402	804
Median	79.25	81.00	80.00
Mean	82.56	82.51	82.54
Std Dev	18.66	17.50	18.08
Range(min,max)	(45, 169)	(48, 178)	(45, 178)
BMI at Baseline (kg/m^2)			
n	401	396	797
Median	27.00	27.35	27.20
Mean	27.70	27.84	27.77
Std Dev	5.04	5.11	5.08
Range(min,max)	(16, 51)	(16, 59)	(16, 59)

PFIZER CONFIDENTIAL SDTM Creation: 26SEP2022 (18:27) Source Data: adsl Table Generation: 12OCT2022 (18:51)
(Data cutoff date : 16AUG2022 Database snapshot date : 06SEP2022) Output File: ./nda1/C3441021_part02_csr1/ads1_s001
Table 14.1.2.1 Talazoparib is for Pfizer internal use.

	TALAZOPARIB + ENZALUTAMIDE (N=402) n (%)	PLACEBO + ENZALUTAMIDE (N=403) n (%)	Total (N=805) n (%)
Time since initial diagnosis (months) [1]			
n	380	389	769
Mean	50.84	50.79	50.81
Median	31.38	36.83	33.15
Std Dev	47.29	43.57	45.42
Range(min,max)	(3.58, 245.36)	(4.83, 292.17)	(3.58, 292.17)
ECOG Performance Status, n (%)			
0	259 (64.4)	271 (67.2)	530 (65.8)
1	143 (35.6)	132 (32.8)	275 (34.2)
Renal impairment at Baseline (mL/min/1.73 m2), n (%)			
Mild (60-89)	179 (44.5)	171 (42.4)	350 (43.5)
Moderate (30-59)	42 (10.4)	41 (10.2)	83 (10.3)
Normal (>=90)	165 (41.0)	176 (43.7)	341 (42.4)
Histopathological Classification, n (%)			
ADENOCARCINOMA	398 (99.0)	401 (99.5)	799 (99.3)
ADENOCARCINOMA WITH NEUROENDOCRINE FEATURES	4 (1.0)	2 (0.5)	6 (0.7)
ACINATED PROSTATE ADENOCARCINOMA	0	0	0
OTHER	0	0	0
Initial AJCC M Stage, n (%)			
M0	172 (42.8)	185 (45.9)	357 (44.3)
M1	204 (50.7)	193 (47.9)	397 (49.3)
MX	22 (5.5)	22 (5.5)	44 (5.5)
Not Reported	4 (1.0)	3 (0.7)	7 (0.9)
Gleason Score, n (%)			
< 8	117 (29.1)	113 (28.0)	230 (28.6)
>= 8	281 (69.9)	283 (70.2)	564 (70.1)
Not Reported	4 (1.0)	7 (1.7)	11 (1.4)
Baseline Serum PSA (ng/mL)			
n	401	402	803
Mean	82.45	81.24	81.84
Median	18.20	16.16	16.80
Std Dev	214.21	216.82	215.39
Range(min,max)	(0.11, 2796.00)	(0.10, 2285.08)	(0.10, 2796.00)
Bone Metastases at Baseline, n (%)			
No	63 (15.7)	67 (16.6)	130 (16.1)
Yes	339 (84.3)	336 (83.4)	675 (83.9)
Number of bone metastases at screening, n (%)			
0	63 (15.7)	67 (16.6)	130 (16.1)
1	37 (9.2)	40 (9.9)	77 (9.6)
2 to 4	83 (20.6)	93 (23.1)	176 (21.9)
5 to 9	83 (20.6)	75 (18.6)	158 (19.6)
10 to 20	72 (17.9)	67 (16.6)	139 (17.3)
>20	64 (15.9)	61 (15.1)	125 (15.5)
Bone Protecting Agent, n (%) [2]			
No	333 (82.8)	312 (77.4)	645 (80.1)
Yes	69 (17.2)	91 (22.6)	160 (19.9)
Baseline Pain Score By BP-SF, n (%)			
0-1	273 (67.9)	251 (62.3)	524 (65.1)
2-3	127 (31.6)	149 (37.0)	276 (34.3)
> 3	1 (0.2)	2 (0.5)	3 (0.4)
Not Reported	1 (0.2)	1 (0.2)	2 (0.2)

	TALAZOPARIB + ENZALUTAMIDE (N=402) n (%)	PLACEBO + ENZALUTAMIDE (N=403) n (%)	Total (N=805) n (%)
Baseline CTC Count (cells/7.5 ml blood)			
n	324	329	653
Mean	25.32	27.65	26.49
Median	1.00	1.00	1.00
Std Dev	111.39	125.52	118.63
Range(min,max)	(0.00, 1218.00)	(0.00, 1126.00)	(0.00, 1218.00)
Baseline CTC Count (cells/7.5 ml blood), n (%)			
>= 5 CTC per 7.5 mL of blood	108 (26.9)	105 (26.1)	213 (26.5)
< 5 CTC per 7.5 mL of blood	216 (53.7)	224 (55.6)	440 (54.7)
Baseline CTC Count (cells/7.5 ml blood), n (%)			
> 0 CTC per 7.5 mL of blood	176 (43.8)	177 (43.9)	353 (43.9)
0 CTC per 7.5 mL of blood	148 (36.8)	152 (37.7)	300 (37.3)
Androgen deprivation therapy at baseline, n (%)			
Chemical Castration	378 (94.0)	376 (93.3)	754 (93.7)
Bilateral orchiectomy	24 (6.0)	27 (6.7)	51 (6.3)
Type of progression at study entry, n (%)			
PSA progression only	193 (48.0)	206 (51.1)	399 (49.6)
Bone progression only	32 (8.0)	26 (6.5)	58 (7.2)
Soft tissue progression only	13 (3.2)	20 (5.0)	33 (4.1)
PSA+ Bone progression only	85 (21.1)	84 (20.8)	169 (21.0)
PSA+ soft tissue only	44 (10.9)	37 (9.2)	81 (10.1)
Bone + soft tissue only	5 (1.2)	4 (1.0)	9 (1.1)
Bone+soft tissue+PSA	28 (7.0)	24 (6.0)	52 (6.5)
Disease Localization at Screening, n (%) [3][4a]			
Bone only	169 (42.0)	154 (38.2)	323 (40.1)
Soft tissue only	48 (11.9)	57 (14.1)	105 (13.0)
Both bone and soft tissue	180 (44.8)	188 (46.7)	368 (45.7)
None	5 (1.2)	4 (1.0)	9 (1.1)
Distribution of Disease at Screening, n (%) [4b]			
Bone (includes bone with soft tissue component) [4c]	349 (86.8)	342 (84.9)	691 (85.8)
Lymph Node [4d]	147 (36.6)	167 (41.4)	314 (39.0)
Visceral Disease (lung or liver)	54 (13.4)	72 (17.9)	126 (15.7)
Visceral disease (lung) [4e]	45 (11.2)	61 (15.1)	106 (13.2)
Visceral disease (liver)	12 (3.0)	16 (4.0)	28 (3.5)
Other Soft Tissue [4f]	37 (9.2)	33 (8.2)	70 (8.7)
Baseline DDR tissue source, n (%) [can be more than one per pt]			
Tumor tissue historical result	17 (4.2)	15 (3.7)	32 (4.0)
Tumor tissue archived	330 (82.1)	332 (82.4)	662 (82.2)
ctDNA - prospective (blood)	0	1 (0.2)	1 (0.1)
ctDNA (blood)/tumor tissue	57 (14.2)	57 (14.1)	114 (14.2)
Measurable Disease at Baseline, n (%)			
Measurable Disease at Baseline per BICR	120 (29.9)	132 (32.8)	252 (31.3)

[1] Time from initial diagnosis to randomization date.
[2] Bisphosphonates or Denosumab Search Terms is define with ADCM.ATC4 contain (bisphosphonates or bisphosphonates combination) or ADCM.ATC5 contain (denosumab).
[3] There were some patients who didn't have metastatic disease at baseline based on investigator assessment. These patients were not included in the calculation of site of metastases.
[4a] Disease localization is based on the target lesion, nontarget lesion, and bone scan case report forms.
[4b] Patients can be summarized for more than 1 category but are counted only once for each category. All tissue attributed to Prostate/Prostate Gland/Seminal Vesicles (locally advanced disease) was excluded as did not meet the definition of metastasis.
[4c] Bone includes lesions with soft tissue components from PELVIS, RIBS, ILIUM, CLAVICULAR, STERNUM, SACRUM and SPINAL CORD.
[4d] Lymph Node includes adenopathy, adenomegaly. [4e] Lung includes PLEURA, PLEURAL EFFUSION.
[4f] Other soft tissue includes ADRENAL, ABDOMEN, BLADDER, COLON, INTESTINE, KIDNEY, PANCREAS, PENIS, PERICARDIUM, PERITONEUM,RECTUM,RENAL PELVIS,SPLEEN,THYROID and URETER.
PFIZER CONFIDENTIAL SDTM Creation: 26SEP2022 (18:27) Source Data: adsl adcm pf Table Generation: 13OCT2022 (01:58)
(Data cutoff date : 16AUG2022 Database snapshot date : 06SEP2022) Output File: ./nda1/C3441021_part02_csr1/adsl_s006

The treatment arms were comparable regarding median age (71.0 years in both treatment arms), median time since diagnosis (31.83 months in the talazoparib + enzalutamide arm vs. 36.83 months in the placebo + enzalutamide arm, respectively), ECOG performance status (64.4% vs. 67.2% ECOG 0 in the respective treatment arms), renal impairment at baseline (54.9% vs. 52.6% mild-moderate impairment, respectively), baseline PSA (401 vs. 402), and Gleason score at diagnosis (69.9% vs. 70.2% ≥8, respectively).

Prior and concomitant therapy

Table 14. Summary of prior and concomitant anti-cancer therapies including surgery – part 2, cohort 1 (all-comers population)

Number (%) of Subjects	TALAZOPARIB + ENZALUTAMIDE N=402	PLACEBO + ENZALUTAMIDE N=403	Total N=805
With Any Prior Anti-Cancer Treatment[a]	399 (99.3)	400 (99.3)	799 (99.3)
With at Least One Cancer Surgery[a]	326 (81.1)	312 (77.4)	638 (79.3)
With at Least One Non-drug Treatments/Procedures[a]	2 (0.5)	5 (1.2)	7 (0.9)
With At Least One Concomitant Non-drug Treatment/Procedure	139 (34.6)	110 (27.3)	249 (30.9)

a. The denominator to calculate percentages is N, the number of subjects in the ITT/full analysis set within each treatment group.

In the overall population in part 2, cohort 1, 99.3% received any prior anti-cancer therapy before enrolling in the study. The treatment arms were generally well balanced with regards to prior hormone therapy, surgery, radiation therapy, and chemotherapy. Prior to study entry, 86/402 (21.4%) patients in the talazoparib + enzalutamide arm and 93/403 (23.1%) in the placebo + enzalutamide arm had received docetaxel treatment in the metastatic castration sensitive setting (data not shown). Corresponding numbers for abiraterone for mCSPC prior to study entry were n=23 (5.7%) for the talazoparib + enzalutamide arm and n=27 (6.7%) for the placebo + enzalutamide arm (data not shown).

The most common concomitant medication in both treatment arms was analgesics.

HRR gene status

In the overall study population in part 2, cohort 1, 20.7% of the participants harboured an HRR-mutation (germline or somatic) in at least one core gene (21.1% in the talazoparib + enzalutamide arm vs. 20.3% in the placebo + enzalutamide arm). This is in line with reports from scientific literature. The most frequently mutated genes were ATM (5.7% vs. 3.5% in talazoparib + enzalutamide vs. placebo + enzalutamide treated patients, respectively), BRCA2 (5.7% vs. 6.9%), and CDK12 (5.7% vs. 7.2%), which is also in line with previous reports.

- **Numbers analysed**

Part 2, cohort 1 randomised treatment

All 805 patients randomised in part 2, cohort 1 were included in the **ITT population**. According to the study protocol, all efficacy analyses were to be conducted using the ITT population or subset of ITT population as appropriate.

All patients that received at least one dose of study drug (talazoparib, placebo, or enzalutamide) were included in the **safety population**. According to the study protocol, all safety analyses were to be conducted using the safety population, and the safety analyses would use the safety population according to the actual treatment received, not the treatment assigned.

In part 2, cohort 1 PRO measures were evaluated as secondary outcome. The **PRO Evaluable population** consisted of 395/402 (98.3%) of the patients in the talazoparib + enzalutamide arm and 398/403 (98.8%) of the patients in the placebo + enzalutamide arm, respectively.

In part 2, cohort 1, randomised participants were stratified for previous treatment with NHT or taxane-based chemotherapy, and HRR mutation status. In the talazoparib + enzalutamide arm, 85/402 (21.1%) of the participants tested positive for HRR gene mutations, 317/402 (78.9%) tested negative for HRR gene mutations or had unknown mutation status, and 109/402 (27.1%) participants had received prior NHT or taxane treatment. In the placebo + enzalutamide arm, 84/403 (20.8%) of the participants tested positive for HRR gene mutations, 319/403 (79.2%) tested negative for HRR gene mutations or had unknown mutation status, and 110/403 (27.3%) had received prior NHT or taxane-based chemotherapy.

- **Outcomes and estimation**

Part 2, cohort 1 randomised treatment

Primary endpoint, all-comers population

Results of the primary analysis with DCO 16 Aug 2022 are presented in this assessment report. During the procedure, the MAH submitted updated OS data from IA2 with a data cut off of 28 March 2023. The results of part 2, cohort 1 are derived from study participants unselected for HRR gene mutation status, unless other specified.

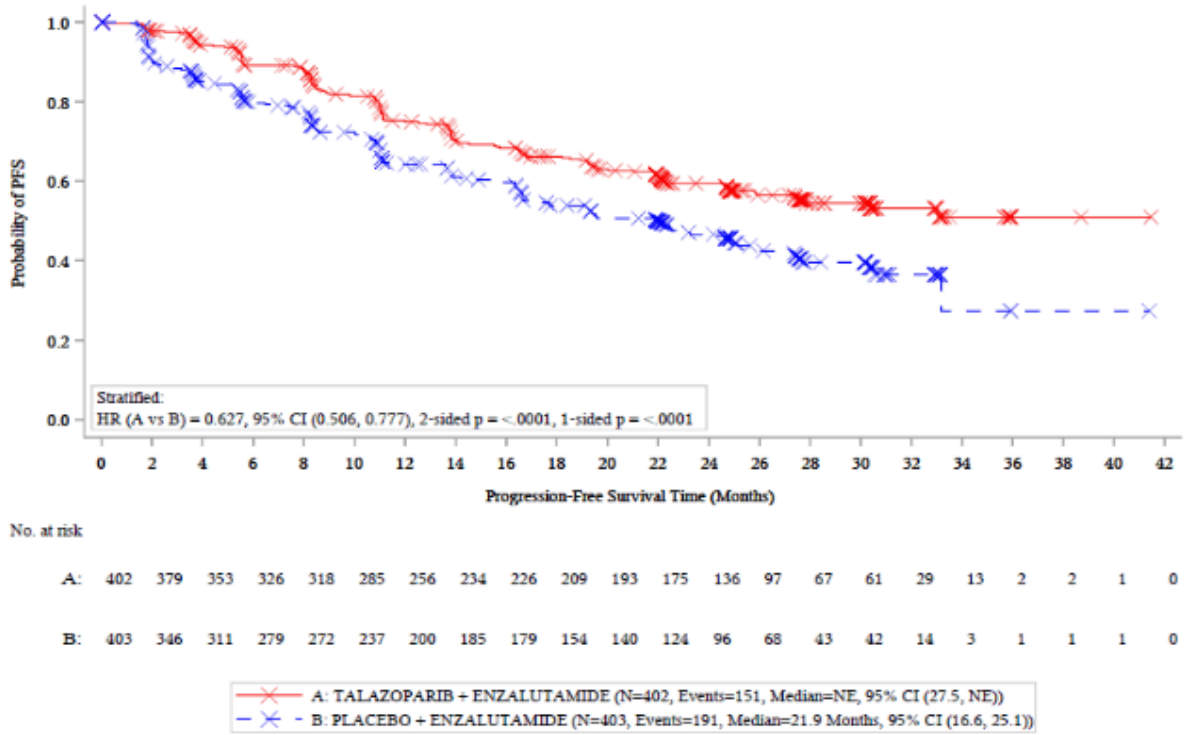
Table 15. BICR-assessed rPFS – ITT part 2, cohort 1 (all-comers population) (DCO 16 Aug 2022)

Table 9. Summary of BICR Assessed rPFS for All-comers - ITT Part 2 All-comers Population Protocol C3441021

	TALAZOPARIB + ENZALUTAMIDE (N=402)	PLACEBO + ENZALUTAMIDE (N=403)
Participants with event, n (%)	151 (37.6)	191 (47.4)
Type of event, n (%)		
Progressive disease	129 (32.1)	171 (42.4)
Death	22 (5.5)	20 (5.0)
Participants censored, n (%)	251 (62.4)	212 (52.6)
Reason for censoring, n (%)		
No adequate baseline assessment	2 (0.5)	2 (0.5)
Start of new anti-cancer therapy	50 (12.4)	57 (14.1)
Event after >= 2 missing or inadequate post-baseline assessments	4 (1.0)	12 (3.0)
Withdrawal of consent	22 (5.5)	21 (5.2)
Lost to follow-up	4 (1.0)	1 (0.2)
No adequate post-baseline tumor assessment	1 (0.2)	1 (0.2)
Ongoing without an event	168 (41.8)	118 (29.3)
Probability of being event-free (95% CI) [1]		
at 6 months	0.892 (0.856, 0.919)	0.796 (0.752, 0.833)
at 12 months	0.749 (0.701, 0.791)	0.643 (0.590, 0.690)
at 24 months	0.594 (0.539, 0.645)	0.466 (0.409, 0.521)
at 36 months	0.510 (0.435, 0.580)	0.274 (0.128, 0.442)
Kaplan-Meier estimates of Time to Event (months)		
Quartiles (95% CI) [2]		
Q1	12.0 (11.0, 13.9)	8.3 (6.5, 10.6)
Median	NE (27.5, NE)	21.9 (16.6, 25.1)
Q3	NE (NE, NE)	NE (33.2, NE)
Stratified analysis [3]		
Comparison vs PLACEBO + ENZALUTAMIDE		
Hazard Ratio [4]	0.627	
95% CI [4]	0.506, 0.777	
1-sided p-value [5]	<.0001	
2-sided p-value [5]	<.0001	

[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] Based on the Brookmeyer-Crowley method.
[3] Stratified by the two randomization stratification factors: 1) previous treatment with any NHT or taxane-based chemotherapy for CSPC (yes vs. no); 2) DDR mutational status (deficient vs. non-deficient/unknown).
[4] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates reduction in hazard rate in favor of TALAZOPARIB + ENZALUTAMIDE compared to PLACEBO + ENZALUTAMIDE;
[5] P-value from a stratified log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 12SEP2022 (08:46) Source Data: adttepb Table Generation: 26SEP2022 (19:37)
(Data cutoff date : 16AUG2022 Database snapshot date : 06SEP2022) Output File: ./nda1/C3441021_part02_csr1/adttepb_pfsp_s001_allcomer
Table 14.2.1.2 Talazoparib is for Pfizer internal use.

Figure 7. Kaplan Meier plot for BICR-assessed rPFS – ITT part 2, cohort 1 (all-comers population) (DCO 16 Aug 2022)



PFIZER CONFIDENTIAL SDTM Creation: 12SEP2022 (08:46) Source Data: adttepb Table Generation: 26SEP2022 (19:37)
(Data cutoff date : 16AUG2022 Database snapshot date : 06SEP2022) Output File: /nda1/C3441021_part02_csr1/adttepb_pfsp_f001_allcomer

Secondary endpoints, all-comers population

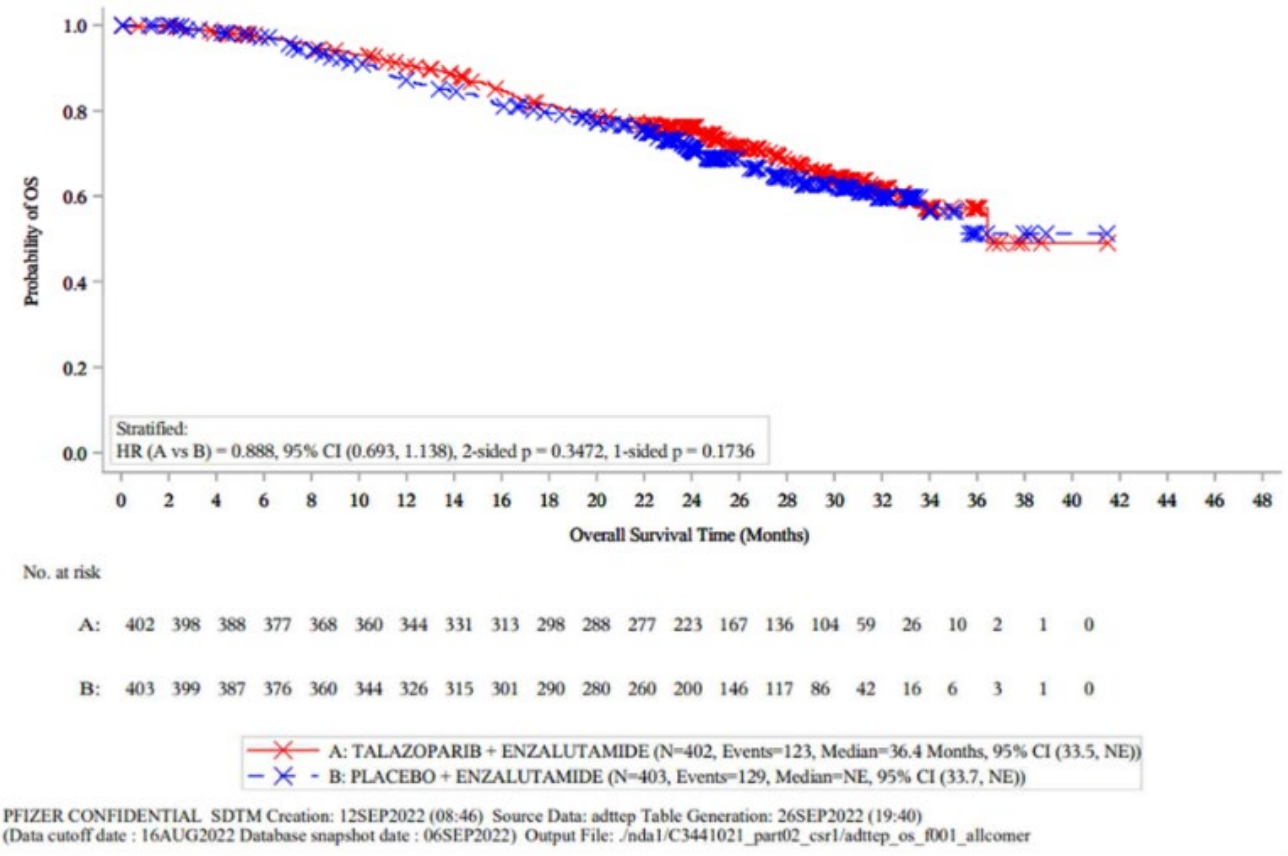
- Overall survival

Table 16. Summary of OS ITT part 2, cohort 1 (all-comers population)

	TALAZOPARIB + ENZALUTAMIDE (N=402)	PLACEBO + ENZALUTAMIDE (N=403)
Participants with event, n (%)	123 (30.6)	129 (32.0)
Type of event, n (%)		
Death	123 (30.6)	129 (32.0)
Death due to COVID-19	1 (0.2)	5 (1.2)
Participants censored, n (%)	279 (69.4)	274 (68.0)
Reason for censoring, n (%)		
Withdrawal of consent	34 (8.5)	46 (11.4)
Lost to follow-up [1]	5 (1.2)	1 (0.2)
Alive	240 (59.7)	227 (56.3)
Probability of being event-free (95% CI) [2]		
at 6 months	0.970 (0.947, 0.983)	0.972 (0.950, 0.984)
at 12 months	0.905 (0.871, 0.930)	0.872 (0.834, 0.902)
at 24 months	0.761 (0.715, 0.801)	0.710 (0.660, 0.754)
at 36 months	0.572 (0.492, 0.644)	0.512 (0.383, 0.628)
at 48 months	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]		
Q1	24.4 (19.0, 27.2)	22.1 (17.9, 24.1)
Median	36.4 (33.5, NE)	NE (33.7, NE)
Q3	NE (NE, NE)	NE (NE, NE)
Stratified analysis [4] Comparison vs PLACEBO + ENZALUTAMIDE		
Hazard Ratio [5]	0.888	
95% CI [5]	0.693, 1.138	
1-sided p-value [6]	0.1736	
2-sided p-value [6]	0.3472	

[1] Includes participants deemed to be lost to follow-up by the Investigator
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] Based on the Brookmeyer and Crowley method.
[4] Stratified by the two randomization stratification factors: 1) previous treatment with any NHT or taxane-based chemotherapy for CSPC (yes vs. no); 2) DDR mutational status (deficient vs. non-deficient/unknown).
[5] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates reduction in hazard rate in favor of TALAZOPARIB + ENZALUTAMIDE compared to PLACEBO + ENZALUTAMIDE;
[6] P-value from a stratified log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 12SEP2022 (08:46) Source Data: adttep Table Generation: 03OCT2022 (19:14)
(Data cutoff date : 16AUG2022 Database snapshot date : 06SEP2022) Output File: ./nda1/C3441021_part02_csr1/adttep_os_s001_allcomer
Table 14.2.1.4 Talazoparib is for Pfizer internal use.

Figure 8. Kaplan Meier plot of OS – ITT part 2, cohort 1 (all-comers population)



The key secondary endpoint OS was immature at interim analysis (IA) 1 (31%). At the second IA, with DCO 28 March 2023 and based on 327 OS-events (approximately 40% maturity), the observed HR was 0.837 (95% CI 0.674, 1.04; 1-sided p-value 0.0537) in favour of talazoparib + enzalutamide treatment arm.

- Objective response rate

Table 17. BICR-assessed ORR – ITT part 2, cohort 1 (all-comers population with measurable disease at baseline)

	TALAZOPARIB + ENZALUTAMIDE (N=120)	PLACEBO + ENZALUTAMIDE (N=132)
Confirmed Objective Response, n (%)		
Complete response (CR)	45 (37.5)	24 (18.2)
Partial response (PR)	29 (24.2)	34 (25.8)
Stable disease (SD)	36 (30.0)	38 (28.8)
Non-CR/Non-PD	0	0
Progressive disease (PD)	7 (5.8)	30 (22.7)
Not evaluable (NE)	3 (2.5)	6 (4.5)
Reason for NE, n (%)		
No post-baseline assessments due to other reasons	0	2 (1.5)
SD too early [< 8 weeks after Randomization date]	3 (2.5)	4 (3.0)
Objective Response (CR+PR), n (%)	74 (61.7)	58 (43.9)
Objective Response Rate (95% CI) [1]	61.7 (52.4, 70.4)	43.9 (35.3, 52.8)
Difference in the rates (95% CI)	17.7 (5.6,29.9)	
1-sided p-value [2]	0.0025	
2-sided p-value [2]	0.0050	

[1] 95% confidence interval based on exact binomial method.
[2] P-value based on CMH (Cochran–Mantel–Haenszel test)
PFIZER CONFIDENTIAL SDTM Creation: 12SEP2022 (07:46) Source Data: adrspb Table Generation: 10NOV2022 (11:08)
(Data cutoff date : 16AUG2022 Database snapshot date : 06SEP2022) Output File: ./nda1/C3441021_part02_csr1/adrspb_boru_s001
Table 14.2.1.5 Talazoparib is for Pfizer internal use.

In the all-comers population, ORR was statistically significant higher for the talazoparib + enzalutamide arm (61.7% [95 % CI 52.4, 70.4]) compared with the placebo + enzalutamide arm (43.9% [95% CI 35.3, 52.8]).

- PFS2

Table 18. INV-assessed PFS2 – ITT part 2, cohort 1 (all-comers population)

	TALAZOPARIB + ENZALUTAMIDE (N=402)	PLACEBO + ENZALUTAMIDE (N=403)
Participants with event, n (%)	126 (31.3)	143 (35.5)
Type of event, n (%)		
Death	112 (27.9)	108 (26.8)
Progression on first new anticancer regimen	14 (3.5)	35 (8.7)
Participants censored, n (%)	276 (68.7)	260 (64.5)
Reason for censoring, n (%)		
No PD by investigator	35 (8.7)	43 (10.7)
Start of new anticancer treatment before PD on follow up cancer treatment	0	6 (1.5)
Lost to follow-up	0	0
Withdrawal of consent	1 (0.2)	8 (2.0)
Ongoing without PFS2 event	240 (59.7)	203 (50.4)
Probability of being event-free (95% CI) [1]		
at 6 months	0.967 (0.944, 0.981)	0.956 (0.930, 0.972)
at 12 months	0.891 (0.855, 0.918)	0.849 (0.809, 0.882)
at 24 months	0.737 (0.688, 0.779)	0.655 (0.601, 0.703)
at 36 months	0.553 (0.474, 0.626)	0.454 (0.318, 0.580)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	21.7 (18.3, 25.6)	18.4 (15.6, 21.3)
Median	36.4 (33.5, NE)	35.3 (28.6, NE)
Q3	NE (NE, NE)	NE (NE, NE)
Stratified analysis [3] Comparison vs PLACEBO + ENZALUTAMIDE		
Hazard Ratio [4]	0.773	
95% CI [4]	0.608, 0.983	
1-sided p-value [5]	0.0178	
2-sided p-value [5]	0.0357	

[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] Based on the Brookmeyer-Crowley method.
[3] Stratified by Previous NHT or Taxane per IWRS and DDR Mutation Status per IWRS
[4] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates reduction in hazard rate in favor of TALAZOPARIB + ENZALUTAMIDE compared to PLACEBO + ENZALUTAMIDE;
[5] P-value from a stratified log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 12SEP2022 (07:46) Source Data: adttep Table Generation: 07NOV2022 (20:33)
(Data cutoff date : 16AUG2022 Database snapshot date : 06SEP2022) Output File: ./nda1/C3441021_part02_csr1/adttep_pfs2_s001_inv_alcomr
Table 14.2.1.14 Talazoparib is for Pfizer internal use.

Table 19. Selected subsequent antineoplastic systemic therapies – Safety part 2, cohort 1 (all-comers population)

	TALAZOPARIB + ENZALUTAMIDE (N=398)	PLACEBO + ENZALUTAMIDE (N=401)	Total (N=799)
Post-baseline antineoplastic therapy use	**n (%)**	**n (%)**	**n (%)**
Patients taking any post-baseline antineoplastic therapy	114 (28.6)	176 (43.9)	290 (36.3)
Patients taking any of the following post-baseline antineoplastic therapies with demonstrated overall survival benefit	102 (25.6)	160 (39.9)	262 (32.8)
Cytotoxic Chemotherapy	90 (22.6)	153 (38.2)	243 (30.4)
DOCETAXEL	66 (16.6)	107 (26.7)	173 (21.7)
CABAZITAXEL	24 (6.0)	46 (11.5)	70 (8.8)
Cellular immunotherapy	1 (0.3)	0	1 (0.1)
SIPULEUCEL-T	1 (0.3)	0	1 (0.1)
Second generation Androgen Receptor Inhibitors	0	3 (0.7)	3 (0.4)
APALUTAMIDE	0	3 (0.7)	3 (0.4)
Androgen Biosynthesis Inhibitors	29 (7.3)	49 (12.2)	78 (9.8)
ABIRATERONE	29 (7.3)	49 (12.2)	78 (9.8)
Single-agent PARP Inhibitor Therapies	3 (0.8)	11 (2.7)	14 (1.8)
OLAPARIB	3 (0.8)	11 (2.7)	14 (1.8)
Radiopharmaceuticals	13 (3.3)	27 (6.7)	40 (5.0)
LUTETIUM (177LU) VIPIVOTIDE TETRAXETAN	1 (0.3)	4 (1.0)	5 (0.6)
LUTETIUM (LU 177)	0	2 (0.5)	2 (0.3)
LUTETIUM-177	1 (0.3)	2 (0.5)	3 (0.4)
RADIUM	0	3 (0.7)	3 (0.4)
RADIUM 223	2 (0.5)	1 (0.2)	3 (0.4)
RADIUM RA 223 DICHLORIDE	9 (2.3)	15 (3.7)	24 (3.0)

Patients taking any of the above post-baseline antineoplastic therapies with demonstrated overall survival benefit were reported in the table.
PFIZER CONFIDENTIAL SDTM Creation: 18OCT2022 (02:43) Source Data: adcm Table Generation: 19OCT2022 (14:36)
(Data cutoff date : 16AUG2022 Database snapshot date : 06SEP2022) Output File: ./nda1/C3441021_part02_csr1/adcm_s007

- Time to PSA progression

The secondary endpoint time to PSA response was in favour of the talazoparib + enzalutamide arm, with a confirmed **PSA response** observed for 396/402 (98.5%) of the patients in the talazoparib + enzalutamide arm, of which 331/402 (83.6%) had a ≥50% PSA decrease. In the placebo + enzalutamide arm, 394/403 (97.8%) had a confirmed PSA response, of which 284/403 (72.1%) had ≥50% decrease. 1-sided p-value for the stratified analysis was <0.0001. The median time to PSA progression was also longer for those who received talazoparib + enzalutamide (26.7 months [95% CI: 21.2, 30.4)] than for those who received placebo + enzalutamide (17.5 months [95% CI 14.1, 20.8]), with a stratified HR of 0.715 (95% CI 0.577, 0.886, 1-sided p-value 0.0010). These results were statistically significant and are considered of clinical relevance.

- Time to initiation of cytotoxic chemotherapy

The median **time to initiation of cytotoxic chemotherapy** was not reached (NR) for neither the patients in the talazoparib + enzalutamide arm (NR [95% CI 37.0, NR]), nor for the patients in the placebo + enzalutamide arm (NR [32.3, NR]). The corresponding HR (talazoparib + enzalutamide vs. placebo + enzalutamide) was 0.494 (95% CI 0.376, 0.649), with 1-sided p-value <0.0001.

***- Time to initiation of* antineoplastic therapy**

The median **time to initiation of antineoplastic therapy** was not reached for patients in the talazoparib + enzalutamide treatment arm (NR [95% CI 37.0, NR] compared with 28.3 months (95% CI 23.5, NE) for patients in the placebo + enzalutamide arm. The corresponding stratified HR was 0.535 (95% CI 0.423, 0.678), with 1-sided p-value <0.0001 in favour of the talazoparib + enzalutamide arm.

- Other secondary endpoints

For the secondary endpoints `time to first skeletal event´, `time to first skeletal event by prior bone protecting agent´, and `time to opiate use for prostate cancer pain´ the results are not considered statistically significant (although the data are immature).

Patient-reported outcomes (PROs) were assessed in participants in part 2 with mCRPC unselected for HRR status and in participants with verified HRR deficiencies. The PROs evaluated were pain symptoms and global health status/quality of life (QoL [function, symptoms including deterioration in urinary symptoms, time to definitive deterioration]). No clinically meaningful differences were observed between the treatment arms for any of the reported PROs. Apart for median time to definitive deterioration, which was 30.8 months (95% CI 27.0, 39.6) for patients who received talazoparib + enzalutamide and 25.0 months (95% CI 22.9, 30.4), with HR=0.789 (95% CI 0.616, 0.987, 2-sided p-value 0.0384), no clinically meaningful differences were observed for the other PROs between the treatment arms.

Ancillary analyses

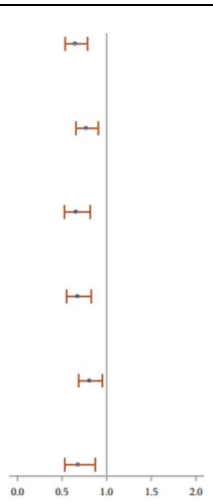
Sensitive Analyses

- **Concordance/discordance analysis between BICR and INV**

Sensitive analyses were conducted for the concordance/discordance between BICR and INV-assessed rPFS results. The overall discrepancy rate between BICR and investigator (INV) assessments of rPFS was 32.3% for the talazoparib + enzalutamide arm and 36.5% for the placebo + enzalutamide arm, i.e., 4.2% higher for the placebo than the talazoparib arm. The highest differences for concordance/discordance between BICR and INV-assessed rPFS were for agreement on no event (10.3% higher in the talazoparib + enzalutamide arm) and for timing and occurrence of event (within 28 days) (6.2% higher in the placebo plus enzalutamide arm) and was most similar for events assessed by investigator and no event by BICR (0.5% difference between treatment arms). The probability of being event-free at 24 months was 69.2% (63.8%, 74.0%) in the talazoparib + enzalutamide arm vs. 55.9% (50.0%, 61.3%) in the placebo enzalutamide arm.

Figure 9. Forest plot for sensitivity analyses of rPFS – ITT part 2, cohort 1 (all-comers population) (DCO 16 Aug 2022)

	TALAZOPARIB+ENZA / PLACEBO+ENZA			
Sensitivity Analysis	N(E)	Median (mo)	Hazard Ratio (95% CI)	1-sided p-value

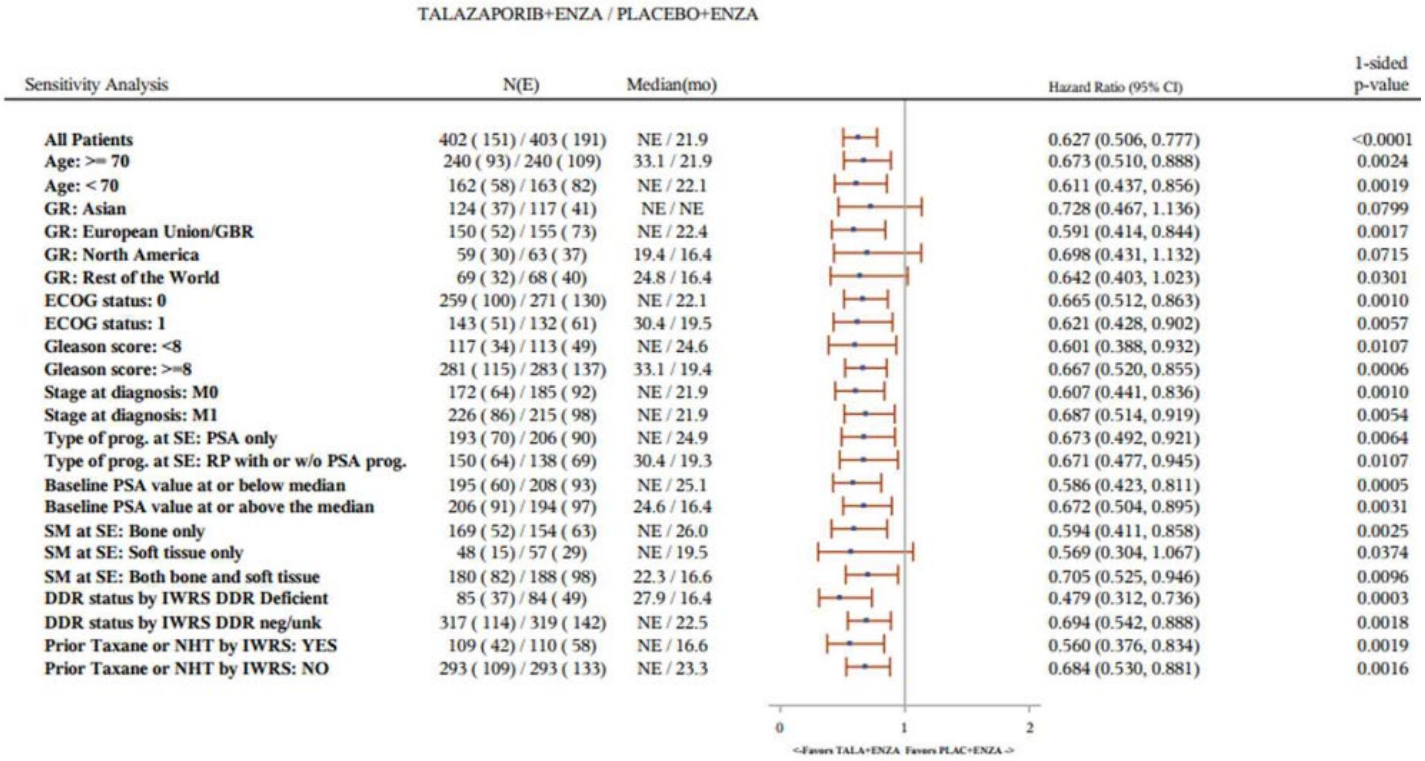
Sen1_BICR	402 (188)/403 (239)	27.5/19.0		0.649 (0.535, 0.786)	<.0001
Sen2_BICR	402 (285)/403 (309)	13.8/11.0		0.771 (0.656, 0.907)	0.0008
Sen3_BICR	402 (149)/403 (182)	NE/24.3		0.656 (0.528, 0.816)	<.0001
Sen1_INV	402 (170)/403 (212)	29.7/22.8		0.676 (0.552, 0.827)	<.0001
Sen2_INV	402 (281)/403 (301)	14.8/11.4		0.808 (0.686, 0.952)	0.0053
Sen3_INV	402 (114)/403 (139)	NE/35.9		0.681 (0.531, 0.873)	0.0011

- **Pre-specified subgroup analyses**

Pre-specified subgroup analyses of rPFS in the all-comers population were conducted for:

- Age (<70 years/≥70 years)
- Geographic region (North America, EU/GBR, Asia, rest of the world [ROW])
- ECOG performance status at baseline (0/1)
- Total Gleason score at diagnosis (<8/≥8)
- Stage at diagnosis (M0/M1)
- Type of progression at study entry (PSA only, radiographic progression with or without PSA progression)
- Baseline PSA (< vs. ≥overall median)
- Site of metastasis at study entry (bone only, soft tissue only, both bone and soft tissue, none)
- HRR status by Interactive Web Response System (IWRS) (HRR-deficient, non-deficient/unknown)
- Prior taxane or NHT by IWRS (yes/no)

Figure 10. Forest plot of BICR-assessed rPFS subgroup analyses – ITT part 2, cohort 1 (all-comers population)



TALA - TALAZOPARIB, ENZA - ENZALUTAMIDE, PLAC - PLACEBO, RP - radiographic progression,
SE - study entry, w/o - without, SM - Site of metastasis, prog - progression,
neg/unk - Non-DDR Deficient/Unknown, GR - Geographic region, N= the number of Participants,
E= rPFS event.
Percentages calculated based on N, the number of Participants in the full analysis set in each treatment group.
Hazard ratio for all patients was based on a Cox model stratified by the randomization stratification factors.For all subgroups, hazard ratio was based on an unstratified Cox model with treatment as the only covariate.
PFIZER CONFIDENTIAL SDTM Creation: 12SEP2022 (08:46) Source Data: adttepb Table Generation: 07OCT2022 (11:55)
(Data cutoff date : 16AUG2022 Database snapshot date : 06SEP2022) Output File: ./nda1/C3441021_part02_csr1/adttepb_forest_bicr

All pre-specified rPFS subgroup analyses in the all-comers population indicated results in favour of talazoparib + enzalutamide, although it is noted that the confidence intervals crossed 1 for all geographic region subgroups except for EU/GBR and for `Site of metastasis at study entry, soft tissue only´.

The pre-planned sensitivity analyses were in line with the primary analysis.

In exploratory subgroup analyses of rPFS in the all-comers population based on **prior docetaxel and abiraterone treatment** for mCSPC (yes/no for the respective treatments), the rPFS results were in favour of talazoparib + enzalutamide treatment and the rPFS benefit was consistent regardless of prior treatment.

Table 20. Summary of BICR-assessed rPFS for all-comers by prior taxane for CSPC (Yes/No) – ITT part 2, cohort 1 (all-comers population)

		TALAZOPARIB + ENZALUTAMIDE (N=86)	PLACEBO + ENZALUTAMIDE (N=93)
Prior Taxane for CSPC			
Yes	Participants with event, n (%)	29 (33.7)	49 (52.7)
	Type of event, n (%)		
	Progressive disease	24 (27.9)	46 (49.5)
	Death	5 (5.8)	3 (3.2)
	Participants censored, n (%)	57 (66.3)	44 (47.3)
	Reason for censoring, n (%)		
	No adequate baseline assessment	0	0
	Start of new anti-cancer therapy	6 (7.0)	12 (12.9)
	Event after >= 2 missing or inadequate post-baseline assessments	1 (1.2)	2 (2.2)
	Withdrawal of consent	2 (2.3)	1 (1.1)
	Lost to follow-up	2 (2.3)	1 (1.1)
	No adequate post-baseline tumor assessment	1 (1.2)	0
	Ongoing without an event	45 (52.3)	28 (30.1)
	Probability of being event-free (95% CI) [1]		
	at 6 months	0.903 (0.816, 0.950)	0.789 (0.689, 0.860)
	at 12 months	0.749 (0.639, 0.831)	0.609 (0.495, 0.705)
	at 24 months	0.625 (0.506, 0.723)	0.409 (0.294, 0.521)
	at 36 months	NE (NE, NE)	NE (NE, NE)
	Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
	Q1	11.1 (8.4, 16.6)	8.2 (4.0, 11.0)
	Median	NE (NE, NE)	19.3 (11.7, 25.0)
	Q3	NE (NE, NE)	NE (25.1, NE)
	Unstratified analysis Comparison vs PLACEBO + ENZALUTAMIDE		
	Hazard Ratio [3]	0.508	
	95% CI [3]	0.321, 0.805	
	1-sided p-value [4]	0.0017	
	2-sided p-value [4]	0.0034	

		TALAZOPARIB + ENZALUTAMIDE (N=313)	PLACEBO + ENZALUTAMIDE (N=307)
Prior Taxane for CSPC			
No	Participants with event, n (%)	121 (38.7)	139 (45.3)
	Type of event, n (%)		
	Progressive disease	105 (33.5)	122 (39.7)
	Death	16 (5.1)	17 (5.5)
	Participants censored, n (%)	192 (61.3)	168 (54.7)
	Reason for censoring, n (%)		
	No adequate baseline assessment	2 (0.6)	2 (0.7)
	Start of new anti-cancer therapy	44 (14.1)	45 (14.7)
	Event after >= 2 missing or inadequate post-baseline assessments	3 (1.0)	10 (3.3)
	Withdrawal of consent	20 (6.4)	20 (6.5)
	Lost to follow-up	2 (0.6)	0
	No adequate post-baseline tumor assessment	0	1 (0.3)
	Ongoing without an event	121 (38.7)	90 (29.3)
	Probability of being event-free (95% CI) [1]		
	at 6 months	0.887 (0.845, 0.919)	0.796 (0.745, 0.839)
	at 12 months	0.750 (0.695, 0.797)	0.649 (0.589, 0.703)
	at 24 months	0.584 (0.521, 0.642)	0.488 (0.422, 0.550)
	at 36 months	0.480 (0.395, 0.561)	0.271 (0.086, 0.498)
	Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
	Q1	12.5 (11.0, 14.0)	8.3 (5.7, 10.8)
	Median	33.1 (24.8, NE)	22.8 (16.6, 27.7)
	Q3	NE (NE, NE)	NE (33.2, NE)
	Unstratified analysis Comparison vs PLACEBO + ENZALUTAMIDE		
	Hazard Ratio [3]	0.703	
	95% CI [3]	0.551, 0.897	
	1-sided p-value [4]	0.0022	
	2-sided p-value [4]	0.0045	

[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] Based on the Brookmeyer-Crowley method.
[3] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of TALAZOPARIB + ENZALUTAMIDE compared to PLACEBO + ENZALUTAMIDE.
[4] p-value from the log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 12SEP2022 (08:46) Source Data: adttepb Table Generation: 06OCT2022 (14:54)
(Data cutoff date : 16AUG2022 Database snapshot date : 16AUG2022) Output File: ./nda1/C3441021_part02_sce1/adttepb_pfsp5_s001_allcomer

Table 21. Summary of BICR-assessed rPFS for all-comers by prior NHT for CSPC (Yes/No) – ITT part 2, cohort 1 (all-comers population)

		TALAZOPARIB + ENZALUTAMIDE (N=23)	PLACEBO + ENZALUTAMIDE (N=27)
Prior NHT for CSPC			
Yes	Participants with event, n (%)	15 (65.2)	16 (59.3)
	Type of event, n (%)		
	Progressive disease	11 (47.8)	16 (59.3)
	Death	4 (17.4)	0
	Participants censored, n (%)	8 (34.8)	11 (40.7)
	Reason for censoring, n (%)		
	No adequate baseline assessment	0	0
	Start of new anti-cancer therapy	4 (17.4)	4 (14.8)
	Event after >= 2 missing or inadequate post-baseline assessments	1 (4.3)	1 (3.7)
	Withdrawal of consent	1 (4.3)	4 (14.8)
	Lost to follow-up	0	0
	No adequate post-baseline tumor assessment	0	0
	Ongoing without an event	2 (8.7)	2 (7.4)
	Probability of being event-free (95% CI) [1]		
	at 6 months	0.714 (0.469, 0.861)	0.315 (0.131, 0.519)
	at 12 months	0.440 (0.217, 0.642)	0.252 (0.087, 0.459)
	at 24 months	0.188 (0.048, 0.399)	0.252 (0.087, 0.459)
	at 36 months	NE (NE, NE)	NE (NE, NE)
	Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
	Q1	5.6 (0.2, 10.8)	1.8 (1.4, 1.9)
	Median	11.0 (5.6, 16.4)	1.9 (1.8, 11.0)
	Q3	16.8 (11.0, NE)	NE (3.6, NE)
	Unstratified analysis Comparison vs PLACEBO + ENZALUTAMIDE		
	Hazard Ratio [3]	0.566	
	95% CI [3]	0.277, 1.157	
	1-sided p-value [4]	0.0581	
	2-sided p-value [4]	0.1162	

		TALAZOPARIB + ENZALUTAMIDE (N=376)	PLACEBO + ENZALUTAMIDE (N=373)
Prior NHT for CSPC			
No	Participants with event, n (%)	135 (35.9)	172 (46.1)
	Type of event, n (%)		
	Progressive disease	118 (31.4)	152 (40.8)
	Death	17 (4.5)	20 (5.4)
	Participants censored, n (%)	241 (64.1)	201 (53.9)
	Reason for censoring, n (%)		
	No adequate baseline assessment	2 (0.5)	2 (0.5)
	Start of new anti-cancer therapy	46 (12.2)	53 (14.2)
	Event after >= 2 missing or inadequate post-baseline assessments	3 (0.8)	11 (2.9)
	Withdrawal of consent	21 (5.6)	17 (4.6)
	Lost to follow-up	4 (1.1)	1 (0.3)
	No adequate post-baseline tumor assessment	1 (0.3)	1 (0.3)
	Ongoing without an event	164 (43.6)	116 (31.1)
	Probability of being event-free (95% CI) [1]		
	at 6 months	0.901 (0.865, 0.928)	0.824 (0.780, 0.860)
	at 12 months	0.768 (0.719, 0.809)	0.663 (0.609, 0.712)
	at 24 months	0.616 (0.559, 0.667)	0.482 (0.423, 0.539)
	at 36 months	0.525 (0.446, 0.598)	0.285 (0.133, 0.459)
	Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
	Q1	13.7 (11.0, 16.5)	8.5 (8.2, 11.0)
	Median	NE (30.4, NE)	22.5 (17.7, 26.1)
	Q3	NE (NE, NE)	NE (33.2, NE)
	Unstratified analysis Comparison vs PLACEBO + ENZALUTAMIDE		
	Hazard Ratio [3]	0.641	
	95% CI [3]	0.512, 0.804	
	1-sided p-value [4]	<.0001	
	2-sided p-value [4]	0.0001	

[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] Based on the Brookmeyer-Crowley method.
[3] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of TALAZOPARIB + ENZALUTAMIDE compared to PLACEBO + ENZALUTAMIDE;
[4] p-value from the log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 12SEP2022 (08:46) Source Data: adttepb Table Generation: 06OCT2022 (14:54)
(Data cutoff date : 16AUG2022 Database snapshot date : 16AUG2022) Output File: ./nda1/C3441021_part02_sce1/adttepb_pfsp4_s001_allcomer

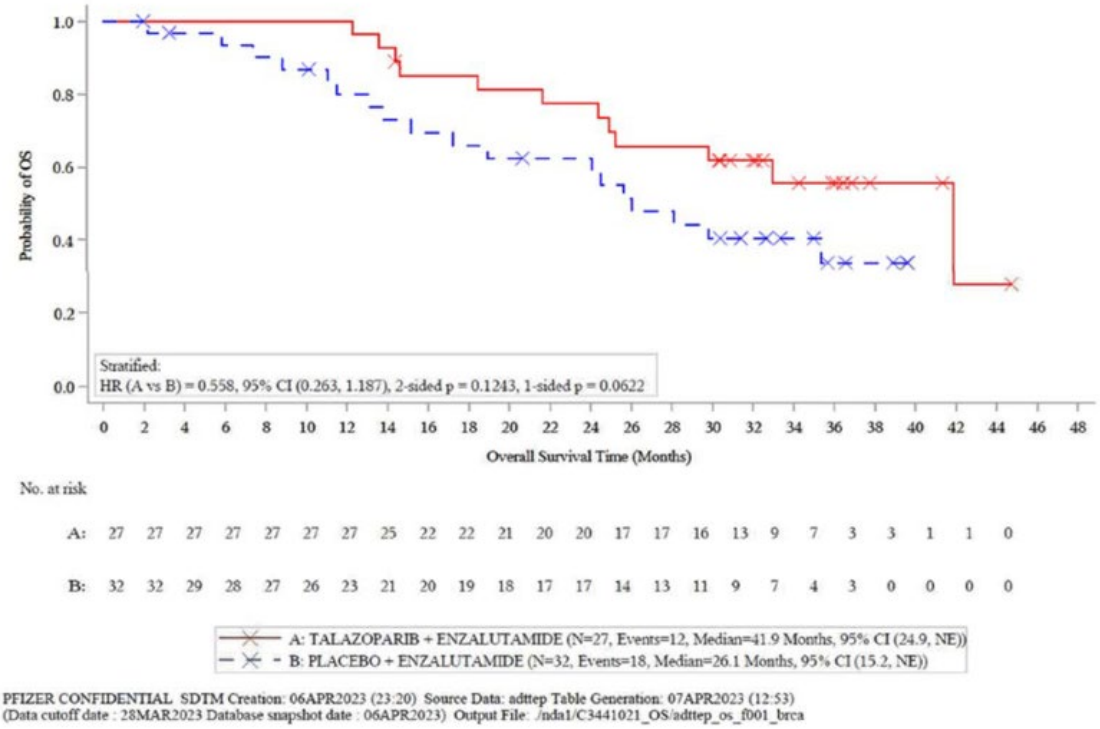
- **Subgroup analyses of OS**

Efficacy in BRCA/HRR subgroups

HRR mutation status – part 2, cohort 1 (all-comers population)

In the BRCA1/2-mutated subgroup, updated OS data from IA2 revealed a stratified OS HR=0.558 (95% CI 0.263, 1.187; 1-sided p-value 0.0622).

Figure 11. Kaplan Meier plot of OS, IA2 – BRCA-mutant participants by prospective tumour tissue and blood in ITT part 2, cohort 1 (all-comers population)



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(Data cutoff date : 28MAR2023 Database snapshot date : 06APR2023) Output File: /nda1/C3441021_OS/adttep_os_f001_brca

Table 22. Summary of primary and secondary efficacy results based on prospective testing for HRR status subgroups – part 2, cohort 1 (all-comers population). OS data from IA2.

	HRR-deficient by Prospective Tumor Tissue and Blood[a]		Non-HRR-deficient by Prospective Tumor Tissue and Blood		HRR Unknown by Prospective Tumor Tissue and Blood	
Endpoint	TALA + ENZA N = 85	PLAC + ENZA N = 82	TALA + ENZA N = 207	PLAC + ENZA N = 219	TALA + ENZA N = 110	PLAC + ENZA N = 102
rPFS by BICR						
Events	37	49	73	95	41	47
Median time to event (95% CI),[b] months	27.9 (16.8, NE)	13.8 (10.9, 19.5)	NE (25.8, NE)	22.4 (16.6, NE)	NE (24.6, NE)	27.3 (16.4, NE)
HR (95% CI)[c,d]	0.424 (0.275, 0.653)		0.695 (0.511, 0.944)		0.753 (0.493, 1.150)	
1-sided p-value[e]	<0.0001		0.0097		0.0942	
Overall Survival						
Events, n	30	41	82	96	44	37
Median time to event (95% CI), months	41.9 (36.4, NE)	30.8 (25.6, 38.8)	NE (33, NE)	38 (33.9, NE)	NE (31.6, NE)	45.3 (34.4, NE)
HR (95% CI)[d]	0.516 (0.320, 0.831)		0.880 (0.654, 1.182)		1.167, 95% CI (0.748, 1.820)	
1-sided p-value[e]	0.0028		0.1969		0.7518	
ORR						
With measurable disease at baseline, N	33	25	62	74	25	33
CR, n (%)	19 (57.6)	5 (20.0)	19 (30.6)	12 (16.2)	7 (28.0)	7 (21.2)
Objective response (CR+PR), n (%)	26 (78.8)	12 (48.0)	33 (53.2)	30 (40.5)	15 (60.0)	16 (48.5)
ORR (95% CI)[f]	78.8 (61.1, 91.0)	48.0 (27.8, 68.7)	53.2 (40.1, 66.0)	40.5 (29.3, 52.6)	60.0 (38.7, 78.9)	48.5 (30.8, 66.5)
Difference (95% CI)	30.8 (6.7, 54.8)		12.7 (-4.0, 29.4)		11.5 (-14.2, 37.2)	
1-sided p-value[g]	0.0077		0.0705		0.1940	
DOR						
Participants with Confirmed CR or PR, N	26	12	33	30	15	16
Events, n (%)	14 (53.8)	7 (58.3)	15 (45.5)	11 (36.7)	6 (40.0)	10 (62.5)
Probability of being event-free at 2 years % (95% CI)	0.355 (0.160, 0.557)	0.164 (0.008, 0.506)	0.454 (0.238, 0.647)	0.559 (0.340, 0.731)	0.538 (0.248, 0.760)	0.350 (0.127, 0.586)
Median time to event (95% CI), months	18.2 (8.0, NE)	9.2 (6.3, NE)	22.2 (16.1, NE)	NE (12.0, NE)	NE (11.9, NE)	19.8 (9.0, NE)
PSA response						
Participants with baseline PSA, n (%)	84 (98.8)	82 (100.0)	207 (100.0)	218 (99.5)	110 (100.0)	102 (100.0)
Evaluable, N[h]	84	81	205	213	107	100
Responder, n (%)	77 (91.7)	49 (60.5)	169 (82.4)	150 (70.4)	85 (79.4)	85 (85.0)
Response rate (95% CI)	91.7 (83.6, 96.6)	60.5 (49.0, 71.2)	82.4 (76.5, 87.4)	70.4 (63.8, 76.5)	79.4 (70.5, 86.6)	85.0 (76.5, 91.4)
Diff in rates (95% CI)	31.2 (19.0, 43.3)		12.0 (4.0, 20.1)		-5.6 (-15.9, 4.8)	
1-sided p-value[e]	<0.0001		0.0014		0.8793	
Time to PSA progression						
Number of events, n (%)	39 (45.9)	41 (50.0)	86 (41.5)	87 (39.7)	39 (35.5)	49 (48.0)
Median time to event (95% CI), months	26.7 (15.7, NE)	11.1 (9.2, 19.3)	24.9 (19.3, 34.1)	17.6 (14.1, 23.1)	28.8 (21.1, NE)	19.4 (15.6, 26.3)
HR (95% CI)[d]	0.524 (0.337, 0.815)		0.826 (0.611, 1.117)		0.672 (0.440, 1.028)	
1-sided p-value[e]	0.0018		0.1066		0.0325	
Time to Initiation of Cytotoxic Chemotherapy						
Number of events, n (%)	25 (29.4)	24 (29.3)	37 (17.9)	80 (36.5)	21 (19.1)	35 (34.3)
Median time to event (95% CI), months	NE (30.5, NE)	NE (28.7, NE)	NE (37.0, NE)	NE (28.3, NE)	NE (NE, NE)	32.3 (29.4, NE)
HR (95% CI)[d]	0.693 (0.394, 1.219)		0.405 (0.274, 0.599)		0.575 (0.333, 0.994)	
1-sided p-value[g]	0.1004		<0.0001		0.0223	
Time to Initiation of Antineoplastic Therapy						
Number of events, n (%)	28 (32.9)	35 (42.7)	54 (26.1)	98 (44.7)	32 (29.1)	43 (42.2)
Median time to event (95% CI), months	NE (30.5, NE)	25.7 (15.0, NE)	37.0 (37.0, NE)	25.6 (20.0, NE)	NE (31.1, NE)	30.4 (23.5, NE)
HR (95% CI)[d]	0.515 (0.312, 0.849)		0.492 (0.352, 0.688)		0.663 (0.418, 1.054)	
1-sided p-value[e]	0.0041		<0.0001		0.0400	
Time to First Symptomatic Skeletal Event						
Number of events, n (%)	20 (23.5)	19 (23.2)	48 (23.2)	54 (24.7)	23 (20.9)	20 (19.6)
Median time to event (95% CI), months	NE (33.9, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
HR (95% CI)[d]	0.721 (0.383, 1.355)		0.892 (0.604, 1.318)		1.081 (0.590, 1.980)	
1-sided p-value[e]	0.1536		0.2825		0.6000	
PFS2 Based on Investigator Assessment						
Events, n (%)	20 (23.5)	34 (41.5)	65 (31.4)	82 (37.4)	41 (7.3)	27 (26.5)
Probability of being event-free at 2 years % (95% CI)	0.808 (0.696, 0.882)	0.621 (0.496, 0.723)	0.723 (0.652, 0.781)	0.623 (0.547, 0.690)	0.709 (0.611, 0.787)	0.746 (0.642, 0.824)
Median time to event (95% CI), months	36.4 (36.4, NE)	28.1 (22.8, NE)	NE (33.0, NE)	31.8 (26.3, NE)	31.6 (29.2, NE)	NE (NE, NE)
HR (95% CI)	0.415 (0.236, 0.728)		0.751 (0.541, 1.041)		1.333 (0.817, 2.175)	
1-sided p-value	0.0008		0.0425		0.8756	

a. There were 2 fewer HRR-deficient patients captured in the HRR-deficient subgroup by prospective tissue and blood (n=167) compared with the subgroup by IWRS HRR categories (n=169, as shown in Module 2.5 CO Table 5): 1) 4 participants classified as HRR-deficient per IWRS were classified as either non-HRR deficient or Unknown per prospective tissue and blood testing, and 2) 2 participants classified as Non-HRR deficient/Unknown per IWRS were classified as HRR-deficient per prospective testing (Source: Listing 16.2.1.4).

b. Based on the Brookmeyer-Crowley method

c. Stratified by the two randomization stratification factors: 1) previous treatment with any NHT or taxane-based chemotherapy for CSPC (yes vs. no); 2) DDR mutational status (deficient vs.non-deficient/unknown)

d. Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates reduction in hazard rate in favor of TALAZOPARIB + ENZALUTAMIDE compared to PLACEBO + ENZALUTAMIDE.

e. P-value from a stratified log-rank test.

f. 95% confidence interval based on exact binomial method.

g. P-value based on CMH (Cochran–Mantel–Haenszel test).

h. The number of patients with a baseline PSA value and at least one post-baseline PSA value.

It is noted that the updated OS data from IA2, although still immature, now reach statistical significance in the HRR-deficient subgroup indicating both a clinically relevant and statistically significant prolongation of OS for HRR-deficient patients treated with talazoparib + enzalutamide.

Exploratory analyses of HRR mutation status were performed using data from prospective + retrospective plasma, prospective + retrospective plasma + saliva, tumour tissue only, and prospective and retrospective ctDNA. Overall, high concordance was observed between results on HRR-deficiency status based on prospective blood samples and tumour tissue samples as well as between prospective and retrospective ctDNA.

Supportive data part 2, cohort 2 (HRR-deficient)

HRR-mutation status by IWRS – part 2, cohort 2 (HRR-deficient), supportive data from top line report

Survival results in cohort 2 (HRR-deficient) were based on a pre-planned efficacy IA performed on DCO 03 October 2022. In the talazoparib + enzalutamide arm, 95/198 (48.0%) were still on talazoparib and 99/198 (50.0%) were still on enzalutamide. In the placebo + enzalutamide arm, 60 /199 (30.2%) were still on placebo and enzalutamide, respectively. The main reason for treatment discontinuation in both treatment arms was progressive disease, although disease progression was reported more frequently for placebo + enzalutamide (30.2% for both substances, respectively) than talazoparib + enzalutamide (19.7% and 20.2%, respectively). No follow-up time and no detailed statistical data are reported yet.

Figure 12. Kaplan Meier Plot of BICR-assessed rPFS – part 2, cohort 2 (HRR-deficient) (DCO 03 Oct 2022)

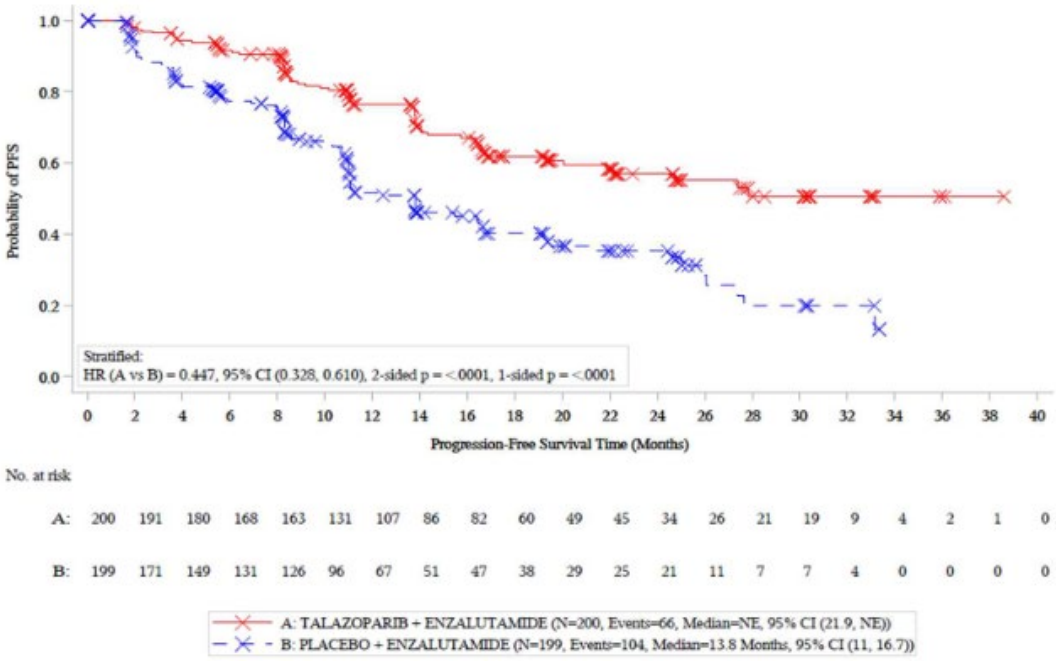
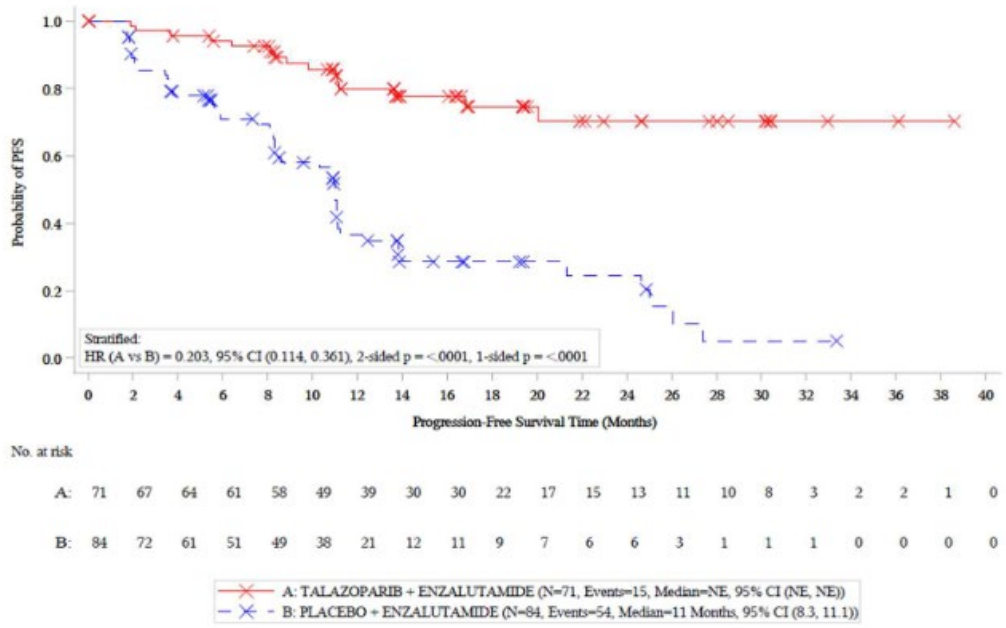


Figure 13. Kaplan Meier Plot of BICR-assessed rPFS – part 2, cohort 2 (BRCA-mutated) (DCO 03 Oct 2022)



OS data were immature at the prespecified IA (24% maturity) but were still in line with the effect in favour of talazoparib + enzalutamide seen in the HRR-deficient population. For HRR-deficient subjects, the observed stratified hazard ratio (talazoparib + enzalutamide vs. placebo + enzalutamide) was 0.687 (95% CI: [0.458, 1.031]; one-sided *p*-value: 0.0338) in favour of talazoparib + enzalutamide. Median OS was NE (95% CI: [36.4, NE]) for the talazoparib + enzalutamide group and 33.7 months (95% CI: [27.6, NE]) for the placebo + enzalutamide group. A similar trend was seen for the BRCA-mutated subset of patients.

Summary of main efficacy results

The following table summarises the efficacy results from the main study 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 23. Summary of Efficacy for study 1021 part 2, cohort 1

Title: TALAPRO-2, a phase III, randomised, double-blind study of talazoparib plus enzalutamide versus placebo plus enzalutamide in metastatic castration-resistant prostate cancer (mCRPC)	
Study identifier	C3441021 EudraCT number 2017-003295-31 ClinicalTrials.gov identifier NCT03395197

Design	**Part 2, cohort 1**; randomised, double-blind, multi-centre, phase III study. Patients were unselected for HRR gene mutations (all-comers population). Patients were stratified for HRR gene mutation status (HRR-deficient vs. non-HRR-deficient or unknown HRR status), previous NHT or previous taxane-based chemotherapy. **Part 2, cohort 2**; randomised, double-blind, multi-centre, phase III study. Patients were selected for HRR gene deficiency. Cohort 2 also includes patients with confirmed HRR gene deficiency from cohort 1. This part of the study is still ongoing. *There are only preliminary efficacy results from part 2.*	
	Duration of main phase:	Part 2, cohort 1 08 Aug 2017 – 16 Aug 2022 Talazoparib/placebo + enzalutamide administered orally QD. Treatment continued until progression, intolerable toxicity, or loss of clinical benefit as determined by the Investigator.
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority of talazporaib + enzalutamide over placebo + enzalutamide Statistical hypothesis: H_{01}: $HR_{rPFS} \geq 1$ vs. H_{11}: $HR_{rPFS} < 1$ H_{02}: $HR_{rPFS+} \geq 1$ vs. H_{12}: $HR_{rPFS+} < 1$ Comparison of BICR-assessed rPFS between the two treatment arms in the all-comers population and HRR-deficient subpopulation (rPFS+), respectively. H_{01} and H_{02} refer to talazoparib + enzalutamide, and H_{11} and H_{12} refer to placebo+ enzalutamide treatment.	
Treatments groups	Part 2, cohort 1 talazoparib + enzalutamide arm	Talazoparib was administered orally once daily in a fixed dose. Enzalutamide was administered orally once daily in a fixed dose together with talazoparib. Talazoparib + enzalutamide treatment was continued until progression, intolerable toxicity, or loss of clinical benefit as determined by the Investigator. N=402 patients were randomised to receive talazoparib + enzalutamide.

	Part 2, cohort 1 placebo + enzalutamide arm		Placebo was administered orally once daily in the same number of capsules as talazoparib. Enzalutamide was administered orally once daily in a fixed dose together with placebo. Placebo + enzalutamide treatment was continued until progression, intolerable toxicity, or loss of clinical benefit as determined by the Investigator. N=403 patients were randomised to receive talazoparib + enzalutamide.
Endpoints and definitions	Primary endpoint: radiographic progression-free survival	rPFS	The time from the date of randomisation to first objective evidence of radiographic progression as assessed in soft tissue per RECIST 1.1 or in bone (upon subsequent confirmation) per PCWG3 guidelines, or death due to any cause, whichever occurs first.
	Key secondary endpoint: overall survival	OS	The time from randomisation to the date of death due to any cause.
	Secondary endpoint, other: overall response rate	ORR	The proportion of patients with measurable soft tissue disease at baseline with a best overall confirmed soft tissue response of CR or PR according to RECIST 1.1.
	Secondary endpoint, other: duration of soft tissue response	DoR	The time from the date of the first soft tissue response to the first documented objective evidence of progression (in soft tissue per RECIST 1.1 or in bone per PCWG3 guidelines) or start of new antineoplastic therapy.
	Secondary endpoint, other: PSA response	PSA response $\geq$50%	A decline from baseline PSA (ng/mL) by at least 50%.
	Secondary endpoint, other: time to PSA progression		The time from the date of randomisation to the date of the first PSA value demonstrating progression, which is subsequently confirmed.
	Subgroup analysis: survival by HRR-mutation status		rPFs, OS, ORR, and DoR in HRR-deficient vs. non-HRR-deficient/unknown subpopulation.
Database lock	Data cut-off 16 Aug 2022		
Results and Analysis			

Analysis description	**Primary Analysis**			
Analysis population and time point description	The primary population for efficacy analyses was the intention-to-treat (ITT) population, comprising all patients to whom study treatment had been assigned by randomisation regardless of whether treatment was administered or not. The primary analysis was conducted when approximately 333 rPFS events were observed in the all-comers population.			
Descriptive statistics and estimate variability	Treatment group	Talazoparib + enzalutamide arm	Placebo + enzalutamide arm	Effect estimates per comparison
	Number of subjects	402	403	
	Median rPFS (months) (95% CI)	NE (27.5, NE)	21.9 (16.6, 25.1)	HR 0.627 (95% CI 0.506, 0.777) 1-sided p-value <0.0001
	Median OS (months)* (95% CI)	NE (37.3, NE)	38.2 (34.1, 43.1)	HR 0.837 (95% CI 0.674, 1.040) 1-sided p-value 0.0537
	ORR**, % (n) (95% CI)	61.7 (74) (52.4, 70.4)	43.9 (58) (35.3, 52.8)	 1-sided p-value 0.0025
	Median DoR (months)[#] (95% CI)	NE (18.8, NE)	23.5 (14.3, NE)	
	PSA response ≥50%, % (n) (95% CI)	83.6 (331) (79.6, 87.1)	72.1 (284) (67.4, 76.5)	 1-sided p-value <0.0001
	Median time to PSA progression (months) (95% CI)	26.7 (21.2, 30.4)	17.5 (14.1, 20.8)	HR 0.715 (95% CI 0.577,0.886) 1-sided p-value 0.0010
Notes	*OS data from IA2, DCO 28 March 2023 (approximately 40% maturity) **Total number of participants evaluated in BICR-assessed ORR analysis n=252 (talazoparib + enzalutamide arm n=120, placebo + enzalutamide arm n=132) [#]Total number of participants evaluated in BICR-assessed DoR analysis n=132 (talazoparib + enzalutamide arm n=74, placebo + enzalutamide arm n=58)			

Analysis description	**Survival analysis per HRR gene mutation status**			
	Treatment group **HRR-deficient**	Talazoparib + enzalutamide arm	Placebo + enzalutamide arm	Effect estimates per comparison
	Number of subjects	85	82	
	Median rPFS (months) (95% CI)	27.9 (16.6, NE)	13.8 (10.9, 19.5)	HR 0.424 (95% CI 0.275, 0.653) 1-sided p-value 0.0001
	Median OS (months)* (95% CI)	41.9 (36.4, NE)	30.8 (25.6, 38.8)	HR 0.516 (95% CI 0.320, 0.831) 1-sided p-value 0.0028
	Median ORR, % (n) (95% CI)	78.8 (26) (61.1, 91.0)	46.2 (12) (26.6, 66.6)	1-sided p-value 0.0050
	Median DoR (months) (95% CI)	18.4 (10.1, NE)	14.8 (6.3, 25.8)	
Analysis description	**Survival analysis per HRR gene mutation status**			
	Treatment group **HRR-proficient**	Talazoparib + enzalutamide arm	Placebo + enzalutamide arm	Effect estimates per comparison
	Number of subjects	207	219	
	Median rPFS (months) (95% CI)	NE (25.8, NE)	22.4 (16.6, NE)	HR 0.695 (95% CI 0.511, 0.944) 1-sided p-value 0.0097
	Median OS (months)* (95% CI)	NE (33.0, NE)	38.0 (33.9, NE)	HR 0.880 (95% CI 0.654, 1.182) 1-sided p-value 0.1969
	Median ORR, % (n) (95% CI)	53.2 (33) (40.1, 66.0)	40.5 (30) (29.3, 52.6)	1-sided p-value 0.0705
	Median DoR (months) (95% CI)	22.2 (16.1, NE)	NE (12.0, NE)	
Notes	*OS data from IA2, DCO 28 March 2023			

2.5.5.3. Clinical studies in special populations

No specific studies have been submitted.

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Approximately 20% of patients with prostate cancer harbour mutations in HRR genes, of which a majority are somatic (non-inheritable). The Applicant has used the Foundation One CDx and FoundationOne Liquid to identify HRR gene alterations. Both tests are NGS-based in vitro diagnostic devices comprising >300 genes. Participants were considered HRR-deficient if the participant had at least one mutation in one or more of the 12 specified genes (see below) or if there was a discordant result between the tissue and liquid results. If prospective results from blood and tumour tissue samples were both available, a positive result from either was considered prospectively HRR-deficient.

According to the Applicant, the overall non-HRR alteration landscape in study 1021 was consistent with expectations based on the literature for advanced prostate cancer (Chung *et al*, 2019).

Table 24. DDR genes analysed in study 1021

Gene	Variant Class	Biomarker rules
ATM ATR BRCA1 BRCA2 CDK12 CHEK2 FANCA MLH1 MRE11A NBN PALB2 RAD51C	short variants	Any inactivating missense, nonsense, frameshift, or splice site event. • For BRCA2, truncating mutations must occur upstream of bases encoding amino acid 3326.
	copy number	Homozygous copy number loss. • Liquid samples include homozygous losses for BRCA1 or BRCA2 only.
	rearrangements	Any inactivating rearrangement

`DDR genes´ used synonymously with `HRR genes´

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

Not applicable

2.5.5.6. Supportive study(ies)

The Applicant submitted the phase II, open-label, multi-centre, soft tissue response study C3441006, TALAPRO-1, (`study 1006´) with supportive efficacy data for talazoparib treatment. Talazoparib 1 mg was administered orally QD to patients with mCRPC and verified HRR gene mutations. The study participants had progressed on NHT (enzalutamide and/or abiraterone) for mCRPC and had received prior taxane-based chemotherapy for metastatic disease.

The study started on 04 July 2017, with primary DCO on 04 Sept 2020 and was completed on 04 January 2021. In total, n=128 patients were enrolled, n=127 received study intervention and were included in the safety population, and n=104 patients had measurable disease and verified HRR gene mutations and were included in the efficacy analysis.

Study 1006 met its primary endpoint with a BICR-assessed ORR of 29.8% (95% CI 21.2, 39.6) for all patients. The ORR was higher for patients harbouring BRCA1/2 mutations than other HRR gene mutations. Data not shown.

Due to the single arm study design and HRR-deficient only patient population, the results from the study 1006 are considered exploratory. The results, however, are in line with the results of study 1021 and support the overall efficacy conclusion for part 2, cohort 1 in study 1021.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

With this application, the Applicant seeks approval for a new indication of oral combination treatment with talazoparib 0.5 mg once daily (QD) + enzalutamide 160 mg QD and an extension with a new strength of 0.1 mg hard capsules. The approved indication is:

> *Talzenna is indicated in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), in whom chemotherapy is not clinically indicated.*

Data to support the application are derived from the multi-centre phase III study C3441021 (TALAPRO-2), conducted in 270 centres across 26 countries. The study comprises two parts.

Part 1 was an open-label dose-finding part with talazoparib monotherapy aiming at identifying the appropriate starting dose of talazoparib for part 2. Patients were unselected for HRR gene mutations, and HRR gene analysis was optional in this study part.

Part 2 was a placebo-controlled, double-blind, randomised study evaluating the efficacy and safety of talazoparib + enzalutamide in male patients with mCRPC. Part 2 comprised two cohorts:

Cohort 1(all-comers population) and Cohort 2 (HRR-deficient population).

Supportive data were provided with the results of the open-label, multi-centre, phase II study C3441006 (TALAPRO-1).

The Applicant presented a mechanistic rationale to justify that the combination of a PARP inhibitor (talazoparib) and an NHA (enzalutamide), is effective in mCRPC independent of HRR gene mutational status (the term HRR used interchangeably with DDR).

HRR gene mutation analysis was a prerequisite in study part 2 and was performed using the FoundationOne CDx (de novo or archival tumour tissue) or the FoundationOne Liquid (peripheral blood) CDx tests. In the pivotal study, the following 12 HRR genes, referred to as HRR 12 or core genes/mutations, were used as classifiers for HRR deficiency: *ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, and RAD51C*.

If at least one mutation in one or more of the 12 specified genes was identified, the participant was considered HRR-deficient. If the test failed due to either not meeting specified quality control metrics, or due to insufficient or inadequate blood or tumour tissue sample the HRR gene mutation status was considered unknown. Furthermore, HRR deficiency was also considered to be present if there was a discordant result between the tissue and liquid results.

Overall, the study entry criteria in the pivotal study defined an appropriate population for the proposed treatment. Moreover, results are based on an RCT with placebo + enzalutamide as comparator.

The study population comprises both a subgroup of patients who have received docetaxel (28%), or abiraterone in the metastatic hormone-sensitive disease setting and a subgroup of patients that have not received docetaxel yet. Of the latter subgroup, some patients, for whom chemotherapy is not clinically indicated, have been treated with enzalutamide within the study setting in line with the approved indication for enzalutamide in mCRPC. The remaining patients with visceral disease, who have not yet received docetaxel in the hormone-sensitive disease setting, are according with international guidelines not eligible for enzalutamide treatment as given within the study, questioning the external validity of the obtained results in this subset. The initially proposed indication was modified in line with precedents to specify that treatment is indicated in patients in whom chemotherapy is not clinically indicated.

Talazoparib and enzalutamide were administered orally QD in the morning at fixed doses of 1 mg talazoparib (part 1), 0.5 mg talazoparib (part 2) and 160 mg enzalutamide (parts 1 and 2). Talazoparib was provided as 0.25 and 0.1 mg hard capsules, and enzalutamide as gelatine capsules of 40 mg.

Due to a potential drug-drug interaction of talazoparib with Pgp drug transporters, part 1 was performed as a dose-finding part. PK data suggested that 0.5 mg talazoparib + 160 mg enzalutamide maintained similar talazoparib AUC_{tau} levels as those obtained with 1 mg talazoparib QD monotherapy, which is the approved dose in breast cancer. Therefore, talazoparib 0.5 was the recommended starting dose for combination treatment in part 2. Talazoparib did not affect enzalutamide exposure.

In the placebo arm, placebo capsules were administered orally together with enzalutamide.

In part 1, target safety events were evaluated as primary endpoint.

In part 2, the primary endpoint was BICR-assessed rPFS and key secondary endpoint was BICR-assessed OS. These endpoints are considered relevant time-dependent endpoints in an RCT. Other endpoints were ORR, DoR, and PSA response $\geq$50%, which are considered supportive.

According to the CSR, approximately 1,037 subjects (19 enrolled in part 1 and approximately 1,018 in part 2) with mCRPC were enrolled. In part 2, there were 805 participants randomised. All randomised subjects were included in the primary analyses and analysis populations.

Presentations of protocol deviations show that 34 (4.2%) subjects were randomised under wrong stratification (13 subjects in talazoparib + enzalutamide group, and 21 subjects in the control group). The primary stratified analysis was based on the stratification in IWRS, which is endorsed. Although the circumstances/reasons for the miss-stratification are not clear, relatively small number of subjects is concerned and therefore the impact on the efficacy results is expected to be negligible.

The cut-off date for the primary analysis of study data in part 2, cohort 1, was pre-specified to be when approximately 333 rPFS events were observed in cohort 1. Primary DCO took place on 16 Aug 2022.

The statistical methodology applied is considered standard for oncology studies. However, the censoring rules in the primary analysis of rPFS did not followed EMA guideline. Intercurrent events, such as new antineoplastic therapy were defined such that participants were censored, thus removing them from the primary analysis. Therefore, it is considered misleading to name this population ITT. However, sensitivity analyses were included which fulfils the definition of a more conventional ITT population, and thereby the EMA's recommendation on treatment policy strategy.

This procedure maintained the overall type-I error at 1-sided 0.025 and is acceptable. However, although statistical significance of the primary endpoint in one or both populations was crucial for decision making by the Applicant, results of other endpoints are important, in particular overall survival which was controlled for multiplicity.

There were two protocol amendments with major impact on the statistical methodology in the study part 2. In Amendment 4 (dated 22 July 2019) the planned sample size was increased from 560 to 750 for all-comers and the interim analyses were adjusted accordingly to align with the updated timeline for the all-comers cohort. This amendment occurred approximately 5 months after the study started, which is relatively early considering the studied patient population and intended treatment length and is therefore not deemed to have been driven by potential study data on hand.

Although no sample size re-estimation was planned (according to the SAP) for the time to event endpoints, in the Amendment 8 (dated 17 June 2021) the number of events required were updated for the interim and final analyses of rPFS and OS in the HRR-deficient population, and the increased number of events required for the final OS analysis in all-comers population. Additional interim analysis for efficacy in the HRR-deficient cohort was introduced. These changes were implemented shortly after the futility analysis for rPFS in all-comers which occurred on 24 May 2021. Considering that the assessment of MAA and the intended indication focuses on all-commers with support of data for the HRR-deficient population, and given that the attained p-values show strong statistical significance for both primary endpoints the increased number of events and addition of interim analyses for the HRR-deficient population can be disregarded as not potentially impacting the overall Type I error rate.

Efficacy data and additional analyses

All-comers population

In the part 2, cohort 1 all-comers population, n=402 patients were randomised to receive talazoparib + enzalutamide treatment and n=403 patients randomised to receive placebo + enzalutamide treatment.

At primary DCO on 16 Aug 2022, 245 (61.6%) patients in the talazoparib + enzalutamide arm and 280 (69.8%) patients in the placebo + enzalutamide arm had discontinued talazoparib/placebo treatment respectively. The main reason for discontinuing talazoparib/placebo treatment was disease progression, followed by AEs (n=76 [19.1%] and n=69 [17.3%] in the talazoparib + enzalutamide arm, n=123 [30.7%] and n=43 [10.7%] in the placebo + enzalutamide arm, respectively). Overall, at primary DCO 152 patients in the talazoparib + enzalutamide arm were still on talazoparib, and 170 patients were still on enzalutamide treatment, respectively, and 120 patients in the placebo + enzalutamide arm were still on placebo and 124 were still on enzalutamide, respectively.

Overall, the baseline demographic and disease characteristics are generally well balanced between the two treatment arms, with median age 71.0 years in both treatment arms and comparable median time since diagnosis, ECOG performance status, renal impairment at baseline, baseline PSA, Gleason score at diagnosis, and presence of bone metastases at baseline.

The study met its primary objective, demonstrating a statistically significant and clinically relevant improvement of BICR-assessed rPFS for treatment with talazoparib + enzalutamide compared to placebo + enzalutamide with HR 0.627 (95% CI 0.506, 0.777) in the all-comers population, unselected for HRR gene

mutations. The median rPFS for the talazoparib + enzalutamide arm was not reached (95% CI 27.5, NR) compared to 21.9 months in the placebo arm (95% CI 16.6, 25,1).

All pre-specified subgroup analyses indicated results in favour of talazoparib + enzalutamide and the pre-planned sensitivity analyses were in line with the primary analysis and indicate robustness of the rPFS results.

With a median follow-up time of 28.0 months for the talazoparib + enzalutamide group and 27.1 months for the placebo + enzalutamide group, 58% of the planned events for the final analysis, and a total maturity of 31% at the time of primary DCO (IA1, 16 Aug 2022), OS data were immature. Updated OS data from IA2 (DCO 28 March 2023), with approximately 40% total maturity, showed a further improvement in OS for treatment with talazoparib + enzalutamide compared to placebo + enzalutamide, although not reaching statistical significance. The stratified OS HR was 0.837 (95% CI 0.674, 1.040) in the all-comers population.

ORR was reported for the subset of patients with measurable disease at baseline (n=120 in the talazoparib + enzalutamide arm and n=132 in the placebo + enzalutamide arm, respectively). CR was reported for 45 patients (37.5%) in the talazoparib + enzalutamide arm and 24 patients (18.2%) in the placebo + enzalutamide arm, respectively.

After completing study treatment, 114/402 (28.6%) of the patients in the talazoparib + enzalutamide arm and 176/403 (43.9%) in the placebo + enzalutamide arm received any post-baseline antineoplastic therapy, of which chemotherapy (docetaxel or cabazitaxel) was most commonly used (90/402 [22.6%] in the talazoparib + enzalutamide arm vs. 153/403 [38.2%] in the placebo + enzalutamide arm. It is expected that the need for subsequent treatments is higher in the comparator arm consisting of placebo and an active substance than in the active study arm consisting of two active substances. Subsequently, the median time to PFS2 was also somewhat longer (36.4 months [95% CI 33.5, NR] for patients in the talazoparib + enzalutamide arm than for patients in the placebo + enzalutamide arm (35.3 months [95% CI 28.6, NR]), although the 1-sided p-value for the corresponding HR was 0.0178, indicating that the results may not be robust.

The secondary endpoint time to PSA response was in favour of the talazoparib + enzalutamide arm, but the data were immature, and the results are not considered statistically significant. These results can only be potentially used to support the benefit of talazoparib, not to confirm its efficacy.

Patients enrolled in the study were allowed to have received prior docetaxel and abiraterone treatment for mCSPC. Of the patients in the talazoparib + enzalutamide arm, 21.4% had received prior docetaxel and 5.7% had received prior abiraterone. In the placebo + enzalutamide arm, 23.1% of the patients had received prior docetaxel and 6.7% had received prior abiraterone. Overall, these prior treatments did not influence the outcome, which was in favour of talazoparib + enzalutamide regardless of previous treatment. It is noted that prior abiraterone treatment was not beneficial, regardless of treatment arm, which is in line with current understanding of the risk of cross resistance between different NHTs, but the subgroup of patients who received prior abiraterone was small, precluding any further conclusions regarding a potential impact on the effect of talazoparib.

According to the PK interaction results, enzalutamide increases talazoparib PK parameters by 2-fold, possibly due to inhibition of Pgp. Considering the higher percentage of enzalutamide dose reductions, dose interruptions, and permanent discontinuations in the experimental arm in comparison to the control arm, data on enzalutamide dose modifications on talazoparib exposure and efficacy for the talazoparib + enzalutamide combination have been provided**.** The subgroups of patients with enzalutamide only dose reductions are very limited. The data on absolute reduction of talazoparib steady state AUC_{0-24} when

enzalutamide is reduced to 120 or 80 mg is scarce and uncertain. Nonetheless, there are no indications of a worse outcome for the few patients who experience enzalutamide dose reductions only.

Efficacy results by HRR gene mutation status

Overall, the rPFS results were in favour of talazoparib + enzalutamide treatment for both the HRR-deficient and HRR-proficient/unknown subgroups. This also applied for BRCA1/2-altered/HRR-deficient participants and non-BRCA1/2-altered/HRR-deficient participants. Although results indicate an effect of talazoparib + enzalutamide in the all-comers population, the rPFS increase was markedly higher for the HRR-deficient group than the HRR-proficient/unknown group. This was underlined by the results from the HRR-deficient population in cohort 2 (supportive top line report), including subgroup results based on BRCA1/2-altered participants.

rPFS results from subgroup analyses separating HRR-proficient patients and those with HRR unknown status have been provided. In the HRR-proficient subgroup, a clinically meaningful and statistically significant improvement of rPFS was shown in favour of talazoparib + enzalutamide treatment (HR=0.695 [95% CI 0.511, 0.944]). A similar trend was seen for the subgroup with unknown HRR status.

A key concern for PARP-inhibitors is that BRCA mutation status as well as HRR status are known and strong effect modifiers with regards to impact on OS. In order to support the positive B/R across the full range of the applied indication, the applicant was requested to provide updated OS data for the following categories: (a) BRCA1/2-mutated; (b) non-BRCA1/2-mutated, HRR-deficient; (c) subjects classified as HRR-proficient; (d) subjects with unknown status. Updated OS data from IA2 enhanced the positive trend seen in favour of talazoparib + enzalutamide in (a) the **BRCA1/2-mutated** subgroup and (b) **non-BRCA1/2-mutated, HRR-deficient** subgroup, even reaching statistical significance in the latter. For (c) **HRR-proficient** patients the updated OS data also showed a trend in favour of talazoparib + enzalutamide treatment with HR 0.888 (95% CI 0.654, 0.94), hence supporting the positive rPFS results shown for this large subset of patients. For (d) patients with **unknown HRR mutation status** rPFS data for certain showed a trend in favour of talazoparib + enzalutamide treatment, but this was not confirmed in the updated OS analysis. Overall, the demonstrated rPFS results, supported by updated OS results, support a favourable effect of talazoparib + enzalutamide regardless of HRR mutation status. Minor imbalances in baseline demographic and disease characteristics were noted for the different HRR subgroups. These are not considered to impact conclusions.

According to Analysis plan 4a, final analysis of OS in the all-comers population will be performed when approximately 438 deaths have occurred in this population. At the same time, a final analysis of OS in the HRR deficient population will be performed. A PAES with final OS data for cohort 1 and cohort 2 of study 1021 is included in Annex IID in the proposed SmPC. The expected DCO is May 2024, with expected data submission by November 2024. At the same time, updated rPFS results will be presented for the all-comers population and in the respective HRR subgroups (deficient, proficient, and unknown status).

2.5.7. Conclusions on the clinical efficacy

An effect on rPFS has been shown in the all-comers population. This effect is evident also in the large subgroup of patients that are HRR-proficient. Updated OS data from IA2 show a positive trend in favour of talazoparib + enzalutamide treatment regardless of HRR mutation status. These results are considered sufficiently reassuring also in patients that are HRR-proficient, as encompassed by the applicant's label claim.

The CHMP considers the following measures necessary to address issues related to efficacy:

Post authorisation efficacy study (PAES): In order to further characterize the long-term efficacy of talazoparib in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated, the MAH should submit the final results of study C3441021 (TALAPRO-2) including the final OS data analyses in the overall patient population and in all biomarker subgroups (by BRCAm and HRRm status) including rPFS and OS KM curves for all the subgroups.

2.5.8. Clinical safety

The safety data to support the use of talazoparib with the proposed posology in combination with enzalutamide for treatment of patients with mCRPC originate from the pivotal study TALAPRO-2.

Supportive safety data from the TALAPRO-1 talazoparib monotherapy study in later line of treatment of mCRPC are presented as well.

2.5.8.1. Study 1021 (TALAPRO-2)

The safety for talazoparib in combination with enzalutamide from the Phase 3 pivotal study is reported separately for the part 1 and part 2. The safety analysis set (SAF) included all subjects who received at least one dose of any study treatment.

2.5.8.1.1. TALAPRO-2/Study 1021 Part 1 (SAF=19)

The primary objective of open-label non-randomised Part 1 was to determine the starting dose of talazoparib when given in combination with enzalutamide during Part 2. Out of 19 participants enrolled, 13 participants received talazoparib (1 mg QD) + enzalutamide (160 mg QD) and 6 participants received talazoparib (0.5 mg QD) + enzalutamide (160 mg QD).

Patient exposure

Table 25. Dosing exposure of talazoparib TALAPRO-2 – Safety analysis set Part 1 (DCO 16 Aug 2022)

	TALAZOPARIB 1MG QD + ENZALUTAMIDE (N=13)	TALAZOPARIB 0.5MG QD + ENZALUTAMIDE (N=6)	Total (N=19)
Duration of Treatment (Weeks)[1]			
n	13	6	19
Mean	77.68	69.52	75.11
Median	38.29	22.79	29.29
Std Dev	77.49	82.88	76.99
Range(min,max)	(4.00, 231.14)	(8.14, 180.00)	(4.00, 231.14)
Duration of Treatment, n (%) [1]			
< 8 Weeks	1 (7.7)	0	1 (5.3)
>= 8 to < 12 Weeks	1 (7.7)	2 (33.3)	3 (15.8)
>= 12 to < 16 Weeks	1 (7.7)	0	1 (5.3)
>= 16 to < 26 Weeks	3 (23.1)	1 (16.7)	4 (21.1)
>= 26 to < 52 Weeks	1 (7.7)	1 (16.7)	2 (10.5)
>= 52 Weeks	6 (46.2)	2 (33.3)	8 (42.1)
Average Daily Dose Administered (mg/day)[2]			
n	13	6	19
Mean	0.58	0.45	0.54
Median	0.52	0.50	0.50
Std Dev	0.28	0.10	0.24
Range(min,max)	(0.24, 1.00)	(0.26, 0.50)	(0.24, 1.00)
Relative Dose Intensity(%)[3]			
n	13	6	19
Mean	57.56	89.42	67.62
Median	51.59	99.71	60.00
Std Dev	27.81	19.10	29.13
Range(min,max)	(23.53, 100.00)	(52.46, 100.00)	(23.53, 100.00)
Number of Participants (%) with Dose Interruptions	8 (61.5)	3 (50.0)	11 (57.9)
Due to AE	8 (61.5)	2 (33.3)	10 (52.6)
Due to other reasons	3 (23.1)	1 (16.7)	4 (21.1)
Number of Participants (%) with Dose Reductions	10 (76.9)	2 (33.3)	12 (63.2)
Due to AE	8 (61.5)	2 (33.3)	10 (52.6)
Due to other reasons	7 (53.8)	0	7 (36.8)

[1]Treatment duration (weeks) is defined as (date of last dose – date of first dose + 1)/7.
[2]Average daily dose (mg/day): The average daily dose is defined as the cumulative dose divided by the actual number of days on the treatment.
[3]Relative dose intensity (%): Relative dose intensity is defined as the ratio of the actual dose intensity to the planned dose intensity expressed in % .

Table 26. Dosing exposure of enzalutamide TALAPRO-2 – Safety analysis set Part 1 (DCO 16 Aug 2022)

	TALAZOPARIB 1MG QD + ENZALUTAMIDE (N=13)	TALAZOPARIB 0.5MG QD + ENZALUTAMIDE (N=6)	Total (N=19)
Duration of Treatment (Weeks)[1]			
n	13	6	19
Mean	98.63	125.74	107.19
Median	60.86	132.86	93.57
Std Dev	73.56	75.48	73.20
Range(min,max)	(17.00, 231.14)	(29.29, 219.29)	(17.00, 231.14)
Duration of Treatment, n (%) [1]			
< 8 Weeks	0	0	0
>= 8 to < 12 Weeks	0	0	0
>= 12 to < 16 Weeks	0	0	0
>= 16 to < 26 Weeks	2 (15.4)	0	2 (10.5)
>= 26 to < 52 Weeks	3 (23.1)	1 (16.7)	4 (21.1)
>= 52 Weeks	8 (61.5)	5 (83.3)	13 (68.4)
Average Daily Dose Administered (mg/day)[2]			
n	13	6	19
Mean	153.22	146.83	151.21
Median	160.00	160.00	160.00
Std Dev	17.94	31.67	22.42
Range(min,max)	(95.90, 160.00)	(82.19, 160.00)	(82.19, 160.00)
Relative Dose Intensity(%)[3]			
n	13	6	19
Mean	95.77	91.77	94.50
Median	100.00	100.00	100.00
Std Dev	11.21	19.80	14.01
Range(min,max)	(59.94, 100.00)	(51.37, 100.00)	(51.37, 100.00)
Number of Participants (%) with Dose Interruptions	5 (38.5)	2 (33.3)	7 (36.8)
Due to AE	2 (15.4)	1 (16.7)	3 (15.8)
Due to other reasons	4 (30.8)	2 (33.3)	6 (31.6)
Number of Participants (%) with Dose Reductions	1 (7.7)	1 (16.7)	2 (10.5)
Due to AE	0	1 (16.7)	1 (5.3)
Due to other reasons	1 (7.7)	0	1 (5.3)

[1]Treatment duration (weeks) is defined as (date of last dose – date of first dose + 1)/7.
[2]Average daily dose (mg/day): The average daily dose is defined as the cumulative dose divided by the actual number of days on the treatment.
[3] Relative dose intensity (%): Relative dose intensity is defined as the ratio of the actual dose intensity to the planned dose intensity expressed in % .

The Part 1 study objective were to determine the start dose for the randomized Part 2, and to evaluate safety, tolerability, and pharmacokinetics. HRR gene testing was optional.

The median age of patients at inclusion in part 1 was 71.0 years. The median time since diagnosis was 51.94 months. The majority of patients (63.2%) did not have any metastases at primary diagnosis (M0) and about 68% had high-grade risk prostate cancer (Gleason score >8).

The main reasons for dose reductions, or interruptions for talazoparib as well as for enzalutamide were AEs. Both dose reductions and dose interruptions were more frequent for talazoparib than for enzalutamide. This is also reflected in longer median time of exposure to the enzalutamide than to talazoparib, especially for the

6 additionally patients that received talazoparib reduced dose by 50%. Nevertheless, taking into account the median exposure, the percentage of dose interruption and reductions due to AE per median exposure for talazoparib was slightly reduced for the group of patients receiving reduced talazoparib dosage to 0.5 mg QD+ enzalutamide in comparison with those receiving 1 mg QD + enzalutamide. Enzalutamide dose interruption and reductions were not affected.

2.5.8.2. TALAPRO-2/Study 1021 Part 2 Cohort 1 (SAF=799)

Focus for the current sought indication is the safety in the population included in Part 2 Cohort 1. A total of 799 participants were treated with at least 1 dose of treatment (SAF). In the talazoparib + enzalutamide treatment arm, consisting of 402 participants, four patients (1.0%) did not receive any treatment. Hence, the safety population for the talazoparib + enzalutamide arm consisted of n=398 patients (99.0%).

In the placebo + enzalutamide treatment arm, consisting of 403 participants, two patients (0.5%) did not receive any treatment. Hence, the safety population for the placebo + enzalutamide arm consisted of n=401 patients (99.5%).

A reduced starting dose of talazoparib 0.35 mg QD was used in 42 participants from Cohort 1 Part 2 with moderate renal impairment to maintain a similar talazoparib exposure to 0.5 mg in participants with mild or no renal impairment.

2.5.8.2.1. Patient exposure

Table 27. Dosing exposure of talazoparib/placebo - Safety part 2, cohort 1 (all-comers population) (DCO 16 Aug 2022)

	TALAZOPARIB + ENZALUTAMIDE (N=398)	PLACEBO + ENZALUTAMIDE (N=401)	Total (N=799)
Duration of Treatment (Weeks)[1]			
n	397	400	797
Mean	79.83	71.67	75.74
Median	86.00	69.86	74.57
Std Dev	46.86	45.46	46.31
Range(min,max)	(0.29, 186.14)	(2.14, 182.00)	(0.29, 186.14)
Duration of Treatment, n (%) [1]			
< 8 Weeks	11 (2.8)	15 (3.7)	26 (3.3)
>= 8 to	23 (5.8)	25 (6.2)	48 (6.0)
>= 12 to	14 (3.5)	13 (3.2)	27 (3.4)
>= 16 to	23 (5.8)	41 (10.2)	64 (8.0)
>= 26 to	71 (17.8)	70 (17.5)	141 (17.6)
>= 52 Weeks	255 (64.1)	236 (58.9)	491 (61.5)
Average Daily Dose Administered (mg/day)[2]			
n	397	400	797
Mean	0.39	0.47	0.43
Median	0.38	0.50	0.50
Std Dev	0.11	0.06	0.10
Range(min,max)	(0.09, 0.50)	(0.20, 0.53)	(0.09, 0.53)
Relative Dose Intensity(%)[3]			
n	397	400	797
Mean	79.94	97.85	88.93
Median	83.54	100.00	99.87
Std Dev	21.51	7.66	18.44
Range(min,max)	(17.66, 104.49)	(53.49, 142.86)	(17.66, 142.86)
Number of Participants(%) with Dose Interruptions	268 (67.3)	134 (33.4)	402 (50.3)
Due to AE	235 (59.0)	68 (17.0)	303 (37.9)
Due to other reasons	110 (27.6)	80 (20.0)	190 (23.8)
Number of Participants(%) with Dose Reductions	218 (54.8)	45 (11.2)	263 (32.9)
Due to AE	209 (52.5)	28 (7.0)	237 (29.7)
Due to other reasons	13 (3.3)	11 (2.7)	24 (3.0)

[1]Treatment duration (weeks) is defined as (date of last dose – date of first dose + 1)/7.
[2]Average daily dose (mg/day): The average daily dose is defined as the cumulative dose divided by the actual number of days on the treatment.
[3]Relative dose intensity (%): Relative dose intensity is defined as the ratio of the actual dose intensity to the planned dose intensity expressed in % .

Table 28. Dosing exposure of enzalutamide – Safety part 2, cohort 1 (all-comers population) (DCO 16 Aug 2022)

	TALAZOPARIB + ENZALUTAMIDE (N=398)	PLACEBO + ENZALUTAMIDE (N=401)	Total (N=799)
Duration of Treatment (Weeks)[1]			
n	398	401	799
Mean	84.76	72.24	78.48
Median	96.57	72.00	77.43
Std Dev	45.22	45.73	45.88
Range(min,max)	(0.14, 186.14)	(0.14, 182.00)	(0.14, 186.14)
Duration of Treatment, n (%) [1]			
< 8 Weeks	9 (2.3)	15 (3.7)	24 (3.0)
>= 8 to	12 (3.0)	24 (6.0)	36 (4.5)
>= 12 to	11 (2.8)	14 (3.5)	25 (3.1)
>= 16 to	16 (4.0)	39 (9.7)	55 (6.9)
>= 26 to	75 (18.8)	71 (17.7)	146 (18.3)
>= 52 Weeks	275 (69.1)	238 (59.4)	513 (64.2)
Average Daily Dose Administered (mg/day)[2]			
n	398	401	799
Mean	150.52	155.75	153.14
Median	159.79	160.00	160.00
Std Dev	19.82	12.93	16.91
Range(min,max)	(49.72, 160.00)	(64.00, 160.12)	(49.72, 160.12)
Relative Dose Intensity(%)[3]			
n	398	401	799
Mean	94.07	97.34	95.71
Median	99.87	100.00	100.00
Std Dev	12.39	8.08	10.57
Range(min,max)	(31.08, 100.00)	(40.00, 100.08)	(31.08, 100.08)
Number of Participants(%) with Dose Interruptions	191 (48.0)	122 (30.4)	313 (39.2)
Due to AE	136 (34.2)	64 (16.0)	200 (25.0)
Due to other reasons	101 (25.4)	73 (18.2)	174 (21.8)
Number of Participants(%) with Dose Reductions	74 (18.6)	49 (12.2)	123 (15.4)
Due to AE	58 (14.6)	31 (7.7)	89 (11.1)
Due to other reasons	14 (3.5)	13 (3.2)	27 (3.4)

[1]Treatment duration (weeks) is defined as (date of last dose – date of first dose + 1)/7.
[2]Average daily dose (mg/day): The average daily dose is defined as the cumulative dose divided by the actual number of days on the treatment.
[3] Relative dose intensity (%): Relative dose intensity is defined as the ratio of the actual dose intensity to the planned dose intensity expressed in % .

Overall, the baseline patient characteristics were well balanced between the talazoparib + enzalutamide and the placebo + enzalutamide arm. The median age was 71.0 years in both arms, the median time since initial diagnosis was 31.38 months and 36.83 months respectively, majority had ECOG performance status 0 (64.4% vs. 67.2%), normal renal function (42%) or mild renal impairment at baseline (43%).

The median total duration of exposure was longer in the talazoparib + enzalutamide arm compared to the placebo + enzalutamide arm (talazoparib exposure: 86 and 70 weeks, respectively; enzalutamide exposure 96.57 weeks and 72.00 weeks, respectively).

The median relative dose intensity for talazoparib was reduced to 83.54%, while for enzalutamide was approximatively 100% and alike in the two treatment arms (99.87% vs. 100.0%)

2.5.8.3. Adverse events

Adverse Events of Part 2 Cohort 1 of Talopro-201 Study are presented below.

2.5.8.3.1. Common Adverse Events

Table 29. Overview of Treatment Emergent Adverse Events (All Causalities) - Safety Part 2 All-comers Population Protocol C3441021 (DCO 16 Aug 2022)

Number (%) of Participants	TALAZOPARIB + ENZALUTAMIDE (N=398) n (%)	PLACEBO + ENZALUTAMIDE (N=401) n (%)	Total (N=799) n (%)
Participants evaluable for adverse events	398	401	799
Number of TEAEs	3928	2871	6799
Participants with TEAEs	392 (98.5)	379 (94.5)	771 (96.5)
Participants with TEAE due to medication errors	1 (0.3)	0	1 (0.1)
Participants with serious TEAE	157 (39.4)	107 (26.7)	264 (33.0)
Participants with Maximum Grade 3 or 4 TEAE	286 (71.9)	163 (40.6)	449 (56.2)
Participants with Maximum Grade 5 TEAE	13 (3.3)	18 (4.5)	31 (3.9)
Participants discontinued from study due to TEAE (a)	15 (3.8)	20 (5.0)	35 (4.4)
Participants discontinued from ONLY Talazoparib/Placebo due to TEAE	39 (9.8)	8 (2.0)	47 (5.9)
Participants discontinued from ONLY Enzalutamide due to TEAE	6 (1.5)	3 (0.7)	9 (1.1)
Participants discontinued from BOTH Talazoparib and Enzalutamide due to TEAE	37 (9.3)	41 (10.2)	78 (9.8)
Participants with dose reduction on ONLY Talazoparib/Placebo due to TEAE	201 (50.5)	21 (5.2)	222 (27.8)
Participants with dose reduction on ONLY Enzalutamide due to TEAE	44 (11.1)	24 (6.0)	68 (8.5)
Participants with dose reduction on BOTH Talazoparib/Placebo and Enzalutamide due to TEAE	22 (5.5)	8 (2.0)	30 (3.8)
Participants with dose interruption on ONLY Talazoparib/Placebo due to TEAE	169 (42.5)	25 (6.2)	194 (24.3)
Participants with dose interruption on ONLY Enzalutamide due to TEAE	65 (16.3)	16 (4.0)	81 (10.1)
Participants with dose interruption on BOTH Talazoparib/Placebo and Enzalutamide due to TEAE	131 (32.9)	69 (17.2)	200 (25.0)

The treatment emergent period is from first dose through 28 days after the last dose of study treatment, or before new systemic (i.e. not including surgery or radiotherapy) antineoplastic therapy, whichever occurs first.
TEAE = Treatment–Emergent Adverse Event.
Except for the Number of TEAEs participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Participants who have an AE record that indicates that the AE caused the Participants to be discontinued from the study.
MedDRA v25.0 coding dictionary applied.
Data cutoff date : 16AUG2022

Table 30. Summary of TEAEs by PT and CTCAE Grade (All Grade and Grade 3 or greater) Experienced by >=10% of Participants - Safety Part 2 All-comers Population Protocol C3441021

Number of Participants Evaluable for AEs	TALAZOPARIB + ENZALUTAMIDE (N=398)			PLACEBO + ENZALUTAMIDE (N=401)		
	All Grade	Grade >= 3	Total	All Grade	Grade >= 3	Total
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	373 (93.7)	261 (65.6)	373 (93.7)	329 (82.0)	81 (20.2)	329 (82.0)
Anaemia	262 (65.8)	185 (46.5)	262 (65.8)	70 (17.5)	17 (4.2)	70 (17.5)
Neutrophil count decreased	142 (35.7)	73 (18.3)	142 (35.7)	28 (7.0)	6 (1.5)	28 (7.0)
Fatigue	134 (33.7)	16 (4.0)	134 (33.7)	118 (29.4)	8 (2.0)	118 (29.4)
Platelet count decreased	98 (24.6)	29 (7.3)	98 (24.6)	14 (3.5)	4 (1.0)	14 (3.5)
Back pain	88 (22.1)	10 (2.5)	88 (22.1)	72 (18.0)	4 (1.0)	72 (18.0)
White blood cell count decreased	88 (22.1)	25 (6.3)	88 (22.1)	18 (4.5)	0	18 (4.5)
Decreased appetite	86 (21.6)	5 (1.3)	86 (21.6)	63 (15.7)	4 (1.0)	63 (15.7)
Nausea	82 (20.6)	2 (0.5)	82 (20.6)	50 (12.5)	3 (0.7)	50 (12.5)
Constipation	72 (18.1)	1 (0.3)	72 (18.1)	68 (17.0)	2 (0.5)	68 (17.0)
Fall	71 (17.8)	9 (2.3)	71 (17.8)	59 (14.7)	8 (2.0)	59 (14.7)
Arthralgia	58 (14.6)	2 (0.5)	58 (14.6)	79 (19.7)	2 (0.5)	79 (19.7)
Asthenia	57 (14.3)	11 (2.8)	57 (14.3)	38 (9.5)	3 (0.7)	38 (9.5)
Diarrhoea	57 (14.3)	1 (0.3)	57 (14.3)	55 (13.7)	0	55 (13.7)
Hypertension	55 (13.8)	21 (5.3)	55 (13.8)	62 (15.5)	30 (7.5)	62 (15.5)
Dizziness	48 (12.1)	4 (1.0)	48 (12.1)	23 (5.7)	2 (0.5)	24 (6.0)
Hot flush	47 (11.8)	0	47 (11.8)	53 (13.2)	0	54 (13.5)
Lymphocyte count decreased	45 (11.3)	20 (5.0)	45 (11.3)	20 (5.0)	4 (1.0)	20 (5.0)
Oedema peripheral	42 (10.6)	0	42 (10.6)	23 (5.7)	0	24 (6.0)
Dyspnoea	41 (10.3)	2 (0.5)	41 (10.3)	25 (6.2)	1 (0.2)	25 (6.2)
Weight decreased	40 (10.1)	2 (0.5)	40 (10.1)	33 (8.2)	3 (0.7)	33 (8.2)

MedDRA v25.0 coding dictionary applied.
The denominator to calculate percentages is N, the number of participants in the safety analysis set within each treatment group.
Participants reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For participants reporting more than one AE within a system organ class or preferred term, the AE with maximum grade is included in the table.
Data cutoff date: 16AUG2022

Overall, the Treatment Emergent Adverse Events (Treatment Related) in the Part 2 Cohort 1 were reported to a higher rate for the combination of talazoparib + enzalutamide in comparison with placebo+ enzalutamide. This imbalance is more pronounced for the SAEs (19.6 % vs 3.0%) and TEAEs Grade 3 and higher (58.8% vs 17.2%), disfavouring the combination treatment. However, Grade 5 TEAEs were reported only in the placebo + enzalutamide arm in a small proportion of patients (0% vs 0.5%).

Considering the TEAEs leading to drug discontinuations, toxicity of talazoparib requiring discontinuation of talazoparib (9%) was significantly lower than toxicity requiring talazoparib dose interruptions (40%) or reductions (49.5%).

Summary of TEAEs by PT frequently reported in the Part 2 cohort 1 (experienced by >=10% of patients) shows a higher proportion of haematological toxicities in the experimental than in the control arm. Blood transfusions were reported for 42.5% of participants in the talazoparib plus enzalutamide arm and 6.2% in the placebo plus enzalutamide arm. Haematological toxicities, especially anaemia are very common ADRs labelled for talazoparib (all grades 50%, Grade 3 and higher 35%), while haematological toxicities are uncommon, and anaemia not labelled ADR for enzalutamide.

Other TEAEs frequently reported in this cohort of mCRPC patients with a slightly higher incidence in the experimental combination arm were GI tox (decreased appetite, nausea, constipation, diarrhoea), that are known ADRs for both talazoparib and enzalutamide, however reported as very common ADRs for talazoparib and with not known frequency in post-marketing settings for enzalutamide.

2.5.8.3.2. Serious adverse event/deaths/other significant events

Deaths

Table 31. Summary of Deaths - ITT Part 2 All-comers Population TALAPRO-2

	TALAZOPARIB + ENZALUTAMIDE (N=402) n (%)	PLACEBO + ENZALUTAMIDE (N=403) n (%)	Total (N=805) n (%)
Deaths during reporting period	123 (30.6)	129 (32.0)	252 (31.3)
Cause of Death[1]			
Disease Progression	92 (22.9)	91 (22.6)	183 (22.7)
Study Treatment Toxicity	0	1 (0.2)	1 (0.1)
Adverse Event Not Related to Study Treatment	8 (2.0)	7 (1.7)	15 (1.9)
Other	2 (0.5)	8 (2.0)	10 (1.2)
Unknown	21 (5.2)	22 (5.5)	43 (5.3)
Deaths within 5 weeks after first dose of treatment	1 (0.2)	0	1 (0.1)
Cause of Death[1]			
Disease Progression	0	0	0
Study Treatment Toxicity	0	0	0
Adverse Event Not Related to Study Treatment	1 (0.2)	0	1 (0.1)
Other	0	0	0
Unknown	0	0	0
Deaths Within 28 Days After Last Dose of Study Treatment	14 (3.5)	20 (5.0)	34 (4.2)
Cause of Death[1]			
Disease Progression	4 (1.0)	7 (1.7)	11 (1.4)
Study Treatment Toxicity	0	1 (0.2)	1 (0.1)
Adverse Event Not Related to Study Treatment	7 (1.7)	7 (1.7)	14 (1.7)
Other	0	1 (0.2)	1 (0.1)
Unknown	3 (0.7)	4 (1.0)	7 (0.9)

	TALAZOPARIB + ENZALUTAMIDE (N=402) n (%)	PLACEBO + ENZALUTAMIDE (N=403) n (%)	Total (N=805) n (%)
Deaths Beyond 28 Days After Last Dose of Study Treatment	107 (26.6)	108 (26.8)	215 (26.7)
Cause of Death[1]			
Disease Progression	87 (21.6)	83 (20.6)	170 (21.1)
Study Treatment Toxicity	0	0	0
Adverse Event Not Related to Study Treatment	1 (0.2)	0	1 (0.1)
Other	2 (0.5)	7 (1.7)	9 (1.1)
Unknown	17 (4.2)	18 (4.5)	35 (4.3)

[1] Multiple causes of death can be reported for each participant.
The denominator to calculate percentages is N, the number of participants in the ITT Population Part 2 All-comers analysis set within each treatment group
Data cutoff date: 16AUG2022

During the study reporting period, 31.3% deaths occurred in the cohort 1, in a similar proportion (30.6% versus 32.0%) in the talazoparib+ enzalutamide and placebo+ enzalutamide arms, respectively. Disease progression reported in a comparative incidence rate was the most frequent cause of death in each treatment arm (22.9% vs 22.6%). Death due to investigational drugs toxicity was negligible, reported in only one patient in the control, placebo + enzalutamide arm.
The incidences of reported deaths due to AEs for other drugs, of other, or unknown causes were comparable between arms.

No significant differences that would indicate increased risk of death, disregarding causes, in any of the two arms, are observed for the period of 28 days after the last dose of study drugs or beyond.

Serious adverse events (SAEs)

Table 32. Summary of Treatment-Emergent Serious Adverse Events by Preferred Term and Max CTCAE Grade (All Causalities) Experienced by >= 2% of Participants - ITT Part 2 All-comers Population TALAPRO-2

Number of Participants Evaluable for AEs	TALAZOPARIB + ENZALUTAMIDE (N=398)			PLACEBO + ENZALUTAMIDE (N=401)		
Number (%) of Participants: by Preferred Term	All Grade n (%)	Grade >= 3 n (%)	Total n (%)	All Grade n (%)	Grade >= 3 n (%)	Total n (%)
With Any Adverse Event	68 (17.1)	62 (15.6)	68 (17.1)	8 (2.0)	7 (1.7)	8 (2.0)
Anaemia	55 (13.8)	49 (12.3)	55 (13.8)	1 (0.2)	1 (0.2)	1 (0.2)
Haematuria	10 (2.5)	10 (2.5)	10 (2.5)	4 (1.0)	4 (1.0)	4 (1.0)

Number of Participants Evaluable for AEs	TALAZOPARIB + ENZALUTAMIDE (N=398)			PLACEBO + ENZALUTAMIDE (N=401)		
Number (%) of Participants: by Preferred Term	All Grade n (%)	Grade >= 3 n (%)	Total n (%)	All Grade n (%)	Grade >= 3 n (%)	Total n (%)
Urinary tract infection	9 (2.3)	7 (1.8)	9 (2.3)	3 (0.7)	2 (0.5)	3 (0.7)

The denominator to calculate percentages is N, the number of Participants in the safety analysis set within each treatment group.
Participants reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For Participants reporting more than one AE within a system organ class or preferred term, the AE with maximum grade is included in the table.
The treatment emergent period is from first dose through 28 days after the last dose of study treatment, or before new systemic (i.e. not including surgery or radiotherapy) antineoplastic therapy, whichever occurs first.
Data cutoff date: 16AUG2022

Table 33. Summary of Treatment-Emergent Adverse Events by Descending Preferred Term and Max CTCAE Grade Equal to 5 (All Causalities) - ITT Part 2 All-comers Population TALAPRO-2

Number of Participants Evaluable for AEs	TALAZOPARIB + ENZALUTAMIDE (N=398)	PLACEBO + ENZALUTAMIDE (N=401)	Total (N=799)
Number (%) of Participants: by Preferred Term	Grade 5 n (%)	Grade 5 n (%)	Grade 5 n (%)
With Any Adverse Event	13 (3.3)	18 (4.5)	31 (3.9)
Disease progression	4 (1.0)	5 (1.2)	9 (1.1)
Death	3 (0.8)	3 (0.7)	6 (0.8)
SARS-CoV-2 test positive	1 (0.3)	3 (0.7)	4 (0.5)
Cardiac failure	1 (0.3)	2 (0.5)	3 (0.4)
Pneumonia	2 (0.5)	0	2 (0.3)
Acute pulmonary oedema	0	1 (0.2)	1 (0.1)
Brain contusion	0	1 (0.2)	1 (0.1)
COVID INFECTION WITH COMPLICATIONS@@	0	1 (0.2)	1 (0.1)
Cardiac arrest	1 (0.3)	0	1 (0.1)
Cerebral haematoma	0	1 (0.2)	1 (0.1)
Craniocerebral injury	0	1 (0.2)	1 (0.1)
Disseminated intravascular coagulation	1 (0.3)	0	1 (0.1)
Lung neoplasm malignant	0	1 (0.2)	1 (0.1)
Prostate cancer	0	1 (0.2)	1 (0.1)
Renal failure	0	1 (0.2)	1 (0.1)

Number of Participants Evaluable for AEs	TALAZOPARIB + ENZALUTAMIDE (N=398)	PLACEBO + ENZALUTAMIDE (N=401)	Total (N=799)
	Grade 5	Grade 5	Grade 5
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)

MedDRA v25.0 coding dictionary applied.
The denominator to calculate percentages is N, the number of participants in the safety analysis set within each treatment group.
Participants reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For participants reporting more than one AE within a preferred term, the AE with maximum grade is included in the table.
The treatment emergent period is from first dose through 28 days after the last dose of study treatment, or before new systemic (i.e. not including surgery or radiotherapy) antineoplastic therapy, whichever occurs first.
Data cutoff date: 16AUG2022

2.5.8.4. Adverse Events of Special Interest (AESI)

2.5.8.4.1. AESI Specific to Talazoparib – Treatment Emergent

AESIs specific to talazoparib were defined based on a list of MedDRA PT and included:

- Acute Myeloid Leukemia and Myelodysplastic Syndrome (MDS)

- second primary malignancies (excluding nonmelanoma skin cancer)

-Pneumonitis

- Venous embolic and thrombotic events (VTE)

Table 34. Summary Treatment-Emergent Adverse Events of Special Interest for Talazoparib/Placebo by Preferred Term and Max Toxicity Grade (Treatment Related) - Safety Part 2 All-comers Population Protocol C3441021

Number of Participants Evaluable for AEs	TALAZOPARIB + ENZALUTAMIDE (N=398)			PLACEBO + ENZALUTAMIDE (N=401)		
	All Grade	Grade >= 3	Total	All Grade	Grade >= 3	Total
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	5 (1.3)	4 (1.0)	5 (1.3)	1 (0.2)	1 (0.2)	1 (0.2)
EMBOLIC AND THROMBOTIC EVENTS, VENOUS	4 (1.0)	3 (0.8)	4 (1.0)	1 (0.2)	1 (0.2)	1 (0.2)
Pulmonary embolism	3 (0.8)	3 (0.8)	3 (0.8)	1 (0.2)	1 (0.2)	1 (0.2)
Renal vein thrombosis	1 (0.3)	0	1 (0.3)	0	0	0
MYELODYSPLASTIC SYNDROME (MDS)	1 (0.3)	1 (0.3)	1 (0.3)	0	0	0
Myelodysplastic syndrome	1 (0.3)	1 (0.3)	1 (0.3)	0	0	0

Adverse Events of Special Interest (AESI):
Acute Myeloid Leukemia (AML), Myelodysplastic Syndrome (MDS), second primary malignancies (other than hematologic), pneumonitis, and venous thrombotic events.
For participants reporting more than one AE within a system organ class or preferred term, the AE with maximum grade is included in the table.
The treatment emergent period is from first dose through 28 days after the last dose of study treatment, or before new systemic (i.e. not including surgery or radiotherapy) antineoplastic therapy, whichever occurs first.
PFIZER CONFIDENTIAL SDTM Creation: 12SEP2022 (08:45) Source Data: adae Table Generation: 26SEP2022 (20:41)
(Data cutoff date : 16AUG2022 Database snapshot date : 06SEP2022) Output File:

Venous embolic and thrombotic events

Among the AESI considered treatment related, imbalance in incidence rate between arms is noticed for venous embolic and thrombotic events (VTE: 1% vs 0.2%), specifically for pulmonary embolism indicating an increased risk for PE in the experimental arm (PE: 0.8% vs 0.2%), when talazoparib is administered in combination with enzalutamide.

When VTE are reported disregarding the causes (All Causalities), the imbalance is even more pronounced disfavoring talazoparib + enzalutamide combination (4.0% vs 0.7%). Other events of VTE besides pulmonary embolism were reported only in the experimental arm (PE: 2.5% vs 0.7%, Deep vein thrombosis 0.5% vs 0%, and Embolism venous, Jugular vein thrombosis, Superficial vein thrombosis, Venous thrombosis, 0.3% each in experimental vs 0% in control arm).

An ad-hoc analysis of AESI VTE rates adjusting for time of treatment shows a slightly lower incidence of VTE events for talazoparib+ enzalutamide 2.4% vs 0.5% for placebo plus enzalutamide.

Secondary primary malignancies, other than hematologic

No increased incidence for Secondary primary malignancies other than hematologic is observed with talazoparib + enzalutamide combination: 3.0% vs 5.0% in the talazoparib plus enzalutamide vs placebo plus enzalutamide treatment arms.

MDS/AML

One case of MDS AESI was reported for 1 participant in the talazoparib plus enzalutamide treatment arm (within the period Day 1 through 28 days after the last dose of study treatment). No patients in the placebo plus enzalutamide arm experienced MDS/AML. One additional AESI of AML in the talazoparib plus enzalutamide treatment arm was reported during follow-up.

Pneumonitis

Two case reports of pneumonitis have been identified. In one case the event was reported by the investigator as related to the radiation therapy with pneumonitis appearing after treatment. In the second case, the cause of pneumonitis has not been identified by the investigator, however, considered not related to medication.

2.5.8.4.2. AESI Specific to Enzalutamide – All Causalities

Table 35. Summary Treatment-Emergent Adverse Events of Special Interest for Enzalutamide by Preferred Term and Max Toxicity Grade (All Causalities) -Safety Part 2 All-comers Population Protocol C3441021 (source CSR)

Number of Participants Evaluable for AEs	TALAZOPARIB + ENZALUTAMIDE (N=398)			PLACEBO + ENZALUTAMIDE (N=401)		
	All Grade	Grade >= 3	Total	All Grade	Grade >= 3	Total
Number (%) of Participants: by Categories for AESI to Enzalutamide and by Preferred Terms	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	259 (65.1)	128 (32.2)	259 (65.1)	179 (44.6)	76 (19.0)	179 (44.6)
NEUTROPENIA/NEUTROPHIL COUNT DECREASED	142 (35.7)	73 (18.3)	142 (35.7)	28 (7.0)	6 (1.5)	28 (7.0)
Neutrophil count decreased	142 (35.7)	73 (18.3)	142 (35.7)	28 (7.0)	6 (1.5)	28 (7.0)
Neutropenia	0	0	0	1 (0.2)	0	1 (0.2)
Neutrophil percentage decreased	1 (0.3)	0	1 (0.3)	0	0	0
FALL	71 (17.8)	9 (2.3)	71 (17.8)	59 (14.7)	8 (2.0)	59 (14.7)
Fall	71 (17.8)	9 (2.3)	71 (17.8)	59 (14.7)	8 (2.0)	59 (14.7)
FRACTURE	79 (19.8)	18 (4.5)	79 (19.8)	48 (12.0)	12 (3.0)	48 (12.0)
Rib fracture	32 (8.0)	3 (0.8)	32 (8.0)	16 (4.0)	1 (0.2)	16 (4.0)
Spinal fracture	4 (1.0)	2 (0.5)	4 (1.0)	9 (2.2)	1 (0.2)	9 (2.2)
Lumbar vertebral fracture	6 (1.5)	0	6 (1.5)	3 (0.7)	1 (0.2)	3 (0.7)
Pathological fracture	7 (1.8)	4 (1.0)	7 (1.8)	2 (0.5)	2 (0.5)	2 (0.5)
Spinal compression fracture	8 (2.0)	0	8 (2.0)	1 (0.2)	0	1 (0.2)
Femur fracture	2 (0.5)	2 (0.5)	2 (0.5)	5 (1.2)	3 (0.7)	5 (1.2)
Foot fracture	4 (1.0)	0	4 (1.0)	1 (0.2)	0	1 (0.2)
Humerus fracture	4 (1.0)	0	4 (1.0)	1 (0.2)	0	1 (0.2)
Thoracic vertebral fracture	3 (0.8)	0	3 (0.8)	2 (0.5)	0	2 (0.5)

The denominator to calculate percentages is N, the number of participants in the safety analysis set within each treatment group.
Participants reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
Participants reporting multiple preferred terms within the same AESI to Enza Category are counted only once within each Category.
For participants reporting more than one AE within a AESI to Enza Category or preferred term, the AE with maximum grade is included in the table.
The treatment emergent period is from first dose through 28 days after the last dose of study treatment, or before new systemic (i.e. not including surgery or radiotherapy) antineoplastic therapy, whichever occurs first.

The AESI of enzalutamide were balanced between arms with some exceptions. A significant higher proportion of AESI neutropenia (containing all related PT) is noted in the experimental arm in comparison to control arm (35.7% vs 7%). Neutropenia is labelled for both components of the combination regimen, however with very common frequency for talazoparib and uncommon for enzalutamide. Hence, increased risk for neutropenia

including high grade neutropenia for the talazoparib+ enzalutamide combination might be mainly linked to talazoparib, however synergistic contribution of both components cannot be excluded.

Fall (17.8% vs 14.7%) and Fracture (19.8% vs 12%) were also reported with slightly higher incidence rate in the experimental than in control arm. Both Fall and Fracture are labelled ADRs for enzalutamide reported with frequency very common in enzalutamide clinical studies.

According to a post hoc analysis of bone fracture incidence in the subgroup of patients with or without bone metastases, there was no difference in the incidence of fractures between arms in the subgroup of patients with no underlying bone metastases.

A numerically higher incidence of Fractures was observed in the subgroup of patients with underlying bone metastases for the combination talazoparib plus enzalutamide.

No information regarding prophylactic use of bone protective agents for the patients with bone metastases has been provided.

2.5.8.5. Laboratory findings

Haematology

Shifts in haematology values from Grade ≤2 at baseline to Grade 3 or 4 postbaseline occurred in more participants (≥5% absolute difference between treatment arms) in the talazoparib plus enzalutamide arm than in the placebo plus enzalutamide arm for most haematology laboratory parameters. This result parallels the increase in haematological AEs observed in the talazoparib plus enzalutamide arm.

Chemistry

Shifts in chemistry values from Grade ≤2 at baseline to Grade 3 or 4 postbaseline occurred at a similar rate between treatment arms for all values. No participants met the criteria of concurrent elevations in ALT and AST ≥3 × ULN and total bilirubin >2 × ULN with alkaline phosphate level <2 × ULN at any time. No participants met the criteria for Hy's Law.

Vital Signs

No evidence of a clinically significant effect on vital signs was observed; abnormalities in vital signs were reported as AEs.

Table 36 Shift Summary Results of Labs from Grade <=2 at Baseline to Grade 3 or 4 Postbaseline (Haematology) Safety Part 2 All-comers Population Protocol C3441021

	TALAZOPARIB + ENZALUTAMIDE N=398			PLACEBO + ENZALUTAMIDE N=401		
Participants with Shift from Grade <= 2 at Baseline to Grade 3 or 4:	**N***	**Grade 3 n(%)**	**Grade 4 n(%)**	**N***	**Grade 3 n(%)**	**Grade 4 n(%)**
Anemia	395	185 (46.8)	0	399	18 (4.5)	0
Hemoglobin increased	395	1 (0.3)	0	399	0	0
Leukocytosis	395	0	0	399	1 (0.3)	0
Lymphocyte count decreased	395	49 (12.4)	4 (1.0)	399	28 (7.0)	1 (0.3)
Lymphocyte count increased	395	0	0	399	1 (0.3)	0
Neutrophil count decreased	395	73 (18.5)	5 (1.3)	399	5 (1.3)	3 (0.8)
Platelet count decreased	395	30 (7.6)	10 (2.5)	399	4 (1.0)	1 (0.3)
White blood cell decreased	395	39 (9.9)	0	399	0	0

Includes unplanned laboratory test results.
CTCAE version 4.03 criteria have been used.
N* = The number of participants with at least one post baseline value on-treatment.
n = The number of participants whose lab results met the criteria of CTCAE v4.03

Table 37 Shift Summary Results of Labs from Grade <=2 at Baseline to Grade 3 or 4 Postbaseline (Chemistry) Safety Part 2 All-comers Population Protocol C3441021

	TALAZOPARIB + ENZALUTAMIDE N=398			PLACEBO + ENZALUTAMIDE N=401		
Participants with Shift from Grade <= 2 at Baseline to Grade 3 or 4:	**N***	**Grade 3 n(%)**	**Grade 4 n(%)**	**N***	**Grade 3 n(%)**	**Grade 4 n(%)**
Alanine aminotransferase increased	395	4 (1.0)	0	399	7 (1.8)	1 (0.3)
Alkaline phosphatase increased	395	14 (3.5)	0	399	13 (3.3)	0
Aspartate aminotransferase increased	395	3 (0.8)	0	399	7 (1.8)	2 (0.5)
Blood bilirubin increased	395	2 (0.5)	0	399	3 (0.8)	0
CPK increased	138	0	0	135	1 (0.7)	0
Creatinine increased	395	4 (1.0)	0	399	7 (1.8)	2 (0.5)

Participants with Shift from Grade <= 2 at Baseline to Grade 3 or 4:	TALAZOPARIB + ENZALUTAMIDE N=398			PLACEBO + ENZALUTAMIDE N=401		
	N*	Grade 3 n(%)	Grade 4 n(%)	N*	Grade 3 n(%)	Grade 4 n(%)
GGT increased	3	0	0	3	0	0
Hypercalcemia	395	0	0	398	1 (0.3)	2 (0.5)
Hyperglycemia	395	20 (5.1)	1 (0.3)	399	20 (5.0)	2 (0.5)
Hyperkalemia	395	4 (1.0)	0	399	5 (1.3)	1 (0.3)
Hypermagnesemia	395	2 (0.5)	0	398	2 (0.5)	0
Hypernatremia	395	0	0	398	0	0
Hypoalbuminemia	395	0	0	398	1 (0.3)	0
Hypocalcemia	395	3 (0.8)	0	398	1 (0.3)	2 (0.5)
Hypoglycemia	395	0	1 (0.3)	399	1 (0.3)	0
Hypokalemia	395	3 (0.8)	3 (0.8)	399	7 (1.8)	1 (0.3)
Hypomagnesemia	395	1 (0.3)	0	398	0	0
Hyponatremia	395	10 (2.5)	0	398	12 (3.0)	2 (0.5)
Hypophosphatemia	395	7 (1.8)	0	398	5 (1.3)	0
INR increased	1	0	0	2	0	0

Includes unplanned laboratory test results.
CTCAE version 4.03 criteria have been used.
N* = The number of participants with at least one post baseline value on-treatment.
n = The number of participants whose lab results met the criteria of CTCAE v4.03.

2.5.8.6. Safety in special populations

Table 38 Summary of TEAE by Age Group-Safety part 2-All-comers population (DCO August 2022)

MedDRA Terms	TALAZOPARIB + ENZALUTAMIDE				PLACEBO + ENZALUTAMIDE			
	Age <65 n (%) (N=78)	Age 65-74 n (%) (N=186)	Age 75-84 n (%) (N=120)	Age 85+ n (%) (N=14)	Age <65 n (%) (N=94)	Age 65-74 n (%) (N=174)	Age 75-84 n (%) (N=125)	Age 85+ n (%) (N=8)
Total AEs (Number of patients having at least one TEAE)	76 (97.4)	183 (98.4)	119 (99.2)	14 (100)	90 (95.7)	165 (94.8)	116 (92.8)	8 (100)
Serious AEs (Number of patients having at least one serious TEAE)	20 (25.6)	74 (39.8)	58 (48.3)	5 (35.7)	23 (24.5)	45 (25.9)	35 (28)	4 (50)
- Fatal (Number of Patients with Grade 5 TEAEs)	2 (2.6)	5 (2.7)	5 (4.2)	1 (7.1)	2 (2.1)	4 (2.3)	9 (7.2)	3 (37.5)
- Hospitalization/prolong existing hospitalization [1]	NA	NA	NA	NA	NA	NA	NA	NA
- Life-threatening (Number of Patients with Grade 4 SAEs)	7 (9)	12 (6.5)	10 (8.3)	0	1 (1.1)	5 (2.9)	6 (4.8)	1 (12.5)
- Disability/incapacity [1]	NA	NA	NA	NA	NA	NA	NA	NA
- Other (medically significant) [1]	NA	NA	NA	NA	NA	NA	NA	NA
AE Leading to discontinuation of Talazoparib/Placebo treatment	6 (7.7)	25 (13.4)	39 (32.5)	5 (35.7)	10 (10.6)	15 (8.6)	20 (16)	4 (50)
AE Leading to discontinuation of Enzalutamide treatment	5 (6.4)	14 (7.5)	19 (15.8)	5 (35.7)	9 (9.6)	14 (8)	17 (13.6)	4 (50)
SOC - Psychiatric disorders	10 (12.8)	34 (18.3)	21 (17.5)	4 (28.6)	12 (12.8)	24 (13.8)	19 (15.2)	1 (12.5)
SOC - Nervous system disorders	28 (35.9)	73 (39.2)	50 (41.7)	9 (64.3)	34 (36.2)	65 (37.4)	44 (35.2)	3 (37.5)
Accidents and injuries (SOC - Injury, Poisoning And Procedural Complications)	16 (20.5)	56 (30.1)	48 (40)	5 (35.7)	19 (20.2)	42 (24.1)	34 (27.2)	3 (37.5)
SOC Cardiac disorders	3 (3.8)	14 (7.5)	20 (16.7)	1 (7.1)	5 (5.3)	13 (7.5)	15 (12)	2 (25)
SOC Vascular disorders	23 (29.5)	60 (32.3)	26 (21.7)	7 (50)	30 (31.9)	57 (32.8)	27 (21.6)	2 (25)
Cerebrovascular disorders [2]	0	2 (1.1)	7 (5.8)	0	0	1 (0.6)	1 (0.8)	1 (12.5)
SOC Infections and infestations	28 (35.9)	74 (39.8)	47 (39.2)	4 (28.6)	32 (34)	47 (27)	34 (27.2)	1 (12.5)
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures (Cluster Term)	21 (26.9)	61 (32.8)	55 (45.8)	7 (50)	20 (21.3)	41 (23.6)	40 (32)	2 (25)
other AE appearing more frequently in older patients:	36 (46.2)	119 (64)	95 (79.2)	12 (85.7)	13 (13.8)	27 (15.5)	28 (22.4)	3 (37.5)
Anaemia (Cluster Term)								
Neutropenia (Cluster Term)	13 (16.7)	70 (37.6)	50 (41.7)	9 (64.3)	10 (10.6)	10 (5.7)	7 (5.6)	1 (12.5)
Thrombocytopenia (Cluster Term)	10 (12.8)	45 (24.2)	38 (31.7)	6 (42.9)	1 (1.1)	5 (2.9)	7 (5.6)	1 (12.5)
Leukopenia (Cluster Term)	14 (17.9)	37 (19.9)	31 (25.8)	7 (50)	3 (3.2)	8 (4.6)	7 (5.6)	1 (12.5)
Fall	4 (5.1)	32 (17.2)	33 (27.5)	2 (14.3)	12 (12.8)	24 (13.8)	22 (17.6)	1 (12.5)
Decreased appetite	9 (11.5)	36 (19.4)	35 (29.2)	6 (42.9)	12 (12.8)	23 (13.2)	25 (20)	3 (37.5)

The treatment emergent period is from first dose through 28 days after the last dose of study treatment, or before new systemic (i.e. not including surgery or radiotherapy), antineoplastic therapy, whichever occurs first.
Participants are only counted once per treatment per event. MedDRA v25.0 coding dictionary applied.
[1] This SAE subcategory was not separately collected in the clinical database
[2] Cerebrovascular disorders were identified based on Central Nervous System Hemorrhages and Cerebrovascular Conditions (narrow SMQ)
LEUKOPENIA: Leukopenia, White blood cell count decreased. THROMBOCYTOPENIA: Thrombocytopenia, Platelet count decreased.
NEUTROPENIA: Neutrophil count decreased, neutropenia, agranulocytosis, granulocyte count decreased, granulocytopenia, febrile neutropenia, neutrophil percentage decreased, band neutrophil count decreased, band neutrophil percentage decreased, neutropenic sepsis, neutropenic infection, neutrophil count abnormal.
ANEMIA: Anemia, Hematocrit decreased, Hemoglobin decreased, Red blood cell count decreased.

Renal Impairment

Participants with normal renal function or mild impairment are grouped in the "normal/mild" subgroup, and participants with moderate renal impairment comprise the "moderate" subgroup.

In the talazoparib plus enzalutamide arm, 42 (10.6%) have moderate and 340 (85.4%) participants have normal/mild; in the placebo plus enzalutamide arm, 40 (10.0%) have moderate and 346 (86.3%) normal/mild impairment. Additional participants had severe renal impairment but were not evaluated due to the low numbers (<4%) in both treatment arms.

Talazoparib/placebo exposure (median duration) was higher in normal/mild subgroup (talazoparib plus enzalutamide 91.8 weeks; placebo plus enzalutamide 71.1 weeks) vs the moderate subgroup (talazoparib plus enzalutamide 60.6 weeks; placebo plus enzalutamide 59.9 weeks).

The frequencies of all-causality AE categories were somewhat higher in the moderate renal impairment subgroup compared with the normal/mild subgroup in both treatment arms, including the following:

Talazoparib plus enzalutamide arm: Moderate subgroup vs Normal/mild subgroup

SAEs: 47.6% vs 37.6%

Grade 3/4 AEs: 71.4% vs 71.5%

Grade 5 AEs: 7.1% vs 2.9%

Grade 5 AEs in the normal renal function/mild impairment subgroup were reported in 12/353 (3.4%) of participants in both treatment arms. The most common event was disease progression in both arms (1.1%). In the moderate renal impairment subgroup, only 1/24 (4.2%) participants in talazoparib plus enzalutamide arm experienced a Grade 5 AE of cardiac failure versus 4/23 (17.4%) participants in placebo plus enzalutamide arm (cardiac failure and disease progression 1 event each, 2 events of SARS-CoV-2 test positive).

The most frequent (≥20%) AEs in either subgroup were: Anaemia: 61.9% vs 66.5%, Fall: 31.0% vs 16.5%,

Platelet count decreased: 28.6% vs 24.4%, Decreased appetite: 26.2% vs 21.5% , Nausea: 26.2% vs 20.3%, Neutrophil count decreased: 23.8% vs 37.9%, Fatigue: 23.8% vs 34.4% ,Back pain: 21.4% vs 22.1% , WBC count decreased: 16.7% vs 22.6% , Diarrhoea: 13.5% vs 23.8%

Placebo plus enzalutamide arm: Moderate subgroup vs Normal/mild subgroup

SAEs: 50% vs 23.4%

Grade 3/4 AEs: 50.0% vs 39.9%

Grade 5 AEs: 20.0% vs 2.3%

The most frequent (≥20%) AEs in either subgroup were:

Fatigue: 45.0% vs 27.2%

Decreased appetite: 32.5% vs 13.9%

Anaemia: 22.5% vs 17.3%

Hypertension: 22.5% vs 14.2%

Fall: 22.5% vs 13.0%

Diarrhoea: 22.5% vs 12.1%

Arthralgia: 20.0% vs 19.1%

There were no meaningful differences in time to onset of AEs between renal impairment subgroups in either treatment arm

2.5.8.7. Safety related to drug-drug interactions and other interactions

Based on PK results from Study 1021 Part 1, a drug-drug interaction was observed, with an increase in talazoparib concentration by enzalutamide, as described below. No other drug-drug interactions were identified in Study 1021.

Enzalutamide concentrations were not affected by talazoparib.

2.5.8.8. Discontinuation due to adverse events

Adverse Events Leading to Discontinuation

Table 39. Overview of Treatment Emergent Adverse Events leading to Discontinuation Dose Reduction and Dose Interruption (All Causalities) -Safety Part 2 All-comers Population TALAPRO-2

	TALAZOPARIB + ENZALUTAMIDE (N=398) n (%)	PLACEBO + ENZALUTAMIDE (N=401) n (%)
Participants discontinued from Talazoparib/Placebo due to TEAE[a]	75 (18.8)	49 (12.2)
Participants discontinued from Enzalutamide due to TEAE[b]	43 (10.8)	44 (11.0)
Participants with dose reduction on Talazoparib/Placebo due to TEAE[c]	210 (52.8)	27 (6.7)
Participants with dose reduction on Enzalutamide due to TEAE[d]	58 (14.6)	32 (8.0)
Participants with dose interruption on Talazoparib/Placebo due to TEAE[e]	247 (62.1)	84 (20.9)
Participants with dose interruption on Enzalutamide due to TEAE[f]	156 (39.2)	78 (19.5)

a. Participants discontinued from Talazoparib/Placebo due to TEAE - AEACN1 ='DRUG WITHDRAWN'
b. Participants discontinued from Enzalutamide due to TEAE - AEACN2='DRUG WITHDRAWN'
c. Participants with dose reduction on Talazoparib/Placebo due to TEAE - AEACN1 ='DOSE REDUCED'
d. Participants with dose reduction on Enzalutamide due to TEAE - AEACN2 ='DOSE REDUCED'
e. Participants with dose interruption on Talazoparib/Placebo due to TEAE - AEACN1 ='DRUG INTERRUPTED'
f. Participants with dose interruption on Enzalutamide due to TEAE - AEACN2 ='DRUG INTERRUPTED'

Data cutoff date: 16AUG2022

Anaemia was the most commonly reported AE leading to permanent discontinuation of talazoparib only or enzalutamide only and was reported at a higher incidence in the talazoparib+ enzalutamide treatment arm (8.3%) than the placebo+ enzalutamide treatment arm.

A similar trend is observed for talazoparib and enzalutamide dose reductions or dose interruptions due to All Causalities AEs. The most common adverse drug reaction leading to dose interruption or dose reduction was anaemia (44.0% and 43.2% respectively).

In both treatment arms, dose interruptions of talazoparib/placebo were most frequently reported due to the hematologic AEs of anaemia, neutrophil count decreased, and platelet count decreased. Nonhematologic AEs that led to a dose interruption of talazoparib included fatigue, nausea, and decreased appetite. (Data not shown)

Anaemia and neutrophil count decreased were the most frequently reported AEs leading to enzalutamide dose interruption and both AEs were reported at a higher incidence in the talazoparib+ enzalutamide treatment arm than in the placebo+ enzalutamide treatment arm. Nonhematologic AEs that led to a dose interruption of enzalutamide included decreased appetite, nausea, and fatigue (data not shown).

Anaemia was the most commonly reported AE leading to a dose reduction of talazoparib or enzalutamide.

Exposure-Response Safety Analyses

Exposure-safety analysis showed that higher talazoparib exposure is also associated with a higher risk for Grade 3 or higher haematological AEs (anaemia, neutropenia, and thrombocytopenia

Safety related to drug-drug interactions has been studied as primary objective in the Part 1 Study 1021 which was focused on the PK interactions between the components of regimen and dose finding. PK results showed that talazoparib did not affect enzalutamide exposure, while enzalutamide increased talazoparib PK parameters by 2-fold, possibly due to inhibition of P glycoprotein.

2.5.8.9. Study 1021-Part 2 -Cohort2 Safety results

Topline results from Part2 Cohort 2 have been provided in support for the data in HRR-deficient subgroup in Cohort1.

Table 40 Summary of safety data Study 1021-Part 2 -Cohort2

Dosing exposure Cohort 2

	Talazoparib + Enzalutamide (N=198)	Placebo + Enzalutamide (N=199)
Talazoparib/placebo	197	199
Median duration of treatment (weeks)	63.29	52.14
Median average daily dose administered (mg/day)	0.38	0.50
Median relative dose intensity (%)	81.05	100
Enzalutamide	198	199
Median duration of treatment (weeks)	63.93	52.57
Median average daily dose administered (mg/day)	160	160
Median relative dose intensity (%)	100	100

Treatment-emergent AEs Cohort 2

	Talazoparib + Enzalutamide (N=198)	Placebo + Enzalutamide (N=199)
Patients with any AEs	196 (99.0%)	191 (96.0%)
Patients with maximum Grade 3 or 4 AEs	131 (66.2%)	74 (37.2%)
Patients with maximum Grade 5 AEs	3 (1.5%)	5 (2.5%)
Patients with any SAEs	60 (30.3%)	40 (20.1%)
Patients with AEs leading to ONLY talazoparib/placebo discontinuation	9 (4.5%)	1 (0.5%)
Patients with AEs leading to ONLY enzalutamide discontinuation	4 (2.0%)	1 (0.5%)
Patients with AEs leading to BOTH talazoparib/placebo and enzalutamide discontinuation	11 (5.6%)	13 (6.5%)

Patients with dose reduction on ONLY talazoparib/placebo due to TEAE	100 (50.5%)	8 (4.0%)
Patients with dose reduction on ONLY enzalutamide due to TEAE	21 (10.6%)	8 (4.0%)
Patients with dose reduction on BOTH talazoparib/placebo and enzalutamide due to TEAE	10 (5.1%)	4 (2.0%)

TEAEs in ≥10% Patients – All Causalities (Safety Population)

Preferred Term	Talazoparib + Enzalutamide (N=198)		Placebo + Enzalutamide (N=199)	
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Anaemia	128 (64.6%)	81 (40.9%)	31 (15.6%)	9 (4.5%)
Fatigue	66 (33.3%)	3 (1.5%)	53 (26.6%)	2 (1.0%)
Neutrophil count decreased	64 (32.3%)	37 (18.7%)	13 (6.5%)	2 (1.0%)
Platelet count decreased	49 (24.7%)	14 (7.1%)	5 (2.5%)	1 (0.5%)
Nausea	41 (20.7%)	3 (1.5%)	34 (17.1%)	1 (0.5%)
Decreased appetite	40 (20.2%)	2 (1.0%)	28 (14.1%)	2 (1.0%)
Back pain	39 (19.7%)	3 (1.5%)	44 (22.1%)	2 (1.0%)
White blood cell count decreased	37 (18.7%)	11 (5.6%)	15 (7.5%)	0
Hypertension	36 (18.2%)	16 (8.1%)	38 (19.1%)	16 (8.0%)
Asthenia	31 (15.7%)	4 (2.0%)	29 (14.6%)	0
Constipation	26 (13.1%)	0	33 (16.6%)	0
Fall	26 (13.1%)	4 (2.0%)	24 (12.1%)	3 (1.5%)
Arthralgia	25 (12.6%)	0	44 (22.1%)	0
Diarrhoea	24 (12.1%)	0	22 (11.1%)	0
Hot flush	23 (11.6%)	0	28 (14.1%)	0
Dizziness	20 (10.1%)	1 (0.5%)	15 (7.5%)	2 (1.0%)
Headache	12 (6.1%)	0	22 (11.1%)	1 (0.5%)

There were 3 (1.5%) deaths within 28 days after last dose of study treatment in the talazoparib + enzalutamide group and 6 (3.0%) deaths within 28 days after last dose in the placebo + enzalutamide group, respectively.

The safety population in Cohort 2 consists of 397 patients receiving at least one dose of study treatment. All patients randomized 1:1 in Cohort 2 were HRD selected. At the DCO for primary analysis of the Cohort 2 study results, the safety results confirm the safety results observed in Cohort 1 Part 2 of Study 1021, taking in account a slightly shorter median exposure to study drugs in comparison to Cohort 1. A slightly higher incidence of SAEs and Grade 3/ 4 AEs in the experiment versus arm is observed. However, no increased incidence of Grade 5 AEs during study period or for the 28 days period after last administered dose is observed with addition of talazoparib. Increased toxicity in talazoparib + enzalutamide arm is however confirmed by the higher incidence in this arm of SAEs, particularly anaemia. Higher incidence of dose reductions, interruptions, and drug discontinuations in talazoparib + enzalutamide arm than in placebo + enzalutamide is also observed. This is in line with the imbalances observed for the Cohort 1, although to a lower extent, possibly due to shorter exposure and follow-up.

2.5.8.10. Study 1006 - Safety Results

Study 1006 was an open-label, Phase 2, international, open-label, soft tissue response rate study of talazoparib to evaluate the efficacy and safety of talazoparib monotherapy in adult male participants with mCRPC with HRR deficiencies (n=128). Participants received talazoparib 1 mg QD orally. If participants were determined to have moderate renal impairment at screening (eGFR: 30-59 mL/min/1.73 m2 per central laboratory) then the talazoparib starting dose was reduced to 0.75 mg QD orally. Sparse PK samples were collected for talazoparib.

As of the data cut-off (04 Sep 2020), of the 128 participants enrolled, 127 participants received study intervention. The median exposure time was 6.05 months for all participants in the safety population.

The most frequent (≥20%) AEs reported were anaemia (48.8%), nausea (33.1%), decreased appetite (28.3%), and asthenia (23.6%).

AEs leading to talazoparib dose reduction were reported in 26.0% of participants. Low rates of permanent discontinuation due to all causality AEs occurred in 11.8% of participants.

Grade 3 AEs were reported in 44.9% of participants, Grade 4 AEs were reported in 3.1% of participants and Grade 5 AEs were reported in 7.9% of participants. The 3 most common Grade 3 AEs were anaemia (30.7%), neutrophil count decreased (7.9%), and platelet count decreased (5.5%). All of the Grade 4 AEs reported was platelet count decreased (3.1%). No Grade 5 AEs were considered treatment-related, and only disease progression occurred in more than 1 participant (4 [3.1%]).

The most frequent (≥2%) SAEs reported were pulmonary embolism (6.3%), anaemia (3.9%), disease progression (3.1%), pneumonia (2.4%) and urinary tract infection (2.4%).

Deaths were reported in 69 (54.3%) participants. The most common cause of death was disease progression in 46.5% (59/127) of participants. No deaths were attributed to study treatment.

No events of AML or MDS were reported for any participant in the safety population. In addition, no treatment-related events of secondary primary malignancies were reported.

Adverse drug Reaction (ADR)

For the purpose of identification of the ADR in patients treated with Talazoparib the MAH pool data from 1088 patients, including 690 patients who received talazoparib monotherapy at 1 mg daily in clinical studies for solid tumours and 398 patients with mCRPC who received talazoparib 0.5 mg in combination with enzalutamide 160 mg in the TALAPRO-2 study.

Table 42 summarises adverse reactions based on pooled dataset listed by system organ class, and frequency category. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 41 Adverse reactions based on pooled dataset from 8 studies (N=1088)

System organ class **Frequency** **Preferred term**	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Uncommon			
Myelodysplastic syndrome/Acute myeloid	2 (0.2)	1 (< 0.1)	1 (< 0.1)

Table 41 Adverse reactions based on pooled dataset from 8 studies (N=1088)

System organ class Frequency Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
leukaemia[a]			
Blood and lymphatic system disorders			
Very common			
Thrombocytopenia[b]	274 (25.2)	88 (8.1)	33 (3.0)
Anaemia[c]	605 (55.6)	411 (37.8)	16 (1.5)
Neutropenia[d]	330 (30.3)	163 (15.0)	17 (1.6)
Leukopenia[e]	195 (17.9)	52 (4.8)	2 (0.2)
Common			
Lymphopenia[f]	88 (8.1)	37 (3.4)	4 (0.4)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	230 (21.1)	11 (1.0)	0 (0.0)
Nervous system disorders			
Very common			
Dizziness	157 (14.4)	4 (0.4)	1 (< 0.1)
Headache	207 (19.0)	8 (0.7)	N/A
Common			
Dysgeusia	68 (6.3)	0 (0.0)	0 (0.0)
Vascular disorders			
Common			
Venous thromboembolism*[g]	36 (3.3%)	23 (2.1%)	2 (0.2%)
Gastrointestinal disorders			
Very common			
Vomiting	167 (15.3)	9 (0.8)	0 (0.0)
Diarrhoea	205 (18.8)	4 (0.4)	0 (0.0)
Nausea	389 (35.8)	10 (0.9)	N/A
Abdominal pain[h]	162 (14.9)	12 (1.1)	N/A
Common			
Stomatitis	54 (5.0)	0 (0.0)	0 (0.0)
Dyspepsia	69 (6.3)	0 (0.0)	N/A
Skin and subcutaneous tissue disorders			
Very common			
Alopecia	189 (17.4)	N/A	N/A
General disorders and administration site conditions			
Very common			
Fatigue[i]	571 (52.5)	58 (5.3)	N/A

Abbreviations: n=number of patients; N/A=not applicable.

* Grade 5 adverse reactions were reported.

a. See also section 4.4.

b. Includes preferred terms of thrombocytopenia and platelet count decreased.

c. Includes preferred terms of anaemia, haematocrit decreased, haemoglobin decreased and red blood cell count decreased.

d. Includes preferred terms of neutropenia and neutrophil count decreased.

e. Includes preferred terms of leukopenia and white blood cell count decreased.

f. Includes preferred terms of lymphocyte count decreased and lymphopenia.

g Includes preferred terms of pulmonary embolism, deep vein thrombosis, embolism venous and venous thrombosis. See also section 4.4.

h. Includes preferred terms of abdominal pain, abdominal pain upper, abdominal discomfort and abdominal pain lower.

i. Includes preferred terms of fatigue and asthenia.

2.5.8.11. Post marketing experience

Talazoparib received the first regulatory approval on 16 October 2018 in the United States and on 20 June 2019 in the European Union; it has received regulatory approval in 75 countries and is currently marketed in 40 countries.

Cumulatively, the exposure to talazoparib since the product was first approved is estimated to be 1088 patients in the US and 1990 patients in non-US countries. Post marketing experience with talazoparib is described in periodic aggregate reports that Pfizer has submitted to regulatory authorities, including the New Drug Application (NDA), Annual Report, Periodic Adverse Drug Experience Report (PADER) submitted to the US FDA, and Periodic Safety Update Reports (PSURs) submitted to the EMA.

There were no important identified risks for talazoparib, as per the Risk Management Plan (RMP) Version 1.0 dated 05 Dec 2019. The important potential risks were myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), second primary malignancies (other than MDS/AML) and reproductive and developmental toxicity were important potential risks for talazoparib. There were neither important identified risks nor missing information for talazoparib.

No additional safety data relevant for the current application emerged from pots-marketing activities. There are no missing information or important identified risks in the list of safety specifications in the latest approved version of RMP. No safety risks that qualify for inclusion in the list of safety specifications arises from the current application. No additional information to change the known important potential risk such myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), second primary malignancies (other than MDS/AML) and reproductive and developmental toxicity is identified either.

2.5.9. Discussion on clinical safety

The safety for talazoparib in combination with enzalutamide from the Phase 3 pivotal study C3441021 (study TALOPRO-2; 1021) is reported separately for the part 1 and part 2. The safety analysis set (SAF) included all subjects who received at least one dose of any study treatment.

TALOPRO-2 Part 2 Cohort 1

Part 2 cohort 1 of Study TALAPRO-2/1021 safety analysis constitutes of a population of 398 patients treated with talazoparib and enzalutamide provide a substantial amount of safety data, with sufficient exposure (up to 2 years) for this new association in metastatic castration resistant prostate cancer, not previously treated with chemotherapy in castration resistant setting.

TALOPRO-2 Part 1

The Part 1 study objective were to determine the start dose for the randomized Part 2, and to evaluate safety, tolerability, and pharmacokinetics. HRR gene testing was optional.

The median age of patients at inclusion in part 1 was 71.0 years. The median time since diagnosis was 51.94 months. The majority of patients (63.2%) did not have any metastases at primary diagnosis (M0) and about 68% had high-grade risk prostate cancer (Gleason score >8).

In Study TALOPRO-2 Part 1 the main reasons for dose reductions, or interruptions in talazoparib as well as for enzalutamide were AEs. Both dose reductions and dose interruptions were more frequent for talazoparib than for enzalutamide. This is also reflected in longer median time of exposure to the enzalutamide than to talazoparib, especially for the 6 additionally patients that received talazoparib reduced dose by 50%.

Nevertheless, taking into account the median exposure, the percentage of dose interruption and reductions due to AE per median exposure for talazoparib was slightly reduced for the group of patients receiving reduced talazoparib dosage to 0.5 mg QD+ enzalutamide in comparison with those receiving 1 mg QD + enzalutamide. Enzalutamide dose interruption and reductions were not affected.

Altogether, the exposure data during the Part 1 suggest a higher toxicity for talazoparib when administered 1 mg QD in combination with enzalutamide 160 mg QD. The toxicity was lowered by reducing the dosage of talazoparib to 0.5 mg. Further assessment of safety for the chosen posology for talazoparib in combination with enzalutamide was performed in the more representative safety population from the Part 2.

TALAPRO-2/1021 Part 2 Cohort 2

Preliminary analyses of safety data from HRD population included in Cohort 2 of TALAPRO-2/1021 Study are in line with safety data observed in the safety population of Cohort 1.

TALAPRO-1/1006

Additional safety data in 127 patients with HRR deficiency from the TALAPRO-1/1006 talazoparib monotherapy study in later line of treatment of mCRPC, although with a shorter median exposure time of 6.05 months are in general supporting the safety of talazoparib observed in the pivotal study.

Exposure

TALAPRO-2 Part 2 Cohort 1

At the time of the DCO 16 Aug 2022, 99% of patients randomised had received study treatments. Of them, approximately 64% discontinued study treatment mostly due to progressive disease (higher proportion in the control arm) or adverse events (higher proportion in the experimental arm). A higher proportion of patients were still ongoing at DCO in the talazoparib + enzalutamide arms than in placebo + enzalutamide arm. The median total duration of exposure was therefore longer in the talazoparib + enzalutamide arm compared to the placebo + enzalutamide arm (talazoparib exposure:86 and 70 weeks, respectively; enzalutamide exposure 96.57 weeks and 72.00 weeks, respectively).

The median relative dose intensity for talazoparib was reduced to 83.54%, while for enzalutamide was approximatively 100% and alike in the two treatment arms (99.87% vs. 100.0%)

Dose interruptions and dose reductions

Higher incidences of dose reduction and dose interruptions for talazoparib and enzalutamide were noted in the talazoparib+enzalutamide arm.

The imbalance between arms for the SAEs and higher grade TEAEs seems to correlate with a notably higher proportion of dose reductions and interruption due to TEAEs mostly for talazoparib (dose reduction 49.5% vs 4.5%, dose interruption 40.5% vs 4.2%). These differences for talazoparib versus placebo are not unexpected.

Altogether these data suggest that talazoparib have a high toxicity when given in combination with enzalutamide, however this toxicity is manageable with high rate of dose reductions or dose interruptions, drug discontinuation being required to a low extent.

Adverse events

Baseline characteristics were generally balanced between the two treatment arms to support an acceptable safety comparative analysis.

Overall, the safety profile of talazoparib is well characterised and is consistent with previous data from talazoparib monotherapy.

However, characteristic for the combination with enzalutamide used to treat the elderly study population with metastatic prostate cancer is the higher incidence of haematological toxicities, predominantly for anaemia.

Overall, the Treatment Emergent Adverse Events (Treatment Related) in the Part 2 Cohort 1 were reported to a higher rate for the combination of talazoparib + enzalutamide in comparison with placebo+ enzalutamide. This imbalance is more pronounced for the SAEs (19.6 % vs 3.0%) and TEAEs Grade 3 and higher (58.8% vs 17.2%), disfavouring the combination treatment. However, Grade 5 TEAEs were reported only in the placebo + enzalutamide arm and in a small proportion of patients (0% vs 0.5%).

Summary of TEAEs by PT frequently reported in the Part 2 cohort 1 (experienced by >=10% of patients) shows a higher proportion of haematological toxicities in the experimental than in the control arm, with overrepresentation of anaemia (all grades 66% vs 17.5%, Grade 3 and higher 46.5% vs 4.2%). Haematological toxicities, especially anaemia are very common ADRs labelled for talazoparib (all grades 50%, Grade 3 and higher 35%), while haematological toxicities are uncommon for enzalutamide for which anaemia is not labelled as an ADR. Thus, talazoparib when used in combination with enzalutamide appear to be linked with a high risk for anaemia, including high grade.

Other TEAEs frequently with a slightly higher incidence in the experimental combination arm were Gastrointestinal (GI) toxicity (decreased appetite, nausea, constipation, diarrhoea), that are known ADRs for both talazoparib and enzalutamide (reported as very common ADRs for talazoparib and with not known frequency in post-marketing settings for enzalutamide).

On the other hand, TEAES reported frequently in the current study that are known ADRs for enzalutamide such as hypertension, or arthralgia do not seem to have a higher incidence in the experimental arm in comparison to control arm. Hence, addition of talazoparib to enzalutamide does not appear to worsen enzalutamide toxic profile.

Deaths

During the study reporting period, 31.3% deaths occurred in the cohort 1, in a similar proportion (30.6% versus 32.0%) in the talazoparib+ enzalutamide and placebo+ enzalutamide arm, respectively. Disease progression reported in a comparative incidence rate was the most frequent cause of death in each treatment arm (22.9% vs 22.6%). Death deemed due to investigational drug toxicity was negligible, reported in only one patient in the control, placebo + enzalutamide arm.

The incidences of reported deaths due to AEs for other drugs, of other, or unknown causes were comparable between arms.

No significant differences that would indicate increased risk of death, disregarding causes, in any of the two arms, are observed for the period of 28 days after the last dose of study drugs or beyond.

SAEs

During the study reporting period, All Grade and Grade ≥3 SAEs were reported at higher incidence rates for participants in the talazoparib +enzalutamide arm than the placebo+ enzalutamide arm (all grades 17% vs 2%, Grade ≥3 SAEs 16% vs 1.7%), mainly due to high grade anaemia (all grades 13.8% vs 0.2%, Grade ≥3 12.3% vs 0.2%).

Grade 5 TEAEs All Causalities were reported with a similar incidence rate between arms, 3.3% vs 4.5% in the talazoparib + enzalutamide and placebo +enzalutamide arm, respectively. With a low number of Grade 5 TEAEs reported per individual PT in both arms, there is no visible trend for death related to a specific TEAE Grade 5 in any of the two arms.

Treatment-related Grade 5 AEs were reported in 2 participants in the placebo plus enzalutamide arm due to 'Unknown' cause and COVID-19. There were no Grade 5 AEs in the talazoparib plus enzalutamide arm that were considered treatment related. These data are in line with reported data on the deaths due to study treatment toxicity reported during the study period and after.

Adverse Events Leading to Permanent Treatment Discontinuation or Dose Modifications

Permanent discontinuations of talazoparib/placebo due to an AE were reported for 18.8% vs 12.2% patients in the talazoparib plus enzalutamide treatment arm versus the placebo plus enzalutamide treatment. Permanent discontinuations of enzalutamide were reported at similar incidence rate for both arms 10.8% in the talazoparib+ enzalutamide treatment arm and 11.0% in the placebo+ enzalutamide treatment arm, respectively.

Anaemia was the most commonly reported AE leading to permanent discontinuation of talazoparib only or enzalutamide only and was reported at a higher incidence in the talazoparib+ enzalutamide treatment arm than the placebo+ enzalutamide treatment arm.

A similar trend is observed for talazoparib and enzalutamide dose reductions or dose interruptions due to All Causalities AEs.

In both treatment arms, dose interruptions of talazoparib/placebo were most frequently reported due to the hematologic AEs of anaemia, neutrophil count decreased, and platelet count decreased. Nonhematologic AEs that led to a dose interruption of talazoparib included fatigue, nausea, and decreased appetite.

Anaemia and neutrophil count decreased were the most frequently reported AEs leading to enzalutamide dose interruption and both AEs were reported at a higher incidence in the talazoparib+ enzalutamide treatment arm than in the placebo+ enzalutamide treatment arm. Nonhematologic AEs that led to a dose interruption of enzalutamide included decreased appetite, nausea, and fatigue.

Anaemia was the most commonly reported AE leading to a dose reduction of talazoparib or enzalutamide.

AESI for Talazoparib

Venous embolic and thrombotic events (VTE)

Among the AESI considered treatment related, imbalance in incidence rate between arms is noticed for venous embolic and thrombotic events (VTE: 1% vs 0.2%), specifically for pulmonary embolism (PE) indicating an increased risk for PE in the experimental arm (PE: 0.8% vs 0.2%), when talazoparib is administered in combination with enzalutamide.

When VTE were reported disregarding the causes (All Causalities), the imbalance was more pronounced disfavoring talazoparib + enzalutamide combination (4.0% vs 0.7%). Other events of VTE besides pulmonary embolism were reported only in the experimental arm (PE: 2.5% vs 0.7%, Deep vein thrombosis 0.5% vs 0%, and Embolism venous, Jugular vein thrombosis, Superficial vein thrombosis, Venous thrombosis, 0.3% each in experimental vs 0% in control arm).

An ad-hoc analysis of AESI VTE rates adjusting for time of treatment shows a slightly lower incidence of VTE events for talazoparib+ enzalutamide 2.4% vs 0.5% for placebo plus enzalutamide.

Although the numbers reported are rather small in an elderly population with cardiovascular risk factors and advanced cancer, an increased incidence rate for VTE and particularly Pulmonary embolism is not negligible, especially in comparison with the lower incidence rate observed in the control arm, where enzalutamide has known risk for cardiovascular events related to androgen deprivation. Furthermore, an increased risk for VTE, predominantly for pulmonary embolism it has been reported for other PARPi approved for the treatment of advanced prostate cancer in combination with abiraterone.

In addition, in the supportive Study 1006 with talazoparib as monotherapy, pulmonary embolism has also been reported with significant incidence rate of 6.3%.

A warning for VTE, specifically for pulmonary embolism when talazoparib is given in combination with enzalutamide in studies in patients with metastatic prostate cancer is included in section 4.4 of the talazoparib SmPC. Furthermore, Table 4 in section 4.8 of the SmPC was amended with VTE as ADR with frequency common.

Secondary primary malignancies, other than haematologic

No increased incidence for Secondary primary malignancies other than hematologic was observed with talazoparib + enzalutamide combination: 3.0% vs 5.0% in the talazoparib plus enzalutamide vs placebo plus enzalutamide treatment arms.

MDS/AML

One case of MDS AESI was reported for 1 participant in the talazoparib plus enzalutamide treatment arm (within the period Day 1 through 28 days after the last dose of study treatment). No patients in the placebo plus enzalutamide arm experienced MDS/AML. One additional AESI of AML in the talazoparib plus enzalutamide treatment arm was reported during follow-up. MDS/AML are known ADRs described for PARPi in general, and in < 1% of solid tumour patients treated with talazoparib in clinical studies. The SmPC Section 4.8 Table 4 has been updated to include MDS/AML with the frequency uncommon.

Pneumonitis

Two case reports of pneumonitis have been identified. In one case the event was reported by the investigator as related to the radiation therapy with pneumonitis appearing after treatment. In the second case, the cause of pneumonitis has not been identified by the investigator, however, considered not related to medication. In conclusion, data do not indicate an increased risk of pneumonitis with talazoparib.

Laboratory findings

Laboratory findings confirms the differences observed between the two arms. An increased rate of lab values indicating Grade 3 anaemia, thrombocytopenia and leukopenia, including neutropenia was observed in the talazoparib + enzalutamide vs placebo + enzalutamide arm. The imbalance in haematological lab values was predominant for Grade 3 anaemia (46.8% vs 4.5%) than for lymphopenia (12.4% vs 7%) and thrombocytopenia (7.6% vs 1%). This is in line with the imbalances observed for haematological toxicities TEAEs that were reported with a higher proportion in the experimental than in the control arm, with overrepresentation of anaemia (all grades 66% vs 17.5%, Grade 3 and higher 46.5% vs 4.2%). Haematological toxicities, especially anaemia are very common ADRs labelled for talazoparib (all grades 50%, Grade 3 and higher 35%), while haematological toxicities are uncommon, and anaemia not labelled ADR for enzalutamide. As stated above, talazoparib when used in combination with enzalutamide appears to be linked with a high risk for anaemia, including high grade. This information is included in the SmPC section 4.8.

A balanced proportion of shifts in liver lab values are observed between arms and no cases meeting Hy's Law criteria were reported either with the combination talazoparib+ enzalutamide, or with placebo + enzalutamide. Transient transaminitis with elevated levels of transaminases, or bilirubin are commonly reported for GNRH analogues and are labelled ADRs for GNRH analogues which represent the backbone treatment in both arms.

Safety in special populations

Effect of Age

Owing to the imbalance in the number of patients per age group and in particular in the median talazoparib and enzalutamide exposure between talazoparib + enzalutamide and placebo + enzalutamide arms, differences in safety between age groups are interpreted with caution.

No significant differences in the SAEs, Grade 3/ 4 AEs incidence rates with age are observed when comparing subgroup Age <75 years vs ≥75 years, or Age - <65 years vs ≥65 years, respectively. However, an increased incidence with age of Grade 5 AEs is observed in both arms. In the elderly patients ≥75 years and ≥65 years the incidence of Grade 5 TEAEs was numerically higher with the enzalutamide than with enzalutamide and talazoparib combination. However, this was driven by the imbalance in the progressive disease events.

Effect of renal impairment

The imbalance in size of subgroups and median exposure to talazoparib and enzalutamide between arms are relevant in the comparative evaluation of the safety profile per grade of renal impairment. No clinically significant differences are observed in the incidence rates of SAEs, or Grade 3/ 4 AEs between the moderate renal impairment versus normal/mild renal impairment subgroups. However, a higher incidence rate of Grade 5 AEs in the moderated versus normal/mild subgroup is observed in both arms. An increased incidence of AEs with grade of renal impairment is expected. No trend of imbalance in the incidence of Grade 5 TEAEs were observed with the talazoparib and enzalutamide combination in the subgroup with moderate renal impairment. Therefore, lowering the exposure by dosing interruption or dose reduction will lead to a lower probability of having these events which supports the recommended dose modification as an effective approach for management of AEs (see section 4.2 of the SmPC). The observed exposure-efficacy and exposure-safety relationships are consistent with that previously identified for talazoparib in breast cancer (EMBRACA [Study C3441009] and ABRAZO [Study C3441008]).

Study 1021-Part 2 -Cohort2 Safety results

The safety population in Cohort 2 consists of 397 patients receiving at least one dose of study treatment. All patients randomized 1:1 in Cohort 2 were HRD selected. At the DCO for primary analysis of the Cohort 2 study results, the safety results confirm the safety results observed in Cohort 1 Part 2 of Study 1021, taking in account a slightly shorter median exposure to study drugs in comparison to Cohort 1. Increased toxicity in talazoparib + enzalutamide arm with higher incidence in this arm of SAEs, particularly anaemia is line with data from Cohort 1. There is no indicator to suggest a different safety profile pending the HRD status based on the safety profile seen in Cohort 2 versus Cohort 1 where the majority of patients were HRR-proficient (ca 80%). No signal of increased mortality when talazoparib was administered as add-on to enzalutamide + GNRH analogue was detected.

Study 1006 - Safety Results

Study 1006 provides supplemental safety data to support the use of talazoparib in mCRPC. Talazoparib 1 mg QD was generally tolerated in participants with mCRPC with HRR deficiencies, and AEs were generally manageable through dosing interruption, dose reduction, and/or standard supportive care.

Overall, the safety in the population with HRR deficiency which represent the SAF=127 in Study 1006 support the safety observed for talazoparib in the experimental arm in all commers in Part 2 Cohort 1 of Study 1021. Pulmonary embolism and anaemia were the most common SAEs in Study 1006 where patients were treated with talazoparib monotherapy. Anaemia was also the most frequently reported Grade 3 AE together with other haematological toxicities. These observations are in line with the safety particularities observed in the talazoparib + enzalutamide arm in Study 1021. It is noted, particularly pulmonary embolism reported with an incidence rate of 6.3%. This frequency of PE reported for talazoparib monotherapy in Study 1006 in addition to the imbalance of VTE and PE incidence rates observed in Study 1021, disfavouring talazoparib + enzalutamide arm which is reflected in the SmPC.).

2.5.10. Conclusions on the clinical safety

Overall, the safety profile of talazoparib is well characterised and consistent with previous data from talazoparib monotherapy.

However, distinctive for the combination of talazoparib with enzalutamide from the perspective of an elderly study population with metastatic prostate cancer is the higher incidence of anaemia, including high grade. In addition, an increased rate of VTE was observed when talazoparib is given as add-on to enzalutamide.

Additional safety data in HRR-deficient population included in Cohort 2 of the pivotal Study 1021 and supportive Study 1006 one does not suggest a different safety profile from the one seen in Cohort 1 where the majority of patients were HRR-proficient (ca 80%). No signal of increased toxicity-related mortality when talazoparib was administered as add-on to enzalutamide + GNRH analogue was detected.

2.6. Risk Management Plan

The MAH submitted to submit 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 2.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

2.6.1. Safety concerns

Summary Table of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None

Summary of Safety Concerns	
Important Potential Risks	Second primary malignancies (other than MDS/AML)
	Reproductive and developmental toxicity
Missing Information	None

2.6.2. Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance activities to assess effectiveness of risk minimisation measures.

2.6.3. Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
None.	None.	None.
Important Potential Risks		
Second primary malignancies (other than MDS/AML)	Routine risk minimisation measures: SmPC Section 5.3 which provides in-vitro and in-vivo mutagenesis results Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Reproductive and developmental toxicity	Routine risk minimisation measures: SmPC Section 4.4, 4.6 where advice is given regarding use of contraception. PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Pregnancy follow-up questionnaires (Exposure During Pregnancy Supplemental Forms) will be utilized to collect further data on this safety concern. Additional pharmacovigilance activities: None
Missing Information		
None.	None.	None.

2.6.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication is:

> *Talzenna is indicated in combination with enzalutamide for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC), in whom chemotherapy is not clinically indicated.*

3.1.2. Available therapies and unmet medical need

Prostate cancer is the second leading cause of cancer death in men globally and the most common cancer in men in Europe. Approximately 20% of all prostate cancers harbour mutations in HRR genes, either germline or somatic, of which mutations in *BRCA2*, *ATM,* and *CHEK2* are the most common. HRR-mutations confer sensitivity to PARP inhibitors. (Lukashchuk et al, Front. Oncol., 26 June 2023)

The treatment goal for patients with mCRPC is to prolong overall and progression free survival and alleviate tumour associated symptoms while minimising treatment related morbidity. The relative 5-year OS for prostate cancer in general is approximately 85% but is only approximately 31% in the metastatic setting. (American Cancer Society, 2023).

Despite its resistance against ADT, CRPC continues to rely on the androgen receptor-driven transcriptional program, and ADT is normally part of the treatment also for CRPC. Hence, both androgen receptor (AR) inhibitors (*e.g.*, bicalutamide, enzalutamide) and androgen synthesis inhibitors (abiraterone) are used to treat mCRPC and show a benefit in terms of PSA and symptomatic responses, although the level of scientific evidence varies. (Harris et al Front. Endocrinol, 2022).

According to both the European ESMO guidelines and American NCCN guidelines, taxane-containing chemotherapy (docetaxel, cabazitaxel) is an established treatment of mCRPC too, with prolonged OS demonstrated in phase III trials. The side-effects are, however, more pronounced compared with ADT, and include myelosuppression, febrile neutropenia, alopecia, peripheral neuropathy, and peripheral oedema. For palliation of symptomatic bone metastases, local radiation therapy as well as the bone-targeted alpha-emitter radium-223 can be used. There is no optimal sequence or combination of the above-mentioned treatment modalities. Normally, the treatment decisions are based on disease distribution and aggressiveness, previous treatments, comorbidities, and patient preferences.

3.1.3. Main clinical studies

Data to support the current indication are obtained from study C3441021 (Study TALAPRO-2/1021). This is a phase III, multi-centre study, consisting of two parts. Part 1 was an open-label, non-randomised dose finding on patients with mCRPC to determine the starting dose of talazoparib for part 2.

Part 2 was a randomised, double-blind, placebo-controlled study in patients with mCRPC and consisted of two cohorts:

Part 2 cohort 1 constitutes the basis for the current application

This was an all-comers cohort: 805 patients with mCRPC unselected for HRR-mutation status were randomised 1:1 to either talazoparib 0.5 mg + enzalutamide 160 mg once daily (n=4-2) or placebo + enzalutamide 160 mg once daily (n=403). Patients were stratified for HRR-mutation status (deficient vs. non-deficient/unknown) and previous treatment with any NHT or taxane-based chemotherapy. Prior abiraterone treatment for mCSPC was allowed.

Part 2 cohort 2 – HRR-deficient cohort: 397 patients with mCRPC with known HRR-mutations. Analyses on this cohort also included HRR-deficient patients enrolled in cohort 1. This part of the study is still ongoing and not formally part of the current application, but top line data were used to support the results in the HRR-deficient study population in cohort 1.

Primary endpoint was rPFS assessed by BICR. Key secondary endpoint was BICR-assessed OS. Other endpoints were ORR, DoR, PSA response $\geq$50%, time to PSA progression, and PFS2.In the talazoparib + enzalutamide arm, 85/402 (21.1%) patients were HRR-deficient, 207/402 (51.5%) were HRR-proficient, and 110 (27.4%) had unknown HRR status, respectively.

In the placebo + enzalutamide arm, 84/403 (20.3%) patients were HRR-deficient, 219/403 (54.3%) were HRR-proficient, and 102/403 (25.3%) had unknown HRR status, respectively.

3.2. Favourable effects

Part 2, cohort 1 all-comers population

Median rPFS (primary endpoint) was not reached in the talazoparib + enzalutamide arm vs. 21.9 months in the placebo + enzalutamide arm, with HR 0.627 (95% CI 0.506, 0.777), 1-sided p-value <0.0001.

Investigator-assessed rPFS was consistent with the BICR-assessed rPFS.

Median OS (key secondary endpoint) was 36.4 months in the talazoparib + enzalutamide arm vs. NE in the placebo + enzalutamide arm, with HR 0.888 (95% CI 0.693, 1.138), 1-sided p-value 0.1736. OS data from IA2 (approximately 40% maturity) submitted during the procedure showed a median OS of NE in the talazoparib + enzalutamide arm vs. 38.2 months in the placebo + enzalutamide arm, with HR 0.837 (95% CI 0.674, 1.040), 1-sided p-value 0.0537.

Part 2, cohort 1 efficacy results per HRR-mutation status

Median rPFS in the HRR-deficient subpopulation was 27.9 months in the talazoparib + enzalutamide arm vs. 16.4 months in the placebo + enzalutamide arm with an HR of 0.457 (95% CI 0.297, 0.702), 1-sided p-value 0.0001.

OS in the HRR-deficient subpopulation (IA2) was 41.9 months in the talazoparib + enzalutamide arm vs. 30.8 in the placebo + enzalutamide arm with an HR of 0.516 (95% CI 0.320, 0.831), 1-sided p-value 0.0028.

Median rPFS in the HRR-proficient subpopulation was NE in the talazoparib + enzalutamide arm vs. 22.4 months in the placebo + enzalutamide arm. HR 0.695 (95% CI 0.511, 0.944), 1-sided p-value 0.0097)

OS in the HRR-proficient subpopulation (IA2) was NE in the talazoparib + enzalutamide arm vs.38.0 months in the placebo + enzalutamide. HR 0.880 (95% CI 0.654, 1.182), 1-sided p-value 0.1969.

Data from a top line report on HRR-deficient patients in cohort 2 support the data on HRR-deficient patients in cohort 1.

3.3. Uncertainties and limitations about favourable effects

Overall, OS data are still at a maturity of 40%. The impact of talazoparib + enzalutamide treatment on OS is therefore still uncertain, with the exception of the HHR-deficient subgroup. However, the established rPFS gain and the absence of indication of a detrimental OS effect in any of the subgroups supports approvability of the combination in the all-comers population regardless of the HRR gene status. To further characterise the long-term efficacy of talazoparib in combination with enzalutamide in the patients with mCRPC in study C3441021 (TALAPRO-2), the MAH will provide as Annex II.D condition the final OS data analyses in the overall patient population and in all biomarker subgroups (by BRCAm and HRRm status) including rPFS and OS KM curves for all the subgroups by November 2024.

3.4. Unfavourable effects

Overall, the safety profile of talazoparib is well characterised and consistent with previous data from talazoparib monotherapy.

However, a higher incidence of anaemia, including high grade was reported for the combination of talazoparib with enzalutamide considering the elderly study population with metastatic prostate cancer. In addition, a higher incidence of VTE was observed when talazoparib was given as add-on to enzalutamide.

The most frequently reported ADR of Any Grade (>20% of participants) in the talazoparib plus enzalutamide arm of |Study TALAPRO-2 were anaemia (65.8%), neutrophil count decreased (35.7%), fatigue (33.7%), platelet count decreased (24.6%), back pain (22.1%), white blood cell count decreased (22.1%), decreased appetite (21.6%), and nausea (20.6%). The most frequent (>20%) AE in the placebo plus enzalutamide arm was fatigue (29.4%).

In the talazoparib in combination with enzalutamide arm, anaemia led to talazoparib dose interruption in 44.0% of patients, decreased neutrophil count in 13.6%, and decreased platelet count in 7.8%. Discontinuation due to anaemia, neutropenia and thrombocytopenia occurred, respectively, in 8.3%, 3.3% and 0.5% of patients. Among the AESI considered treatment related, imbalance in incidence rate between arms was noticed for venous embolic and thrombotic events, specifically for pulmonary embolism indicating an increased risk for VTE in the experimental arm, when talazoparib was administered in combination with enzalutamide. The numerical imbalance persisted with exposure adjusted data (2.4% vs 0.5%). A warning for VTE, specifically for pulmonary embolism when talazoparib is given in combination with enzalutamide has been included in section 4.4 of the talazoparib SmPC and listed as an ADR in section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 43. Effects Table for study C3441021 part 2, cohort 1 (all-comers population).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Intention-to-treat (ITT) population, n=805 participants						
			Talazoparib + Enzalutamide N=402	Placebo + Enzalutamide N=403		
Radiographic progression-free survival (rPFS, primary endpoint)	The time from date of randomisation to first objective evidence of radiographic progression or death, whichever comes first.	Median, months 95% confidence interval (CI)Months	NR (27.5, NR)	21.9 (16.6, 25.1)	Assessed by blinded independent central review (BICR) Hazard ratio (HR) 0.627 (95% CI 0.506, 0.777) 1-sided p-value <0.0001	
Overall survival (OS, key secondary endpoint)	The time from date of randomisation to death due to any cause	Median, months 95% CI	NR (37.3, NR)	38.2 (34.1, 43.1)	Assessed by BICR HR 0.837 (95% CI 0.674, 1.040) 1-sided p-value 0.0537 OS data are immature (40%). Updated data are required.	
Efficacy results by HRR-mutation status, HRR-deficient subset, n=167 participants						
			Talazoparib + Enzalutamide N=85	Placebo + Enzalutamide N=82		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
rPFS, (primary endpoint)	The time from date of randomisation to first objective evidence of radiographic progression or death, whichever comes first.	Median, months 95% CI	27.9 (16.8, NE)	13.8 (10.9, 19.5)	Assessed by BICR HR 0.424 (0.275, 0.653)1-sided p-value 0.0001 Limited subpopulation.	
OS (secondary endpoint)	The time from date of randomisation to death due to any cause	Median, months 95% CI	41.9 (36.4, NR)	30.8 (25.6, 38.8)	Assessed by BICR HR 0.516 (95% CI 0.320, 0.831) 1-sided p-value 0.0028 OS data are immature.	
Efficacy results by HRR-mutation status, HRR-proficient subset, n=426 participants						
			Talazoparib + Enzalutamide N=207	Placebo + Enzalutamide N=219		
rPFS, (primary endpoint)	The time from date of randomisation to first objective evidence of radiographic progression or death, whichever comes first.	Median, months 95% CI	NR (25.8, NR)	22.4 (16.6, NR)	Assessed by BICR HR 0.695 (95% CI 0.511, 0.944) 1-sided p-value 0.0097	
OS (secondary endpoint)	The time from date of randomisation to death due to any cause	Median, months 95% CI	NR (33.0, NE)	38.0 (33.9, NE)	Assessed by BICR HR 0.888 (95% CI 0.654, 1.182) 1-sided p-value 0.1969 OS data are immature.	
Unfavourable Effects						
TEAEs		%	98.5	94.5	TEAEs All causalities	Study 1021Part 2 Cohort 1
TEAEs Grade ≥3		%	71.9	40.6		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
AEs Grade 5		%	3.3	4.5		
Serious TEAEs		%	39.4	26.7		
TEAEs leading to dose reductions of talazoparib		%	50.5	5.2		
TEAEs leading to interruptions of talazoparib		%	42.5	6.2		
TEAEs leading to discontinuation of talazoparib		%	9.8	2		

Abbreviations:
Notes: OS data from IA2, DCO 28 March 2023; NR: not reached, TEAEs: treatment emergent adverse events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Study TALAPRO-2/1021, Part 2 cohort 1 met its primary endpoint with a statistically significant improvement in rPFS in the talazoparib + enzalutamide arm compared to placebo + enzalutamide. Median rPFS (primary endpoint) was NE in the talazoparib + enzalutamide arm vs. 21.9 months in the placebo + enzalutamide arm, with HR 0.627 (95% CI 0.506, 0.777), 1-sided p-value <0.0001.

Subgroups analysis of rPFS based on the stratification factors showed that this effect is evident in all comer population which included both the HRR-deficient subpopulation and in the larger subpopulation with no HRR-mutation.

Since a key concern for PARP-inhibitors is that BRCA-mutation status as well as HRR status are known as strong effect modifiers with regards to impact on OS, updated OS data for the respective subgroups of patients with and without HRR mutation (including BRCA1/2 mutations) were submitted at a maturity of approximately 40%. The median OS was not reached (NR) in the talazoparib + enzalutamide arm vs. 38.2 months in the placebo + enzalutamide arm, with HR 0.837 (95% CI 0.674, 1.040), 1-sided p-value 0.0537. For the HRR-proficient population where effects are anticipated to be smaller the point estimate was around 0.9, in line with the recent PARP inhibitor approved in the same treatment niche Lynparza (EMEA/H/C/003726) and Akeega EMEA/H/C/005932. The established rPFS gain and the absence of indication of a detrimental OS effect in any of the subgroups supports approvability of the combination in the all-comers population regardless of the HRR gene status.

The MAH will provide the final OS data from study C3441021 (TALAPRO-2) in the overall patient population (see Annex II).

The safety profile of talazoparib in patients with mCRPC not selected for HRR status in Part 2 cohort 1 of Study TALAPRO-2/1021, is generally consistent with previous safety data from monotherapy studies in other indications.

3.7.2. Balance of benefits and risks

Talzenna in combination with enzalutamide has demonstrated a statistically significant and clinically relevant improvement in rPFS in adult patients with mCRPC in whom chemotherapy is not clinically indicated.

This effect is evident in both the HRR-deficient subpopulation and in the larger subpopulation with no HRR-mutation.

Even though there are currently uncertainties on the magnitude of the benefit in terms of OS in the non-HRRm patients, the results are considered clinically relevant and sufficient to conclude on clinical benefit in the intended treatment setting. The MAH will submit the final OS data from study C3441021 (TALAPRO-2) to further characterise OS as a post authorisation efficacy study (PAES).

Overall the safety profile of talazoparib in patients with mCRPC not selected for HRR status in Part 2 cohort 1 of Study TALAPRO-2/1021, is generally consistent with previous safety data from monotherapy studies in other indications.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The benefits of Talzenna outweigh the risks in the following indication: Talzenna is indicated in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.

The following measures are considered necessary to address issues related to efficacy:

Post authorisation efficacy study (PAES)**:** In order to further characterize the long-term efficacy of talazoparib in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated, the MAH should submit the final results of study C3441021 (TALAPRO-2) including the final OS data analyses in the 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 CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus the granting of an extension of the marketing authorisation for Talzenna new strength: 0.1 mg hard capsules. As a consequence, sections 1, 2, 3, 6.1, 6.3, 6.5, 8 of the SmPC are updated.

In addition, CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change:

Variation(s) requested		Type	Annex(es) 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	II	I, II, and IIIB

Extension of indication for Talzenna in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet are updated in accordance. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. Version 2.0 of the RMP is approved.

The CHMP therefore recommends the extension of the marketing authorisation for Talzenna subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post authorisation efficacy study (PAES): In order to further characterize the long-term efficacy of talazoparib in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated, the MAH should submit the final results of study C3441021 (TALAPRO-2) including the final OS data analyses in the overall patient population and in all biomarker subgroups (by BRCAm and HRRm status) including rPFS and OS KM curves for all the subgroups.	November 2024