TALZENNA (TALAZOPARIB) RISK MANAGEMENT PLAN

RMP Version number: 2.0

Data lock point for this RMP:

Clinical Trial (CT) DLP: 16 August 2022 - Post-marketing (PM) DLP: 15 October 2022

Date of final sign off: 31 October 2023

Rationale for submitting an updated RMP:

The RMP was updated to support the planned submission of a new indication of talazoparib in combination with enzalutamide in patients with metastatic castration resistant prostate cancer (mCRPC) based on study TALAPRO-2/C3441021 "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Talazoparib with Enzalutamide in Metastatic Castration-Resistant Prostate Cancer".

Following the receipt of the CHMP day 120 list of questions related to Procedure No. EMEA/H/C/004674/X/015/G, the MAH is complying with the request to reclassify the important potential risk of Myelodysplastic syndrome/Acute myeloid leukaemia (MDS/AML) as identified risk (not important) and is thus removing it from the RMP.

Following the receipt of the CHMP day 180 list of outstanding issues related to Procedure No. EMEA/H/C/004674/X/015/G, the MAH is complying with the request to include study C3441021 (TALAPRO-2) as post-authorisation efficacy study to further characterise the long-term efficacy of talazoparib in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

Summary of significant changes in this RMP:

- Part I: Updated to include the proposed new indication of mCRPC, the new strength of 0.1 mg hard capsules, and updated ATC code for talazoparib in line with the revised classification of the Poly (ADP-ribose) polymerase (PARP) inhibitors made by the WHO and published on 17 December 2020.
- Part II
    - Module SI: Updated with epidemiology for the proposed indication
    - Module SII: Removal of the important potential risk of MDS/AML.
    - Module SIII: Updated data up to the DLP of 16 August 2022 and inclusion of data from studies TALAPRO-2/C3441021, TALAPRO-1/C3441006 (A Phase 2, open-label, response rate study of talazoparib in men with DNA repair defects and metastatic castration resistant prostate cancer who previously received taxane-based chemotherapy and progressed on at least 1 novel hormonal agent (enzalutamide

and/or abiraterone acetate/prednisone)"[a] and completed study NEOTALA/C3441020 (A Phase 2, Non-Randomized, Open-Label, Single-Arm, Multi-Center Study of Talazoparib for Neoadjuvant Treatment of Germline BRCA1/2 Mutation Patients With Early Human Epidermal Growth Factor Receptor 2 Negative Breast Cancer).

- Module SIV: data from clinical trials updated where applicable
- Module SV: updated up to the DLP of 15 October 2022
- Module SVII.2: reclassification of the important potential risk of MDS/AML as an identified risk
- Module SVII.3: with data up to the respective DLPs of each study CSRs for the CT data and up to the DLP of 15 October 2022 for the PM data. Removal of the important potential risk of MDS/AML.
- Module SVIII: Removal of the important potential risk of MDS/AML.

- Part IV was updated to include study C3441021 (TALAPRO-2) as post-authorisation efficacy study in order to further characterise the long-term efficacy of talazoparib in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated as requested in CHMP 180 list of outstanding issues (Procedure no. EMEA/H/C/004674/X/015/G).

- Part VI and Part VII (Annex 8) were updated to reflect all relevant changes described above.

- Annex 4 was updated with the current version of the form and Annex 7 with search terms included in MedDRA version 25.0.

- Annex 5 was updated to include information about study C3441021 (TALAPRO-2).

Other RMP versions under evaluation: None.

Details of the currently approved RMP:

Version number: 1.0

Approved with procedure: EMEA/H/C/004674/II/0001

Date of approval (opinion date): 28 May 2020 (decision adopted on 26 June 2020)

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

[a] This study is still ongoing, but a clinical study report (dated 04 January 2021) was issued after the primary completion date (04 September 2020).

LIST OF ABBREVIATIONS

ADP	Adenosine diphosphate
ADR	Adverse Drug Reaction
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukaemia
AST	Aspartate Aminotransferase
AR	Androgen Receptor
AUC	Area under the plasma concentration-time curve
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene
BSA	Body surface area
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
C_{max}	maximum plasma concentration
CNS	Central Nervous System
(n)mCRPC	(non) metastatic Castration Resistant Prostate Cancer
CSR	Clinical Study Report
CT	Clinical trial
CTCAE	Common Terminology Criteria for AEs
CTIBL	Cancer Treatment-Induced Bone Loss
DDR	DNA Damage Repair
DLP	Data lock point
ECG	Electrocardiography
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European public assessment report
ESMO	European Society for Medical Oncology
EU	European Union
EU-28	28 States of the European Union
FDA	(US) Food and Drug Administration
gBRCAm	germline BRCA mutated
GI	gastrointestinal
GLOBOCAN	Global Cancer Observatory of the International Agency for Research on Cancer
ICH	International conference on harmonisation
HER2	Human Epidermal Growth Factor Receptor 2
hERG	Human Ether-a-go-go-Related Gene
HR	Hormone Receptor
HRR	Homologous recombination repair
HzR	Hazard Ratio
MAH	Marketing Authorisation Holder

MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	mammalian Target Of Rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHT	Novel hormonal therapy
OS	Overall survival
PC	Prostate Cancer
PCT	Physician's Choice Treatment
PAES	Post-authorisation efficacy study
PARP	Poly ADP Ribose Polymerase
PARPi	PARP inhibitors
(r)PFS	(radiographic) Progression Free Survival
PFS	Progression Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PL	Package Leaflet
PM	Post-marketing
POPPK	Population pharmacokinetics
PSA	Prostate-specific Antigen
PSADT	PSA doubling times
PT	Preferred Term
PY	Person Years
QD	Quaque die
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SPM	Secondd primary malignancy
SPP	Specialty Pharmacy
TALA	Talazoparib
TEAE	Treatment-Emergent Adverse Event
TNBC	Triple Negative Breast Cancer
TTP	Time to Progression
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VTE	Venous Thromboembolism

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PART I. PRODUCT OVERVIEW

Active substance **(INN or common name)**	Talazoparib
Pharmacotherapeutic group (ATC Code)	L01XK04
Marketing Authorisation Holder (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Talzenna®
Marketing authorisation procedure	Centralised
Brief description of the product:	<u>Chemical class</u> Potent, small-molecule inhibitor of poly adenosine diphosphate (ADP)-ribose polymerase (PARP) enzymes.
	<u>Summary of mode of action</u> Talazoparib (TALA) is a potent inhibitor of PARP enzymes, PARP1 and PARP2. PARP enzymes are involved in cellular DNA damage response signalling pathways such as DNA repair, gene transcription, cell cycle regulation and cell death. PARP inhibitors (PARPi) exert cytotoxic effects on cancer cells by 2 mechanisms, inhibition of PARP catalytic activity and by 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 leading to apoptosis and/or cell death. The potent cytotoxicity observed with talazoparib against multiple tumour cell lines harbouring mutations in the DNA Damage Repair (DDR) pathways, can be attributed to its inhibition of PARP catalytic activity and robust PARP trapping. The combination of a PARP inhibitor and androgen receptor signalling inhibitor (ARSi) has been identified as a mechanism-based interaction that expands the functional state of sensitivity to broader inhibition of homologous recombination DNA repair mechanisms. AR signalling inhibition suppresses the expression of homologous recombination repair genes including BRCA1, resulting in sensitivity to PARP inhibition. PARP1 activity has been shown to be required for maximal AR function and thus

	inhibiting PARP may reduce AR signalling and increase sensitivity to AR signalling inhibitors. Clinical resistance to AR blockade is sometimes associated with co-deletion of retinoblastoma RB1 and BRCA2, which is in turn associated with sensitivity to PARP inhibition.
	Important information about its composition None
Hyperlink to the Product Information:	Please refer to Module 1.3.1
Indications in the EEA	Current: Talazoparib is indicated as monotherapy for the treatment of adult patients with germline breast cancer susceptibility gene (BRCA)1/2-mutations, who have Human epidermal growth factor receptor 2 (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. 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.
	Proposed: Talazoparib is indicated as monotherapy for the treatment of adult patients with germline Breast cancer susceptibility gene (BRCA)1/2-mutations, who have Human epidermal growth factor receptor 2 (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. 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. Talazoparib 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.

Dosage in the EEA	Current: *Talzenna monotherapy (breast cancer)* The recommended dose is 1 mg talazoparib once daily. Patients should be treated until disease progression or unacceptable toxicity occurs. Proposed: *Talzenna monotherapy (breast cancer)* The recommended dose is 1 mg talazoparib once daily. Patients should be treated until disease progression or unacceptable toxicity occurs. *Talzenna in combination with enzalutamide (prostate cancer)* The recommended dose is 0.5 mg talazoparib in combination with 160 mg enzalutamide once daily. Patients should be treated until disease progression or unacceptable toxicity occurs. Missing dose If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. See Summary of Product Characteristics (SmPC) for talazoparib for further details (i.e dose adjustment recommendations for managements of adverse reactions, concomitant treatment with P-pg inhibitors, dose adjustments in special populations).
Pharmaceutical form and strengths	Current: Hard capsules of the following strengths: 0.25 mg and 1 mg
	Proposed: Hard capsules of the following strengths: 0.1 mg, 0.25 mg, and 1 mg
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indications and Target Populations

Indication: locally advanced or metastatic breast cancer

Talazoparib is a potent, small-molecule inhibitor of PARP enzymes, PARP1 and PARP2. PARP enzymes are involved in cellular DNA damage response signalling pathways such as DNA repair, gene transcription, cell cycle regulation and cell death. PARP inhibitors (PARPi) exert cytotoxic effects on cancer cells by two mechanisms, inhibition of PARP catalytic activity and by 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 leading to apoptosis and/or cell death. The potent cytotoxicity observed with talazoparib against multiple tumour cell lines harbouring mutations in the DDR pathways, can be attributed to its inhibition of PARP catalytic activity and robust PARP trapping.

Talazoparib is indicated as monotherapy for the treatment of adult patients with germline (BRCA)1/2-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.

Patients with HR-positive breast cancer should have been treated with a prior endocrine-based therapy or be considered unsuitable for endocrine-based therapy.

Literature search strategy: The US National Library of Medicine PubMed database was searched for primary literature and review articles reporting the incidence, prevalence, and mortality estimates and demographic profile of gBRCAm HER2- locally advanced or metastatic breast cancer[b] through 25 January 2018. Searches were confined to English language articles involving humans. Priority was given to data from the EU and North American populations; however, relevant estimates from other regions (eg, Asia) were also included, where appropriate.

While the indication for talazoparib is gBRCAm HER2- locally advanced or metastatic breast cancer, the epidemiology of gBRCAm breast cancer, has been included where literature on gBRCAm HER2- breast cancer was not available, as the vast majority of gBRCAm breast cancers are HER2-.[1]

Incidence

Breast cancer is the most common invasive cancer in women worldwide, representing 25.2% of new cancer cases, with nearly 1.7 million cases diagnosed in 2012.[2] In the 28 States of the

[b] The following search terms were used to characterize the epidemiology of gBRCAm HER2- locally advanced or metastatic breast cancer: (Breast Neoplasms AND ("BRCA" OR Genes, BRCA1 OR Genes, BRCA2) AND ("advanced" OR "metastatic")) AND (Epidemiology OR Incidence OR Prevalence OR Epidemiologic Factors OR Risk Factors OR Mortality OR Morbidity)

European Union (EU-28), there were an estimated 361,608 new cases of female breast cancer in 2012, corresponding to an age-adjusted annualized incidence of 80.3 per 100,000 females.[3] In the US, there were an estimated 255,180 new breast cancer cases (females: 252,710; males: 2,470) in 2017.[4] The age-adjusted annualized incidence was 124.9 per 100,000 females, representing 15% of all new cancer cases.[5]

No studies were identified that reported incidence rates for gBRCAm locally advanced or metastatic breast cancer. However, several population-based studies were identified that evaluated the proportion of gBRCA mutation in invasive breast cancers, without regard to stage. These results are summarized in Table 1.[6-12] Most of these studies were conducted in populations with a predisposition for gBRCAm, such as younger women, women with a family history of breast or ovarian cancers, or women referred for genetic testing. In a Danish study of women with breast cancer who were referred to clinical genetics for testing, 17.2% had a gBRCA mutation.[8] Among populations of women enriched for genetic risk factors, such as early age of onset or family history, the prevalence of gBRCAm ranged from 4.1% to 9.1%.[6,7,9-12] One US study reported that 4.2% of women with breast cancer and no affected first or second degree relatives had gBRCAm.[11] In the same study, 8.3% of women with breast cancer and a first or second degree relative had gBRCAm.[11]

Table 1. Proportion of gBRCA Mutations in Breast Cancer Patients in Population-based Studies

Region or Country	Study Years	N	Study Design/ Data Source	Study Population	gBRCAm
International: Canada, US, and Australia[6]	1995-2000	3220	Population-based cohort study/ cancer registries	Women with invasive breast cancer with evidence for increased genetic susceptibility	5.1% (n=165)
International: US and Denmark[7]	1985-2000	1394	Population-based, case-control study/ cancer registry	Women aged <55 with unilateral localized invasive breast cancer	5.2% (n=73)
Denmark[8]	2004-2011	523	Population-based cohort study /medical registries	Women with breast cancer who were referred to clinical genetics for gBRCAm testing	17.2% (n=90)
France[9]	1995-1997	232	Prospective population-based cohort study/ breast cancer registry	Women aged <46 with early onset invasive breast cancer	9.1% (n=21)
UK[10]	1992-1993	254	Population-based, case-control study/ cancer registries	White women aged <36 with early onset breast cancer diagnosis between 1982-1985	5.9% (n=15)
		363	Population-based, case-control study/ cancer registries	White women aged 36-45 with early onset breast cancer diagnosis between 1988-1989	4.1% (n=15)

Table 1. Proportion of gBRCA Mutations in Breast Cancer Patients in Population-based Studies

Region or Country	Study Years	N	Study Design/ Data Source	Study Population	gBRCAm
US[11]	1994-1998		Population-based case-control study/ cancer registries and hospital records	White and Black women aged 35-64 with invasive breast cancer	
		1628		Sample enriched for family history	5.9% (n=96)
		429		No family history of breast cancer	4.2% (n=18)
		860		Affected first or second degree relative	8.3% (n=71)
US[12]	1989-1994	54	Population-based series/ hospital and health-care facility records	Men with breast cancer	3.7% (n=2)[a]

a. No gBRCA1 mutations were identified.

The lack of robust population-based estimates of the proportions of breast cancers that are gBRCAm precludes estimating the incidence using annualized US or EU incidence rates.

Prevalence:

In the EU-28, the 1-, 3-, and 5-year age-adjusted prevalence of female breast cancer in 2012 was 147.2 per 100,000, 416.1 per 100,000, and 654.0 per 100,000, respectively.[3] In the US, the overall estimated prevalence of breast cancer in 2014 was 3,346,387 (females: 3,327,552; males: 18,835).[4]

Prevalence rates per unit population for persons living with cancer vary substantially depending on the interval considered since the initial cancer diagnosis, as seen in EU-28 age adjusted prevalences above. Interval-specific prevalence rates will vary substantially by stage at diagnosis and cancer subtype. For instance, survival rates are shorter for advanced stage and more aggressive subtypes of breast cancer. Furthermore, prevalence rates are subject to period effects (as new treatments become available, survival rates for specific stages/subtypes may increase). Because the talazoparib target population is advanced stage gBRCAm/HER2-negative breast cancer, and because period effects will likely affect this subgroup of breast cancer patients due to the evolving treatment standards and recent anticipated approval of new targeted cancer treatments for this subgroup, estimating period prevalence rates for advanced stage gBRCAm/HER2-negative breast cancer, in the same way incidence rates were estimated, is likely to be substantially flawed. As such, no prevalence rates per unit population were estimated.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age

Patients with gBRCAm breast cancer tend to be younger in age compared to those with non-gBRCAm breast cancer. A few studies described in Table 1 reported the mean age at diagnosis or age distribution for gBRCAm breast cancer.

In an international population-based cohort study of 3220 women with incident breast cancer and suspected genetic susceptibility, the mean age of diagnosis was 39.9 and 42.2 for gBRCA1 or gBRCA2 mutation carriers, respectively and 45.7 among women in the study were found to have sporadic disease.[6] In a Danish study of women with breast cancer, in the subset found to have gBRCAm, 67.8% were aged less than 50, 16.7% between ages of 50-59, 14.4% between ages of 60-69, and 1.1% age 70 or older.[8] In France, among women of age less than 41 with a breast cancer diagnosis, 12.8% were gBRCA mutation carriers, in contrast to 5.2% of women diagnosed between the ages of 41 and 45 years.[9] Among women diagnosed with breast cancer in the UK, 5.9% of women aged less than 36 were gBRCAm, as were 4.1% of women between the ages of 36-45.[10] In a US study that included women diagnosed with gBRCAm breast cancer between the ages of 35-64, 65.6% were between the age of 35-44 at diagnosis, while 34.4% were between the age of 45-64.[11]

Gender

No studies were identified that examined the gender distribution of gBRCAm breast cancer. The vast majority of breast cancers occur in women and thus the majority of cancer registries and publications report information only for female breast cancer. Therefore, in general the information described for the overall breast cancer incidence reflects the rates for women.

Less than 1% of all breast cancers occur among males.[4]

Race/Ethnicity/Ancestry

No studies were identified that reported the incidence or prevalence of gBRCAm breast cancer by race, ethnicity, or ancestry. One study of patients from 5 population-based breast cancer registries (four US-based; one Denmark-based) found that 87.7% of women with unilateral invasive gBRCAm breast cancer were White, 5.5% were Hispanic White, and 5.5% were Black.[7]

A study of Black and White women diagnosed with gBRCAm breast cancer between age 35 and 64 in the US found that 60.4% were White (non-Jewish), 27.1% of women with gBRCAm breast cancer were Black, and 12.5% were White (Jewish), accounting for the sampling scheme.[11]

Risk Factors

Major risk factors for gBRCAm breast cancer include BRCA mutations, familial breast cancer, Ashkenazi Jewish ancestry, and younger age. The lifetime risk of breast cancer in

BRCA mutation carriers ranges from 46%-87% in females and 1%-7% in males, with greater lifetime risks in female BRCA1 carriers and male BRCA2 carriers.[13-19]

Major risk factors for breast cancer in general include being female, older age, non-Hispanic White race/ethnicity, family history of breast cancer, being overweight/obese, moderate to high consumption of alcohol, low physical activity, and exposure to reproductive hormones (either endogenous or exogenous).[20,21]

The main existing treatment options:

Platinum-based chemotherapy, including cisplatin or carboplatin, has demonstrated anticancer activity in gBRCAm breast cancer with TTP or prolongation of progression free survival (PFS) ranging from 6.8 to 12 months and overall response rates ranging from 68% up to 89%.[22-24] Overall survival in patients treated with cisplatin was 80% at 1 year, 60% at 2 years, and 25% at 3 years with a median survival from the start of cisplatin treatment of 30 months.[22] Based on these and other findings, physicians are increasingly using platinum therapy early in the treatment of metastatic breast cancer, as well as in the neoadjuvant/adjuvant setting. However, platinum-based chemotherapy can cause substantial side effects, including bone marrow suppression (thrombocytopenia, leukopenia), nephrotoxicity, neuropathy, ototoxicity, and gastrointestinal toxicities.

Promising results were also recently reported for the PARP inhibitor olaparib in the OlympiAD trial in gBRCAm, HER2-negative advanced breast cancer (N=302 patients)[25] and were the basis of olaparib's approval by the US FDA for the treatment of patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have previously received treatment with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Based on blinded independent central review assessments, olaparib prolonged PFS compared with physician's choice of single-agent capecitabine, eribulin, or vinorelbine (HzR=0.58 [95% CI: 0.43, 0.80] p<0.001; 7.0 vs 4.2 months).[25] The response rate was higher in the olaparib arm (59.9% [95% CI: 52.0, 67.4]) than in the physician's choice arm (28.8% [95% CI: 18.3, 41.3]). However, median duration of response was slightly shorter in the olaparib arm than the physician's choice arm (6.4 vs 7.1 months). Survival did not differ significantly between arms (19.3 vs 19.6 months).[25] These results demonstrate proof of concept for the benefit of PARP inhibition in the treatment of gBRCAm metastatic breast cancer and led to the US approval of olaparib in January 2018 for this indication.

The utility of PARP inhibitors for the treatment of gBRCAm cancers is further supported by results for olaparib and rucaparib in the treatment of patients with gBRCAm ovarian cancer who were treated with at least 2 or 3 prior lines of chemotherapy.[26,27] Furthermore, olaparib and niraparib are indicated for maintenance treatment of patients with recurrent ovarian cancer who are in a complete or partial response to platinum.[26,28]

Several treatment options are approved for hormone receptor-positive, HER2-negative breast cancer, without specification of BRCA mutation status. Endocrine therapy or aromatase inhibitors in combination with a CDK 4/6 inhibitor are recommended first-line therapies,

according to the current clinical practice guidelines from the ESMO and the National NCCN.[23,29,30]

For second-line treatment and beyond, endocrine agents are used in different combinations and sequences that may also include single-agent abemaciclib or chemotherapies.[23,31] Combinations may include an aromatase inhibitor or fulvestrant with a CDK4/6 inhibitor, a mammalian target of rapamycin (mTOR) inhibitor, or tamoxifen.[23,31-33] The treatment choice is based on menopausal status, prior adjuvant and first-line treatments, and the toxicities and response to those treatments.

Chemotherapy with single-agents or combination regimens is considered for first-line or subsequent therapy for patients with symptomatic visceral disease or endocrine resistance.[23,29] Based on their efficacy/safety profiles and dosing schedules, the preferred chemotherapy agents are anthracyclines (doxorubicin), taxanes (paclitaxel), other microtubule inhibitors (eribulin, vinorelbine), and antimetabolites (capecitabine, gemcitabine). Sequential single-agent chemotherapies are a recommended treatment option. Capecitabine and eribulin are approved in the EU for the treatment of advanced breast cancer.

Combination chemotherapy is also used as it tends to have higher response rates than single agents, but it also causes more toxicity without increasing survival substantially.[23,29]

Metronomic chemotherapy is also recommended[23,34]. The use of low doses of chemotherapy agents for short intervals can control disease with lower toxicity than standard regimens.[34]

Metastatic triple negative breast cancer has primarily been treated with various cytotoxic chemotherapy regimens for advanced/metastatic disease, ie anthracyclines and taxanes. However, platinum therapy is increasingly being used early in the treatment of metastatic breast cancer (Study 673-201, CSR Section 7.1), and carboplatin was recently added to the ESMO treatment guidelines for patients with BRCA-mutated TNBC.[22-24] PARP inhibitors such as olaparib and talazoparib are recommended for patients with germline BRCA mutated, HER2 negative metastatic breast cancer. More recently, immune-targeted therapies, such as pembrolizumab in combination with chemotherapy was approved for the treatment of locally recurrent unresectable or metastatic TNBC in patients whose tumours express PD-L1 with a combined positive score (CPS) ≥10 and who have not received prior chemotherapy for metastatic disease.[35]

Overall, despite recent improvements in duration of PFS and overall survival in unselected populations, treatments for BRCA-mutated breast cancer remain a high unmet medical need. Although platinum treatment has demonstrated encouraging response rates in BRCA-mutated advanced cancer, it also causes substantial toxicities. A more tolerable agent is needed. PARP inhibitors are a targeted therapy causing single-strand DNA damage to which BRCA-mutant bearing breast cancer cells with DNA repair deficiencies are more vulnerable than normal cells carrying 1 normally functioning BRCA allele. Thus, PARP inhibitors may represent a significant advance over existing therapies that cause significant toxicities. The recent approval of olaparib in the US demonstrates proof of concept for the benefit of PARP inhibition in the treatment of gBRCAm metastatic breast cancer.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Important complications for patients with advanced breast cancer include thromboembolic events and osteoporosis/bone fracture/low bone mineral density

Thromboembolic Events

A systematic review of 38 cohort studies published between 1966 and 2011 in patients diagnosed with one of 8 cancers, including breast, found an incidence rate of hospitalization for VTE of 55 per 1000 PY among breast cancer patients at high risk of developing VTE, defined as those with metastatic disease or receiving types of high-risk treatments, and 5 per 1000 PY among breast cancer patients at average risk of VTE. The incidence rate among breast cancer patients overall was 21 per 1000 PY.[36] One study included in the review reported that the incidence rate of VTE among breast cancer patients was 2.87-times higher than the general population.[37]

The incidence of pulmonary embolism in an outpatient cohort of oncology patients (n=13,783) who had imaging studies from 2004-2009 in the US was 1.50% (95% CI 1.02, 2.11) in breast cancer patients.[38]

Osteoporosis/Bone Fracture/Low Bone Mineral Density

Up to 80% of women with breast cancer develop "CTIBL" during treatment due to the consequences of depletion of endogenous oestrogen.[39-41] Breast cancer patients also have a 5-fold increased risk of fracture compared to women who are cancer-free.[42,43]

Mortality

The female breast cancer mortality rate in Europe (EU-28) is 15.5/100,000.[3] In the US, breast cancer is the third leading cause of cancer death in women, with a mortality rate across all breast cancer types of 21.2 per 100,000 women per year.[5] The median age at death from breast cancer is 68 years, and 80.7% of all breast cancer deaths occur at ages 55 and older. The 5-year relative survival for localized disease is 98.9%, 85.2% for regional disease, 26.9% for distant disease.

In a large prospective cohort, the overall survival among gBRCAm compared to gBRCA wild type women aged ≤40 years with invasive breast cancer recruited from 127 hospitals in the UK did not differ (HzR 0.96, 95% CI 0.76-1.22, p=0.76).[44] The 2, 5, and 10 year overall survival estimates for women with gBRCAm breast cancer were 97.0% (95% CI 94.5–98.4), 83.8% (95% CI 79.3–87.5), and 73.4% (95% CI 67.4–78.5), respectively. Similarly, in a recent systematic review of 16 studies comprising of 10,180 individuals with breast cancer, gBRCAm breast cancer was not associated with worse overall survival (HzR 1.06, 95% CI 0.84-1.34, p=0.61).[45]

A population-based study analysed the distribution, clinic-pathological features, survival and excess risk of death among women diagnosed with breast cancer classified by molecular subtype in 10 Spanish-based cancer registries.[46] The 1-, 3- and 5-year relative survival rates

were estimated as the ratio of observed survival in the study population to the survival reported in the general population of the same age, sex, year and province. Among 3480 incident breast cancers diagnosed mainly in 2005, 2771 (79.6%) had molecular subtype data. The 1-, 3-, and 5-year relative survival was highest among women with HR-positive, HER2-negative breast cancer (Table 2). Similar, survival estimates for breast cancer subtypes from the Swiss Ticino Cancer Registry were reported.[47]

Table 2. Relative survival rates at 1, 3, and 5 years, by breast cancer subtype (all stages)

Molecular Subtype	1 Year (95% CI)	3 Year (95% CI)	5 Year (95% CI)
HR-positive, HER2-negative	98.8 (98.1–99.5)	95.4 (94.0–96.8)	91.5 (89.5–93.5)
HR-positive, HER2-positive	97.3 (95.2–99.4)	90.4 (86.7–94.3)	85.8 (81.2–90.7)
HER2-overexpressed (ER-negative, PR-negative, HER2-positive)	95.8 (92.7–99.1)	87.2 (81.9–92.8)	78.6 (72.0–85.8)
Triple-negative (ER-negative, PR-negative, HER2-negative)	93.2 (90.3–96.3)	79.8 (75.2–84.7)	76.3 (71.1–81.8)
Unclassified	87.3 (84.6–90.0)	81.0 (77.6–84.6)	77.0 (72.7–81.4)
Overall	95.7 (94.9–96.5)	90.1 (88.9–91.4)	85.9 (84.3–87.5)

CI: Confidence Interval
HR-positive: ER+ and/or HR+; ER: Estrogen Receptor; PR: Progesterone Receptor

Important co-morbidities:

Important co-morbidities of breast cancer include: hypertension, arthritis, thyroid problem, hypercholesterolemia and hyperlipidemia, previous solid tumour, diabetes, GI disorders or GERD, heart disease, respiratory disease, psychiatric disease, and secondary cancer.[48,49]

An important co-morbidity for gBRCAm breast cancer is ovarian cancer.[50]

Proposed Indication: Metastatic Castration-Resistant Prostate Cancer

Prostate cancer is a disease primarily of older men, with an average age at diagnosis in the mid-sixties and rarely diagnosed before the age of 40.[51] PC typically has an indolent course, and many men may die from other causes first, but it is nevertheless a leading cause of death in many areas of the world.[51]

Recent treatment advances may contribute to declines or stabilization in mortality in many countries.[51] However, treatment of active disease and its symptoms, side effects, and the high prevalence of comorbidities in older men with PC is burdensome – to the patient and his quality of life, as well as economically.[52]

About 77% of men with PC are diagnosed with localized disease.[53] Metastatic castration-resistant PC (mCRPC) is an advanced form of PC that does not respond to initial treatments and has spread beyond the prostate. mCRPC prevalence in PC has been estimated between 1.2% and 2.1% based on two studies, one from the US and one from the UK.[54] Studies on the epidemiology of mCRPC are scarce, in part due to varying terminology, definition, and disease management.[55]

The combination of a PARP inhibitor and androgen receptor signalling inhibitor (ARSi) has been identified as a mechanism-based interaction that expands the functional state of sensitivity to broader inhibition of homologous recombination DNA repair mechanisms. AR signalling inhibition suppresses the expression of homologous recombination repair genes including BRCA1, resulting in sensitivity to PARP inhibition. PARP1 activity has been shown to be required for maximal AR function and thus inhibiting PARP may reduce AR signalling and increase sensitivity to AR signalling inhibitors. Clinical resistance to AR blockade is sometimes associated with co-deletion of retinoblastoma RB1 and BRCA2, which is in turn associated with sensitivity to PARP inhibition.

Summary of Literature Search Methods

A literature review was conducted to evaluate the epidemiology of mCRPC among adults in Europe and the US. PubMed was searched to identify published articles that contained potentially relevant information on the epidemiology of mCRPC from January 2002 through March 2022. Keywords related to incidence, prevalence, morbidity, mortality, natural history, risk factors and comorbidities were combined with terms representing mCRPC.

Iterative unstructured searches of PubMed and Google were further conducted in September 2022 on mCRPC as well as PC epidemiology. Important citations referenced within reviewed articles were obtained if relevant.

For PC incidence and prevalence, the GLOBOCAN database (https://gco.iarc.fr/) and the NCI SEER Program database (https://seer.cancer.gov/) were queried; mCRPC data are not available in these resources.

This work represents a targeted, not systematic, review of the literature.

Incidence:

In 2020, PC was the fourth most commonly diagnosed cancer in the world and the second most commonly diagnosed cancer among men globally.[56] An estimated 1,414,259 new PC cases were diagnosed worldwide in 2020, representing 7.3% of all new cancer cases across both men and women.[56] The global age-standardized incidence rate is 30.7 per 100,000 males annually[56], and varies substantially by region, ranging from 6.3 per 100,000 males annually in South-Central Asia to 83.4 per 100,000 males annually in Northern Europe. [57]

<u>Europe</u>

In 2020, PC was the fourth most commonly diagnosed cancer on the European continent overall[58], and the most commonly diagnosed cancer on the European continent among men, with an age-standardized incidence of 63.4 per 100,000 males[59] and 198.0 per 100,000 males age ≥40[60]. Among EMA member states, PC incidence ranged from 41.5 per 100,000 males (129.8 per 100,000 males age ≥40) in Romania to 110.7 per 100,000 males (345.7 per 100,000 males age ≥40) in Ireland[61,62]. Incidence rates have decreased or stabilized in most (especially high-income) European countries over the last decade.[63] A decline in PSA testing may be at least partially responsible for this trend.[63]

Data on the incidence of mCPRC are scarce. One French study noted the incidence of mCPRC as approximately 21 per 100,000 men aged ≥40 years in 2014.[64] That study found

that incidence of mCRPC increased with increasing age, with <1 case per 100,000 in men aged 40-49 years, peaking at 175 per 100,000 men aged 80-89.

US

In 2020, PC was the third most diagnosed cancer in the US[65], and the most diagnosed cancer in the US among men, with an age-standardized incidence of 72.0 per 100,000 males[66], 224.9 per 100,000 males age ≥40.[67] There has been a decreasing incidence of PC overall by about 6.5% per year since 2007, but an increasing incidence of later-stage PC, with an annual percent change measured from 2010-2017 of about 5.1%. [53,68,69]

There were no studies identified that measured the incidence of mCPRC in the US.

Prevalence:

In 2020, PC was the third most prevalent cancer in the world; the worldwide 5-year limited duration prevalence of PC (people living with PC who were diagnosed in the last 5 years) was 126.1 per 100,000 males, or 4,956,901 cases, representing 9.8% of all prevalent cancer cases diagnosed in the previous year.[70] The global 5-year limited duration prevalence varies substantially by region, ranging from 12.0 per 100,000 males in South-Central Asia to 735.4 per 100,000 males in Northern Europe.[71]

Incidental PC studies (based on autopsies of men who died from causes other than PC) suggest that indolent PC is widely prevalent, found in nearly 6 of every 10 autopsies in men aged >79 years.[72,73]

Europe

In 2020, PC was the second most common cancer on the European continent overall[74], and the most common cancer on the European continent among males, with a 5-year limited duration prevalence of 518.1 per 100,000 males annually, or 1,873,814 cases.[75] Among EMA member states, 5-year limited duration PC prevalence ranged from 319.8 per 100,000 males (613.0 per 100,000 males age ≥40) in Romania to 905.5 per 100,000 males (1,804.1 per 100,000 males age ≥40) in Sweden.[76,77]

One French study reported that mCRPC was present in 62 per 100,000 men aged ≥ 40 years, in 2014, when age-standardized.[64]

US

In 2020, PC was the second most common cancer in the US overall and the most common cancer in the US among males, with a 5-year limited duration prevalence of 496.0 per 100,000 males annually (1,070.9 per 100,000 males age ≥40), or 812,431 cases (812,229 cases in males age ≥40).[78,79]

An analysis of US managed care claims reported that the prevalence of mCPRC was 20 per 100,000 male enrollees in 2017.[80] This prevalence is lower than other estimates, likely due to the inclusion of males <40 years. Among those with PC, the prevalence of mCRPC was 1140 per 100,000 PC patients in 2017.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age

PC

PC incidence and mortality increase dramatically with age, with the average age at diagnosis estimated to be 66 years.[51] It is rare in men under age 40, with a global age-standardized incidence rate of 0.06 per 100,000 males ages 0-39 years[81] rising to 39.1 for those age 40 to 64 years[82], and 299.2 for those age 65+ years[83]. Similar age-related trends are seen in incidence in Europe and the US (Table 3). Additionally, prevalent indolent PC found at autopsy has been shown to increase with age from 5% of men aged <30 years to 59% of men age >79 years.[72]

Table 3. Incidence of Prostate Cancer by Age and Geography

	Age-Standardized Incidence Rate (per 100,000 males)		
	Global[81-83]	*Europe*[84-86]	*US*[87-89]
0-39 years	0.06	0.03	0.10
40-64 years	39.1	94.5	145.3
65+ years	299.2	567.7	509.0

mCRPC

As the risk of PC itself increases with increasing age, mCRPC is also a disease of older men. Observational studies of patients with mCRPC, from Europe and the US, have found that the mean/median age of mCRPC patients was typically in the late 60s to early 70s. [54,80,90-97]

Gender

Not applicable as PC only occurs in males.

Racial and ethnic origin

PC

In reviews of studies examining incidence and prevalence rates in Black and White men in different countries, it is clear that the risk of PC, and risk of poor prognosis, is higher in Black men than in White men worldwide.[98,99] However, it is not clear to what extent this is due to genetic mutations or environmental factors such as diet and socioeconomic status. It is noteworthy that the difference between Black and White Americans is greater than the difference between Black and White Britons, suggesting that access to care may be a factor.[98]

In the US during 2003-2017, the annual incidence rate of PC per 100,000 men varied substantially by race/ethnicity: 202.3 for Black men, 122.2 for White men, 106.0 for Hispanic men, 87.9 for Native men, and 67.2 for Asian and Pacific Islander men.[53]

Indolent PC diagnosed at autopsy is found in 29.3% of US White or European groups, 32.7% of US Black groups, and 13.5% of Asian groups.[73] When stratified by age, the findings of a

racial discrepancy were more pronounced. For example, among men aged 70-79, PC was found in 36% of Caucasians and 51% of Blacks.[73]

mCRPC

Although data on racial breakdown of patients with mCRPC in Europe in the literature are limited, one study in East London found that between 1997-2016, 24% of identified mCRPC cases occurred in Black men. In contrast, the population of Black men in the London boroughs which were included in the study ranged from only 6-17% in 2008-2010.[100]

Though, in PC, Black patients tend to have poorer outcomes than White patients, several studies have suggested that Black mCRPC patients may have similar or better outcomes than white mCRPC patients.[95,100-103]

Risk Factors:

PC

Advancing age, ethnicity, family history of PC, and certain genetic mutations (e.g., BRCA1 and BRCA2) and conditions (Lynch syndrome) are the only established risk factors for PC.[51,56] Black men have a higher risk of PC than other groups, the cause of which, however, may be genetic or environmental, including diet and/or socioeconomic factors.[98]

Other potential endogenous risk factors for PC include hormone levels, metabolic syndrome, gut microbiome, and oxidative stress.[104,105] There have been few lifestyle and environmental factors for which the evidence is convincing; it has been suggested that risk factors may include diet (e.g., fat intake, vitamin E, vitamin D deficiency, low selenium levels, fruits, vegetables, micronutrients, energy intake, multigrains), environmental exposures (chemicals, pesticides), body size/shape (including elevated body mass index, muscle mass, and height), and exercise.[104,105]

mCRPC

Factors associated with rapid progression to metastatic disease in CRPC have been evaluated in a small number of studies with limited sample sizes.[106-109] In an analysis of 201 men with progressive CRPC without detectable metastases (nmCRPC), only higher baseline PSA (>10 ng/mL) and PSA velocity were independently associated with time to detection of first bone metastasis.[106] Notably, these analyses were limited by the small number of covariates and lack of information about host characteristics. Similar results were found in another study which analysed data from the placebo group of a previously reported randomized controlled trial of atrasentan.[109] In multivariate analyses, baseline PSA ≥13.1 ng/mL was associated with shorter time to first bone metastasis.[109] Similarly, another study found bone-metastasis free survival to be associated with rapid alkaline phosphatase rise, and shorter PSADTs in men with CRPC.[107]

A more recent study sought to investigate the predictors of time to metastasis among 458 men treated with ADT for nonmetastatic PC who developed CRPC within the Shared Equal Access Regional Cancer Hospital cohort.[108] In multivariable analysis, Gleason score 8-10, receiving primary localized treatment, higher PSA levels at CRPC diagnosis, and PSA doubling time ≤6 months were independently associated with shorter time to metastasis.

In addition to risk factors specifically identified for mCRPC, patient-specific risk factors for metastasis in PC in general include younger age[110], genetic factors including presence of BRCA1/2 variants[111], obesity[112], and smoking[113]. Males who have short intervals to PSA failure and rapid PSA-doubling time (PSA-DT) after prostatectomy or radiation therapy have significantly increased rates of distant metastases.[114-116] Additional predictors of metastasis included: lymph node or seminal vesicle involvement with tumour, preoperative PSA level, or Gleason score predicted occult distant metastatic disease.[114,117]

The main existing treatment options:

Castration resistant prostate cancer represents a transition in the progression of prostate cancer, with most patients ultimately succumbing to the disease. Prior to the approval of NHT including enzalutamide and abiraterone acetate/prednisone, the only approved therapies for mCRPC were docetaxel, cabazitaxel and sipuleucel-T, which was withdrawn in the EU in 2015. The approval of novel hormonal therapies in mCRPC for those previously treated with docetaxel represented a therapeutic advancement for these patients, followed shortly thereafter by approvals for the larger population of men with chemotherapy-naïve mCRPC.

Based on ESMO 2020 guidelines[118], the current recommended treatment for men with metastatic castrate resistant prostate cancer include abiraterone or enzalutamide for asymptomatic/mildly symptomatic men with chemotherapy-naive mCRPC. Docetaxel is also recommended for men with mCRPC. In patients with mCRPC in the post-docetaxel setting, abiraterone, enzalutamide and cabazitaxel are recommended options.[118] More recently, the EC approved Pluvicto (lutetium (177Lu) vipivotide tetraxetan), a targeted radioligand therapy. Pluvicto is approved in combination with ADT with or without AR pathway inhibition, for the treatment of adult patients with prostate-specific membrane antigen (PSMA)–positive mCRPC. These patients have previously been treated with AR pathway inhibition and taxane-based chemotherapy.[119]

The most common ARs (≥2%) in metastatic castration-resistant prostate cancer for TAXOTERE (docetaxel) 75 mg/m² in combination with prednisone or include infection, neutropenia, anaemia, nausea, fatigue.[120]

Most common all grade ARs across all indications for cabazitaxel include anaemia (99.0%), leukopenia (93.0%), neutropenia (87.9%), thrombocytopenia (41.1%), diarrhoea (42.1%), fatigue (25.0%) and asthenia (15.4%). The most common grade ≥3 adverse reactions occurring in at least 5% of patients were neutropenia (73.1%), leukopenia (59.5%), anaemia (12.0%), febrile neutropenia (8.0%) and diarrhoea (4.7%).[121]

The most common AR's that were observed in ≥10% of patients treated with abiraterone, and prednisone were peripheral oedema, hypokalaemia, hypertension, urinary tract infection, and alanine aminotransferase increased and/or aspartate aminotransferase increased. Other important adverse reactions include, cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis.[122]

The most common adverse reactions for enzalutamide are asthenia/fatigue, hot flush, hypertension, fractures, and fall. Other important adverse reactions include ischemic heart

disease and seizure. Seizure occurred in 0.5% of enzalutamide-treated patients, 0.2% of placebo-treated patients and 0.3% in bicalutamide-treated patients. Rare cases of posterior reversible encephalopathy syndrome have been reported in enzalutamide treated patients.[123]

In patients harbouring DDR alterations, two PARP inhibitors have recently been approved in multiple countries based on results of phase 2 and 3 trials in this patient population. In 2020, olaparib was approved in the USA for patients with a deleterious or suspected deleterious DDR mutation who have progressed following treatment with enzalutamide or abiraterone, and in the EU for patients with germline and/or somatic BRCA1/2 mutations who have progressed following prior therapy that included a new hormonal agent.[124-126]

There remains a significant unmet medical need for the treatment of patients with mCRPC. Combining PARPi with the ARsi's provides an opportunity to treat patients with mCRPC independent of HRR gene mutation status.

Recently, results from a phase 3, double-blind trial of abiraterone and olaparib versus abiraterone and placebo in patients with mCRPC in the first-line setting were reported.[127] Patients were enrolled regardless of HRR gene mutation (HRRm) status. The primary end point was imaging-based progression-free survival (ibPFS) by investigator assessment. Overall survival was among the secondary end points.

Results from the planned primary analysis at the first data cutoff demonstrated that median rPFS was significantly longer in the abiraterone and olaparib arm than in the abiraterone and placebo arm (24.8 vs. 16.6 months; HR, 0.66; 95% CI, 0.54 to 0.81; P<0.001) and was consistent with blinded independent central review (HR, 0.61; 95% CI, 0.49 to 0.74). At this data cutoff, overall survival data were immature (28.6% maturity; hazard ratio, 0.86; 95% CI, 0.66 to 1.12; P=0.29). Most common ARs (≥20%) were anemia, fatigue/asthenia, and nausea. The safety profile of olaparib and abiraterone was consistent with the known safety profiles of the individual drugs.

Based on this data, on 16 December 2022 the European Commission approved Lynparza (olaparib) in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.[128]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

PC

Disease progression

Despite PC affecting millions of men globally each year, relatively little is known about its etiology.[56] Prognosis varies widely with age, ethnicity, genetic background, and stage of progression, and is influenced by the histopathological, anatomical, and molecular profile of the tumour and the health condition of the patient.[129]

In the US, about three-quarters of PC patients are first diagnosed with non-metastatic localized stage PC.[53] For these men, living with PC typically involves active surveillance ("watchful waiting") and local ablation with or without antihormonal treatment. The 5-year overall survival of patients with localized disease is 60–99%.[129]

However, others will experience aggressive disease that is unresponsive to presently available treatments; with current technology, it is not possible to reliably distinguish mild versus aggressive tumours.[129] Survival with distant stage prostate cancer has improved over time, but only about one third of men survive 5 years after diagnosis, with notable

disparities by age and race/ethnicity.[53]

Common sites of metastatic spread in advanced prostate cancer include locoregional spread to lymph nodes (99%) and bone (84%); spread to distant lymph nodes (10.6%), viscera (lung and liver) (~10%) and the brain and dura (<2%) is associated with poorer survival. [129]

Mortality

Mortality among patients with PC (age-standardized to the world) occurred at a rate of 7.7 per 100,000 in 2020, ranging from 3.1 per 100,000 in South-Central Asia to 27.9 per 100,000 in the Caribbean[56]. Among EMA member states, the PC mortality rate (age-standardized to the world) was 10.2 per 100,000 males (31.0 per 100,000 males age ≥40 years) and ranged from 6.1 per 100,000 males (19.1 per 100,000 males age ≥40 years) in Italy to 22.4 per 100,000 males (70.0 per 100,000 in males age ≥40 years) in Estonia.[130,131] Note that using the age distribution of Europe as the standard results in a mortality rate that appears substantially higher (36.4 per 100,000 males across EMA member states).[130]

mCRPC

Disease progression

A systematic review estimated that approximately 10-20% of PC patients advance to CRPC within about 5 years of diagnosis.[55] Further, this review found that about 84% of patients have metastases at the time of CRPC diagnosis; among those who do not, approximately one-third will develop bone metastases within 2 years. A separate study found that approximately 60% of men with non-metastatic CRPC will develop metastases within 5 years of CRPC diagnosis, with most occurring within the first 3 years.[108] Common sites of metastases in mCRPC include (in order of frequency): bone, lymph nodes, lung, and liver.[108,132]

Once PC progresses to mCRPC it cannot be cured and current treatments are considered largely palliative, with some providing a modest additional 3–6-month survival benefit.[80,133] In a 2014 observational study conducted across Europe and Australia that sought to evaluate treatment patterns among mCRPC patients, 35% of mCRPC patients proceeded straight to palliative care, while 43% of patients pursued hormone therapy manipulations for several weeks prior to initiating mCRPC-specific treatment.[134] Similarly, in a 2021 observational study out of the US that sought to evaluate real world treatment patterns among mCRPC patients, 16.1% of mCRPC patients did not pursue therapy aimed at improving survival, and approximately 50% of patients did not receive subsequent treatment after failing their first line of treatment.[97]

Mortality

A model of all-cause mortality among US men with mCRPC estimates annual all-cause mortality at 55.3%, and attributes 90% of deaths in mCRPC patients to PC.[135] Until 2004, care for mCRPC was exclusively palliative; new therapies introduced since that time have offered modest survival benefit.[80] Reported OS in the literature following mCRPC diagnosis ranged from 11 to 31 months and varied by time of study and treatments received by patients, with survival appearing to be slightly higher in more recent studies.[96,102,136-138]

While all mCRPC is considered advanced and carries a poor prognosis, several patient and tumour characteristics at the time of mCRPC diagnosis are predictive of poorer survival.[54,97,135] Patient characteristics associated with worse survival across multiple studies include non-black race [95,100-102,136,137], older age at diagnosis [94,137], higher PSA at diagnosis [94,96,137], higher Gleason or ECOG performance score at diagnosis [94,137,139], and a greater number of bone metastases [96,137]. Other patient characteristics associated with worse survival in individual studies include higher lactate dehydrogenase (LDH) at diagnosis [137], higher alkaline phosphatase (ALP) at diagnosis [137], lower haemoglobin at diagnosis [137], lower body weight at diagnosis [137], lymph node only metastases [137], and prior treatment with taxane-based chemotherapy, abiraterone, or enzalutamide.[137]

Defects in DNA repair, including alterations in the expression of genes involved in homologous recombination repair are estimated to occur in about 25% of mCRPC patients [140] and have also been associated with worse survival.[141]

Important co-morbidities:

Given the older age at diagnosis of PC and mCRPC, most men with mCRPC have one or more comorbidities, with hypertension being the most common [80,92,101,138,142]. Table 4 lists several comorbidities associated with mCRPC, as highlighted in the literature.

Table 4. Important comorbidities in mCRPC patients

Cardiovascular
Hypertension [80,91,92,101,133,138,142,143]
Hypotension [142]
Angina pectoris/Ischaemic heart disease [91,92,101,138,142,143]
History of myocardial infarction [91,92,101,138,142]
Arrhythmia [91,92,101,138,143]
Thromboembolic disease [91,92]
Stroke [91,92,101,138,143]
Congestive heart failure [91,92,101,138,142,143]
Heart disease, NOS [80]
Metabolic
Diabetes mellitus [80,91,92,101,133,138,142,143]
Disorders of lipid metabolism [80,92,101,133,138]
Nutritional, metabolic, or endocrine disorder, NOS [80]

Table 4. Important comorbidities in mCRPC patients

Pulmonary
Chronic obstructive pulmonary disease [91,92]
Dyspnea [142]
Lower respiratory disease, NOS [80,133]
Urinary system
Chronic renal disease [91,92,142]
Urinary tract infection [101,138] Diseases of urinary system, NOS [80,133]
Other
Neurologic disorders [80,91,92]
Anemia [80,133,142,143]
Liver damage/abnormality [101,138]
Peripheral edema [142]
Eye disorders, NOS [80,133]
Joint or connective tissue disorders [80,133]
Back problems [80]
Skin disorders [80]
Gastrointestinal disorders
Neoplasms [80,133]
Impotence [101,138]
Diseases of male genital organs, NOS [80]

NOS = Not otherwise specified

Module SII. Non-Clinical Part of the Safety Specification

The non-clinical toxicologic profile of talazoparib has been characterized through the conduct of studies including repeat-dose toxicity in rat and dog of ≤13-week duration, genetic toxicity (in vitro and in vivo), embryofoetal development in rat, and phototoxicity, in accordance with the ICHS9 guidelines. The rat and dog were the selected rodent and nonrodent species, respectively for the toxicology studies based on their suitable pharmacokinetic profiles, a comparable in vitro metabolic stability profile in liver microsomes, and representation of the metabolic and clearance pathways that are expected in humans. There were no talazoparib-related effects on respiratory or CNS parameters following a single oral administration to rat in the safety pharmacology studies, or on cardiovascular parameters (hERG assessment and ECG evaluations following repeat-dose administration to dog). No ocular findings were observed with talazoparib in rat or dog in the repeat dose studies and talazoparib is not phototoxic in vivo. Based on the cumulative evaluation of the toxicology profile of talazoparib, the primary talazoparib-related target organ findings in both rat and dog include effects on the haematolymphopoietic system, the male reproductive system, and the gastrointestinal system. Additional target organ findings observed in rat only include findings in the female reproductive system and liver.

Talazoparib is clastogenic in vitro in human peripheral blood lymphocytes, in cancer cell lines and in vivo in rat. Talazoparib caused fetotoxicity in an embryofoetal development study in rat.

Table 5 describes the non-clinical key safety findings and relevance to human usage.

Table 5. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicity	
Haematolymphopoietic Toxicity In repeat dose studies in rats and dogs, there were dose-dependent findings of pancytopenia and decreased red blood cell mass, reticulocytes, and platelets correlated microscopically with bone marrow hypocellularity (femur and sternum) and depletion of lymphoid tissue in multiple organs (gut-associated lymphatic tissue, lymph nodes, and spleen). Septicaemia resulting in moribundity, and death was considered secondary to severe haematolymphopoietic toxicities.	Please see Section SVII.1.1, Risks not Considered Important for Inclusion in the List of Safety Concerns in the Risk Management Plan (RMP) (Myelosuppression).
Reproductive and Developmental Toxicity In an embryo-foetal development study in pregnant rats, talazoparib was administered orally at 0, 0.015, 0.05, and 0.15 mg/kg/day. At 0.15 mg/kg/day, talazoparib caused moribundity/mortality in 32% of the dams. At ≥0.05 mg/kg/day, there were no live foetuses and at 0.015 mg/kg/day, 91% of the litters were resorbed. In the 9% of foetuses that survived at 0.015 mg/kg/day, talazoparib caused foetal malformations and structural variations. At the lowest adverse effect level (0.015 mg/kg/day), the unbound maternal C_{max} (0.39 ng/mL) and AUC_{24} (4.97 ng•h/mL) exposures on gestation day 17 are approximately 0.1 -fold the relevant exposure at the recommended dose in patients of 1 mg once daily. Individual focal necrotic changes of ovarian follicular atresia were seen in rat repeat dose studies. Atrophy and/or degenerative changes in testes, epididymis, and seminiferous tubules (with reduced sperm) were observed in rat and dog studies at high doses. Duration of changes in reproductive organs was generally tied to specific cell types and regions (e.g., seminiferous tubules).	Please see Section SVII.3.1, Reproductive and developmental toxicity (Important Potential Risk).

Table 5. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Genotoxicity (Clastogenicity) In an in vitro chromosomal aberration assay in human peripheral blood lymphocytes, talazoparib was clastogenic for the induction of structural chromosome aberrations in both the non-activated and S9-activated assays at ≥125 µg/mL when evaluated after 4-hour exposure, and at ≥2.5 µg/mL in the non-activated assay when evaluated after 20-hour exposure. In another study in Sprague Dawley rats, a single dose of talazoparib at 150, 300, or 600 mg/kg induced statistically significant dose-dependent increase in the incidence of micro nucleated polychromatic erythrocytes at all talazoparib doses indicating positive in vivo clastogenic activity and/or disruption of the mitotic apparatus.	Talazoparib was clastogenic in in vitro chromosomal aberration and in vivo micronucleus assays, indicating potential for genotoxicity in humans. Please see Section SVII.3.1, Second Primary Malignancies (other than MDS/AML) (Important Potential Risks).
Other toxicity-related information or data	
GI Toxicity In a repeat dose study in rats, GI findings noted at ≥1 mg/kg/day included increased apoptosis in the stomach and duodenum, reversible villous atrophy, and increased apoptosis throughout the various segments of the GI tract (small intestine, duodenum, jejunum, and ileum); at 3 mg/kg/day, irreversible toxicity included enteropathy and villous atrophy resulting in mortality. In a repeat dose study in dogs, GI findings included increased apoptosis in sections of small intestine at ≥0.01 mg/kg/day and macroscopic red GI discolouration (potential bleeding) at 0.1 mg/kg/day.	Gastrointestinal ADRs reported in clinical studies were considered to not impact the benefit-risk of talazoparib or the clinical consequences were considered to be acceptable in relation to the severity of the indication. See Section SVII.1.1, Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP.
Hepatic Toxicity Individual hepatocyte necrosis of liver was seen in rat repeat dose studies.	Hepatotoxicity ADRs reported in clinical studies were considered to not impact the benefit-risk of talazoparib.

AUC_{24} = Area under the curve over 24 hours; C_{max} = maximum plasma concentration

Module SIII. Clinical Trial Exposure

The exposure data summarized below is based upon the following 3 pooled studies:

Pool 1 includes patients who received talazoparib monotherapy at the recommended dose of 1 mg once daily for solid tumours, of which the majority were patients with germline BRCA mutation positive locally advanced or metastatic breast cancer. This pool includes:

- pivotal study 673-301
- study 673-201
- study PRP-001
- study MDV3800-14
- extension study MVD3800-13 (includes patients who participated in studies PRP 001, MDV3800-14, MDV3800-01, MDV3800-02, MDV3800-03 and MDV3800-04 who received 1 mg treatment)
- study MDV3800-06/C3441006

- study C3441020

Pool 2 includes patients who received talazoparib monotherapy at doses other than 1 mg once daily. This pool includes:

- study PRP-001
- study MDV3800-13

Exposure data from this integrated safety dataset are presented in Table 6, Table 8, and Table 10.

Pool 3 includes patients who participated in the pivotal TALAPRO-2 (C3441021) study who received talazoparib in combination with enzalutamide for mCRPC. The starting talazoparib dose was reduced to 0.5 mg QD in combination with enzalutamide in order to account for the observed interaction with enzalutamide and maintain similar talazoparib exposure to that achieved with 1 mg QD monotherapy. Exposure data from this study are presented in Table 7, Table 9, and Table 11.

Table 6. Duration of Exposure (Integrated Safety Database)

Breast Cancer and Other Solid Tumours	**Talazoparib 1 mg/day[a] (N=690)**		**Talazoparib non 1 mg/day[b] (N=98)**	
Duration of Exposure	**n (%)**	**Person Months**	**n (%)**	**Person Months**
< 1 month	44 (6.4)	26.5	14 (14.3)	10.6
1 to <3 months	125 (18.1)	264.1	30 (30.6)	57.1
3 to <6 months	221(32.0)	1062.7	20 (20.4)	84.9
6 to <12 months	171 (24.8)	1414.4	22 (22.4)	189.9
≥ 12 months	129 (18.7)	3538.3	12 (12.2)	373.7
Total		6305.9		716.2

a. Includes all participants enrolled in 673-301, 673-201, PRP-001, MDV3800-14, MDV3800-13 (who completed studies 673-201, PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study), MDV3800-06, and C3441020. Participants who started studies PRP-001, MDV3800-14, or 673-201 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once.

b. Includes all participants enrolled in MDV3800-13 (who completed studies PRP-001, MDV3800-03, MDV3800-04, MDV3800-14, and 673-201, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib other than 1 mg once daily either in the originating or extension study).

Final database lock date for 673-301 was 22 March 2021, 673-201 was 31 October 2018, MDV3800-13 was 13 August 2021, C3441006 was 04 September 2020, and C3441020 was 20 November 2020. Date of last participant discontinued study for PRP-001 was 30 January 2017, and MDV3800-14 was 22 June 2017. Participants who initiated treatment in MDV3800-13 at talazoparib doses other than 1 mg/day, 5 of these participants initiated treatment with talazoparib 1 mg/day in the originating study and are also represented in the talazoparib 1 mg population.

Person time is calculated as the sum of duration of treatment with talazoparib (expressed in months) for all patients in the category.

Study drug exposure is defined as (last dose date - first dose date +1). For participants who were still on treatment, data analysis cutoff date is used as the last dose date of study drug if start date of last dose record before data cutoff date is available but stop date of this dose record is missing.

Table 7. Duration of Exposure (Study C3441021)

Metastatic Castration Resistant Prostate Cancer		
Duration of Exposure	**Patients (N=416) n (%)**	**Person Months**
< 1 month	4 (1.0)	2.6
1 to <3 months	40 (9.6)	86.5
3 to <6 months	36 (8.7)	152.1
6 to <12 months	75 (18.0)	690.6
≥ 12 months	261 (62.7)	6681.4
Total person months	**7613.2**	

This table includes data as of 16 August 2022.
Person time is calculated as the sum of duration of treatment with talazoparib (expressed in months) for all patients in the category.
Study drug exposure is defined as (last dose date - first dose date +1).

Table 8. Exposure by Age Group and Gender (Integrated Safety Database)

Breast Cancer and Other Solid Tumours (Talazoparib 1 mg/day)[a]				
	Patients		**Person Months**	
Age Group	**M**	**F**	**M**	**F**
< 50	9 (5.0%)	293 (57.5%)	99.7	2532.3
50 to <65	54 (30.0%)	148 (29.0%)	325.0	1646.4
65 to <75	81 (45.0%)	55 (10.8%)	617.4	744.0
75 to <85	33 (18.3%)	12 (2.4%)	267.7	55.9
>=85	3 (1.7%)	2 (0.4%)	3.6	13.9
Total	**180 (26.1%)**	**510 (73.9%)**	**1313.4**	**4992.5**
Breast Cancer and Other Solid Tumours (Talazoparib non 1 mg/day)[b]				
Age Group	**Patients**		**Person Months**	
	M	**F**	**M**	**F**
<50	3 (12.0%)	19 (26.0%)	2.9	165.8
50 to <65	9 (36.0%)	32 (43.8%)	27.1	311.0
65 to <75	6 (24.0%)	14 (19.2%)	30.8	62.3
75 to <85	7 (28.0%)	8 (11.0%)	39.9	76.4
>=85	0 (0.0%)	0 (0.0%)	0.0	0.0
Total	**25 (25.5%)**	**73 (74.5%)**	**100.6**	**615.6**

a. Includes all participants enrolled in 673-301, 673-201, PRP-001, MDV3800-14, MDV3800-13 (who completed studies 673-201, PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study), MDV3800-06, and C3441020. Participants who started studies PRP-001, MDV3800-14, or 673-201 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once.
Final database lock date for 673-301 was 22 March 2021, 673-201 was 31 October 2018, MDV3800-13 was 13 August 2021, C3441006 was 04 September 2020, and C3441020 was 20 November 2020. Date of last participant discontinued study for PRP-001 was 30 January 2017, and MDV3800-14 was 22 June 2017.
Person time is calculated as the sum of duration of treatment with talazoparib 1 mg once daily (expressed in months) for all patients in the category.
Study drug exposure is defined as (last dose date - first dose date +1). For participants who were still on treatment, data analysis cutoff date is used as the last dose date of study drug if start date of last dose record before data cutoff date is available but stop date of this dose record is missing.

Table 8. Exposure by Age Group and Gender (Integrated Safety Database)

b. Includes all participants enrolled in MDV3800-13 (who completed studies PRP-001, MDV3800-03, MDV3800-04, MDV3800-14, and 673-201, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib other than 1 mg once daily either in the originating or extension study).
Date of last participant discontinued study for PRP-001 was 30 January 2017. Final database lock date for MDV3800-13 was 13 August 2021.
Person time is calculated as the sum of duration of treatment with talazoparib (expressed in months) for all patients in the category.
Study drug exposure is defined as (last dose date - first dose date +1).

Table 9. Exposure by Age Group and Gender (C3441021)

Metastatic Castration Resistant Prostate Cancer				
Age Group	**Patients**		**Person Months**	
	M	**F**	**M**	**F**
<50	4 (1.0%)	NA	47.1	NA
50 to <65	77 (18.5%)	NA	1640.2	NA
65 to <75	198 (47.6%)	NA	3711.4	NA
75 to <85	123 (29.6%)	NA	2025.4	NA
>=85	14 (3.4%)	NA	189.1	NA
Total	**416 (100%)**	**NA**	**7613.2**	**NA**

Include data from Talazoparib C3441021 as of 16 August 2022.
Person time is calculated as the sum of duration of treatment (expressed in months) for all participants in the category.

Table 10. Exposure by Dose (Integrated Safety Database)

Breast Cancer and Other Solid Tumours	**Talazoparib 1 mg/day[a] (N=690)**		**Talazoparib non 1 mg/day[b] (N=98)**	
Dose of Exposure	**n (%)**	**Person Months**	**n (%)**	**Person Months**
1 mg once daily	690 (100%)	6305.9		
0.025 mg once daily			3 (3.1%)	5.5
0.050 mg once daily			3 (3.1%)	11.1
0.100 mg once daily			3 (3.1%)	14.4
0.200 mg once daily			3 (3.1%)	24.4
0.250 mg once daily			2 (2.0%)	2.3
0.400 mg once daily			3 (3.1%)	19.4
0.500 mg once daily			60 (61.2%)	394.8
0.600 mg once daily			6 (6.1%)	35.5

a. Includes all participants enrolled in 673-301, 673-201, PRP-001, MDV3800-14, MDV3800-13 (who completed studies 673-201, PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study), MDV3800-06, and C3441020. Participants who started Studies PRP-001, MDV3800-14, or 673-201 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once. Final database lock date for 673-301 was 22 March 2021, 673-201 was 31 October 2018, MDV3800-13 was 13 August 2021, C3441006 was 04 September 2020, and

Table 10. Exposure by Dose (Integrated Safety Database)

Breast Cancer and Other Solid Tumours	Talazoparib 1 mg/day[a] (N=690)		Talazoparib non 1 mg/day[b] (N=98)	
Dose of Exposure	**n (%)**	**Person Months**	**n (%)**	**Person Months**

C3441020 was 20 November 2020. Date of last participant discontinued study for PRP-001 was 30 January 2017, and MDV3800-14 was 22 June 2017.

b. Includes all participants enrolled in MDV3800-13 (who completed studies PRP-001, MDV3800-03, MDV3800-04, MDV3800-14, and 673-201, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib other than 1 mg once daily either in the originating or extension study).

Participants who initiated treatment in MDV3800-13 at talazoparib doses other than 1 mg/day, 5 of these participants initiated treatment with talazoparib 1 mg/day in the originating study and are also represented in the Talazoparib 1 mg population.

Person time is calculated as the sum of duration of treatment with talazoparib (expressed in months) for all patients in the category.

Study drug exposure is defined as (last dose date - first dose date +1). For participants who were still on treatment, data analysis cutoff date is used as the last dose date of study drug if start date of last dose record before data cutoff date is available but stop date of this dose record is missing.

Table 11. Exposure by Dose (Study C3441021)

Metastatic Castration Resistant Prostate Cancer		
Dose of Exposure	**Patients**	**Person Months**
0.25 mg once daily	2 (0.5%)	9.9
0.35 mg once daily	41 (9.9%)	670.7
0.5 mg once daily	359 (86.3%)	6690.7
1 mg once daily	13 (3.1%)	232.2
1.1 mg once daily[a]	1 (0.2%)	9.7
Total	**416 (100%)**	**7613.2**

a. Please note that one patient was assigned to 0.35 mg but took incorrect first dose as 1.1 mg. All patients are counted only once, based on their actual initial dose.

Includes data from Talazoparib C3441021 as of 16 August 2022.

Person time is calculated as the sum of duration of treatment (expressed in months) for all participants in the category.

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

There has been limited exposure of special populations to talazoparib and no epidemiologic studies have been conducted in pregnant/lactating women, and specific subpopulations that were excluded from the clinical trial development programme.

Following is the important exclusion criterion in the pivotal clinical studies across the development programme:

Patients with Hypersensitivity to Talazoparib

Reason for exclusion: This was included as a conservative measure upon initiation of the talazoparib development program to avoid hypersensitivity reactions if patients were identified with known hypersensitivity to talazoparib.

Is it considered to be included as Missing Information? No

Rationale: No cases of patients developing hypersensitivity to talazoparib have been identified. However, hypersensitivity reactions are unpredictable, regardless of the allergen, and consistent with the development program exclusion criteria, the talazoparib SmPC includes a contraindication for patients with hypersensitivity to talazoparib or any excipient, which is consistent with the Guideline on Summary of Product Characteristics.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table 12 presents these limitations of ADR detection in the talazoparib clinical trial development programme.

Table 12. Limitations of Adverse Drug Reaction Detection

Ability to detect ADRs	Limitation of trial Programme	Discussion of implications on target population
Uncommon ADRs	As of 16 August 2022, 690 participants received talazoparib as a single agent at 1 mg orally once daily.	Uncommon events may be identified, however, rare ADRs may have not been observed in clinical trials.
ADRs that are dose related	No dedicated studies were conducted to establish dose proportionality of ADRs. However, the relationships between talazoparib plasma exposure and Grade 3 or higher AEs of anaemia, thrombocytopenia, and neutropenia were explored using pooled data from Studies 673-301 and 673-201. Higher talazoparib exposure at 1 mg once daily, as measured by time varying average talazoparib concentration ($C_{avg,t}$) was associated with higher risk of Grade 3 or higher anaemia and thrombocytopenia. A trend for association between higher $C_{avg,t}$ and Grade 3 or higher neutropenia was observed although the relationship was not statistically significant. Additionally, the relationship between exposure and Progression Free Survival (PFS was explored in Study 673-301.	Findings from the exposure-efficacy analysis support the dosing of talazoparib at the 1 mg once daily dose to maximize PFS prolongation. Additionally, results from the exploration of the relationships between talazoparib plasma exposure and Grade 3 or higher AEs of anaemia, thrombocytopenia, and neutropenia support the proposed dose modification algorithm for the management of ADRs.

Table 12. Limitations of Adverse Drug Reaction Detection

Ability to detect ADRs	Limitation of trial Programme	Discussion of implications on target population
	Higher talazoparib exposure at 1 mg once daily was associated with longer PFS.	
Due to prolonged exposure	At the time of the final OS analysis (30 September 2019 data cut-off date), the median follow-up time in the talazoparib arm was 44.9 months (95% CI: 37.9, 47.0) and in the PCT arm was 36.8 months (95% CI: 34.3, 43.0). A total of 216 (75.3%) patients in the talazoparib arm and 108 (75.0%) patients in the PCT arm were known to have died at the data cut-off. There are no apparent new specific toxicities that resulted from extended exposure to talazoparib; however, this has not been formally examined, mainly due to the small number of patients treated for prolonged periods of time.	Any additional data on long-term treatment will be evaluated when will become available from ongoing clinical trials.
Which have a long latency	Since the period of observation for patients treated with talazoparib will often be curtailed by death or confounded by participation in subsequent clinical trials, the information regarding potential AEs with a long latency is limited.	Since it is unknown if events with prolonged latency occur, the impact of any such events cannot be assessed yet.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 13 lists the patient populations that have been under-represented in the talazoparib clinical development programme.

Table 13. Exposure of special populations included or not in clinical trial development programmes

Type of special population (in pre-authorisation clinical development programme)	Exposure
Pregnant women	Given the known clastogenic effects of talazoparib in animal studies, pregnant or breastfeeding women were not enrolled in talazoparib clinical trials. No data on pregnant women using talazoparib are available to date. No studies have been conducted in animals or humans to date to assess the effect of talazoparib on milk production, talazoparib presence in
Breastfeeding women	

Table 13. Exposure of special populations included or not in clinical trial development programmes

Type of special population (in pre-authorisation clinical development programme)	Exposure
	breast milk, or its effects on the breast-fed child. It is unknown whether talazoparib is excreted in human milk.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	All studies excluded patients with Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) >2.5 x upper limit of normal (ULN), or if there were liver metastases involvement > 5.0 x ULN or with total bilirubin >1.5 x ULN, or 3.0 x ULN for Gilbert's syndrome. *Talazoparib monotherapy*: Based on a population pharmacokinetic analysis that included 490 patients (372 patients with normal liver function and 118 patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1.0 to 1.5 x ULN and any AST), no difference in the apparent clearance (CL/F) of talazoparib was observed in patients with mild hepatic impairment compared to patients with normal hepatic function. No dose adjustments are recommended for patients with mild hepatic impairment. *Talazoparib in Combination with Enzalutamide:* 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 that indicated that there was no obvious effect of mild hepatic impairment on talazoparib PK parameters as determined by visual inspection of graphical plots of individual ETAs by liver function category. Study MDV3800-02 was an ongoing Phase 1, open-label study to evaluate the PK and safety of daily oral doses of 0.5 mg talazoparib in patients with solid tumours and normal liver function or varying degrees of hepatic impairment. Thirty-eight (38) patients were enrolled; 37 had at least one PK concentration, among which 17 were evaluable for NCA. Population PK analysis using plasma PK data from all 37 patients who had PK data indicated that there is no significant impact of hepatic function on apparent clearance (CL/F) of talazoparib. NCA of data from 17 PK-evaluable patients showed no clear trend for increase in exposure on Day 22 with worsening hepatic function. Talazoparib protein binding was comparable in patients with varying hepatic function. Talazoparib was generally well tolerated, and the safety profile observed in this study was consistent with the known safety profile of the drug. Population PK analysis using data from this PK trial indicated that mild, moderate, or severe hepatic impairment had no significant impact on the

Table 13. Exposure of special populations included or not in clinical trial development programmes

Type of special population (in pre-authorisation clinical development programme)	Exposure
	PK of talazoparib and based on the results of population PK analysis and totality of the data, no dose adjustment is recommended for patients with various degrees of hepatic impairment.
• Patients with renal impairment	Normal renal function was defined as a creatinine clearance (CrCl) of ≥90 mL/min, mild renal impairment 60-89 mL/min, moderate renal impairment 30-59 mL/min, and severe renal impairment ≤29 mL/min. Patients with severe renal impairment were excluded from all studies. *Talazoparib monotherapy:* Among patients with advanced breast cancer who received talazoparib 1 mg once daily, there were 157 patients with mild renal impairment, 36 patients with moderate renal impairment, and 1 patient with severe renal impairment treated with talazoparib. Among patients in the talazoparib arm in Study 673-301, there were 79 patients with mild renal impairment and 12 patients with moderate renal impairment. Based on a population pharmacokinetic analysis that included 490 patients (324 patients with normal renal function, 132 patients with mild renal impairment, 33 patients with moderate renal impairment, and 1 patient with severe renal impairment), patients with mild and moderate renal impairment had 14.4% and 37.1% lower CL/F compared to patients with normal renal function. The impact of severe renal impairment on CL/F could not be concluded due to limited number of severe renal impairment patients. Based on a summary of all treatment-emergent adverse events (TEAEs) by renal function category for patients receiving talazoparib 1 mg once daily, AE frequencies were generally comparable between patients with mild renal impairment and patients with normal renal function, but AE frequencies were higher among patients with moderate renal impairment compared with those who had normal renal function. Study MDV3800-01 was conducted to investigate the effect of mild, moderate, and severe renal impairment on the PK of talazoparib following daily oral dosing of 0.5 mg talazoparib for 22 days in patients with advanced solid tumours. Following multiple daily oral 0.5 mg doses of talazoparib for 22 days, AUC_{0-24} increased by 12.2%, 43.0%, and 163.3% and C_{max} increased by 11.1%, 31.6%, and 89.3% in patients with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function as assessed by ANOVA analyses performed comparing the pre-defined categorical renal function groups defined by BSA-normalized eGFR. Linear regression models generated to describe the relationship between natural log-transformed AUC_{0-24} following multiple daily doses of talazoparib and continuous renal function assessments (BSA-normalized eGFR, absolute eGFR, and CrCl) predict increases in talazoparib exposure (AUC_{0-24}) of approximately 16.2%, 56.8% and 96.4% for patients with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function.

Table 13. Exposure of special populations included or not in clinical trial development programmes

Type of special population (in pre-authorisation clinical development programme)	Exposure
	Overall, there were no notable differences in the TEAE profile between patients with normal renal function and patients with mild, moderate, or severe renal impairment. In addition, there were no unexpected safety findings identified as the reported TEAEs were consistent with the diseases under study and with the known safety profile associated with talazoparib treatment. No dose adjustments are required for patients with mild renal impairment (60 mL/min ≤ CrCl < 90 mL/min). For patients with moderate renal impairment (30 mL/min ≤ CrCl < 60 mL/min), the dose should be reduced from 1 mg once daily to 0.75 mg once daily. For patients with severe renal impairment (15 mL/min≤ CrCl < 30 mL/min), the talazoparib dose should be reduced to 0.5 mg once daily. *Talazoparib in Combination with Enzalutamide*: Based on a POPPK analysis where renal function was modelled as a continuous covariate that included 412 mCRPC participants who received talazoparib co-administered with enzalutamide, where 152 participants had mild renal impairment (60 mL/min≤ CLcr <90 mL/min), 72 participants had moderate renal impairment (30 mL/min≤ CLcr <60 mL/min), and 2 participants had severe renal impairment (CLcr <30 mL/min), talazoparib CL/F was decreased by 8.0%, 27.1%, and 46.7% in participants with mild, moderate, and severe renal impairment, corresponding to increases of 9%, 37%, and 88% in AUC, respectively, when compared to participants with normal renal function. To further confirm the consistency in the magnitude of impact of renal impairment on talazoparib PK in the study C3441021 dataset where talazoparib is used in combination with enzalutamide and when used in monotherapy therapy setting, an additional POPPK analysis was conducted by modeling renal function as a categorical covariate. This additional analysis was also consistent with results of the monotherapy categorical covariate assessment; mild and moderate renal impairment participants had 18.3% and 33.9% lower CL_0/F 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 CL_0/F could not be concluded with this analysis method. No dose adjustment is recommended for patients with mild renal impairment (60 mL/min≤ CLcr <90 mL/min). For patients with moderate renal impairment (30 mL/min≤ CLcr <60 mL/min), the recommended dose of talazoparib is 0.35 mg QD in combination with enzalutamide. For patients with severe renal impairment (CLcr <30 mL/min), the recommended dose of talazoparib is 0.25 mg QD in combination with enzalutamide.

Table 13. Exposure of special populations included or not in clinical trial development programmes

Type of special population (in pre-authorisation clinical development programme)	Exposure
• Patients with breast cancer severity different from inclusion criteria in clinical trials	Talazoparib has been studied in normal healthy volunteers and in patients with advanced breast cancer as well as in other advanced cancer patients.
• Immuno-compromised patients	Not included in the clinical development programme.
• Patients who receive talazoparib together with P-glycoprotein (P-gp) inhibitors or inducers	*Talazoparib Monotherapy:* Data from a drug-drug interaction study in patients with advanced solid tumours indicated that coadministration of multiple daily doses of itraconazole 100 mg twice daily with a single 0.5 mg talazoparib dose increased talazoparib AUC_{inf} and C_{max} by approximately 56% and 40%, respectively, relative to a single 0.5 mg talazoparib dose administered alone. Population pharmacokinetic analysis that included 490 patients (21 patients received strong P-gp inhibitors during the treatment period), also showed that the relative bioavailability of talazoparib was 44.7% higher when co-administered with a strong P-gp inhibitor. A dose reduction from 1 mg once daily to 0.75 mg once daily is required for patients while receiving strong P-gp inhibitors. If the strong P-gp inhibitor is discontinued, the talazoparib dose should be increased (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong P-gp inhibitor. *Talazoparib in Combination with Enzalutamide:* The effect of concomitant administration of potent P-gp inhibitors on talazoparib exposure when talazoparib is given in combination with enzalutamide has not been studied. If concomitant use of these potent P-gp inhibitors cannot be avoided when talazoparib is given in combination with enzalutamide, monitor patients for potential increased adverse reactions. Data from a drug-drug interaction study in patients with advanced solid tumours (Study MDV3800-04) indicated that coadministration of multiple daily doses of a P-gp inducer, rifampin 600 mg, with a single 1 mg dose of talazoparib increased talazoparib C_{max} by approximately 37% whereas AUC_{inf} was not affected relative to a single 1 mg talazoparib dose administered alone. No dose adjustments are required for P-gp inducers.
Population with relevant different ethnic origin	*Talazoparib Monotherapy:* Most patients in both the talazoparib arm (66.9%) and the PCT arm (75.0%) of the pivotal study (Study 673-301) were White. In the talazoparib arm, 10.8% patients were Asian, 4.2% patients were Black, and 1.7% patients were classified as “Other” race. Most patients in both the talazoparib arm (73.1%) and the PCT arm (77.0%) of the pivotal study (Study 673-301) had an ethnicity reported as

Table 13. Exposure of special populations included or not in clinical trial development programmes

Type of special population (in pre-authorisation clinical development programme)	Exposure
	Not Hispanic or Latino. In the talazoparib arm 10.8% of patients were Hispanic or Latino, and ethnicity was not reported for 16.1% of patients. Population PK analysis which included 41 Asian and 449 non-Asian patients indicated that talazoparib exposure was 19.2% lower in Asian patients compared to non-Asian patients at the same dosage. The effect of race on talazoparib exposure was not considered clinically relevant. No dose adjustments based on ethnicity are required. *Talazoparib in Combination with Enzalutamide:* In study C3441021, there were 811 patients in the data set, consisting of pooled data from part 1 and part 2 (cohort 1) of the study, treated with enzalutamide in combination with either placebo or talazoparib. Out of the 811 patients, 412 were treated with talazoparib. Of the 412 pts that received talazoparib, 64.2% of patients were White, 30% were Asian and 2.7% were Black. Population PK modelling of talazoparib in combination with enzalutamide demonstrated that the effects of RACE2 (Asian versus non-Asian) on CL0/F of talazoparib were not significant.
Subpopulations carrying known and relevant genetic polymorphisms	Not included in the clinical development programme.
Children	The safety and efficacy of talazoparib in children and adolescents <18 years of age have not been established.
Male Patients	*Talazoparib Monotherapy* Based on a population pharmacokinetics analysis which included 53 male and 437 female patients, no clinically relevant effect of gender on talazoparib exposure was identified. No dose adjustments based on gender are required. *Talazoparib in combination with Enzalutamide:* All participants treated with talazoparib in combination with enzalutamide in study C3441021 were male, and thus the impact of sex on talazoparib PK in this setting could not be assessed.

AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; C_{max} = maximum plasma concentration

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

The estimated cumulative patient exposure is based on sales data provided by IQVIA[c] from 01 April 2010 through the first quarter of 2022, with data extrapolated to 15 October 2022, and SPP data. The sales data from 01 April 2022 to 15 October 2022 are extrapolated by taking average of sales of previous 2 quarters.

It should be noted that the patient exposure to talazoparib has been estimated in terms of number of patients and not in patient-years because of the absence of average dosage information; to obtain the ratio of SU per patient, SPP data have been used, which provide number of patients exposed to talazoparib during the cumulative period.

Patients in SPP data have been calculated by using gross up factor of 1.3 which assumes that available data represents 74.5% of all channels/overseas sales.

Non-US patients are calculated by applying factor of US sales (calculated from IQVIA data) to non-US sales (calculated from IQVIA data) on US patients (available from SPP data).

SV.1.2. Exposure

It is estimated that 3078 patients were exposed to talazoparib worldwide since the product was first approved. The exposure to talazoparib in the US is estimated to be 1088 patients, and outside the US is estimated to be 1990 patients.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Talazoparib does not have characteristics that would make it attractive for use for illegal purposes.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The safety concerns included in the initial RMP are presented in Table 14.

[c] Of note, IQVIA data should not be regarded as complete sales information. Some countries where talazoparib is sold may not be covered by IQVIA. In addition, IQVIA requires a minimum threshold of sales after which it will start tracking a product; thus, data from countries where the product does not have sizeable sales would not be captured by IQVIA. Furthermore, IQVIA does not capture retail sales data and hospital data in all countries. Therefore, the sales volumes obtained through the use of IQVIA are likely to result in a large underestimate of the actual distributed product.

Table 14. Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	Myelodysplastic syndrome/Acute myeloid leukaemia (MDS/AML)
	Second primary malignancies (other than MDS/AML)
	Reproductive and developmental toxicity
Missing Information	Use in severe renal impairment

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

1) Adverse reactions with clinical consequences, even serious, but occurring with a low frequency, not impacting public health, and considered to be acceptable in relation to the severity of the indication treated: Vomiting, Abdominal pain, Nausea, Headache, Fatigue, Dizziness

2) Known risks for the class of PARP inhibitors that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting collection, evaluation and assessment, and for which the risk minimisation messages in the SmPC are anticipated to be adhered to by prescribers: Myelosuppression (including Anaemia, Neutropenia, Thrombocytopenia).

3) Known risks that do not impact the risk-benefit profile: Decreased appetite, Diarrhoea, Dyspepsia, Stomatitis, Dysgeusia, Alopecia.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

The risks considered important for inclusion in the list of safety concerns in the RMP were characterized based on two cohorts of pooled safety data:

- **Patients who received talazoparib at the proposed starting dose of 1 mg once daily:** Data from all patients with breast cancer and other solid tumours who received talazoparib monotherapy at 1 mg once daily in 5 company sponsored phase I-III clinical studies: PRP-001, 673-201, 673-301, MDV3800-13, and MDV3800-14 (494 patients).

- **Patients who received talazoparib at doses other than 1 mg once daily:** Since the frequencies of some important potential risks are low, pooled safety data from all patients with breast cancer and other solid tumours who received talazoparib monotherapy at

doses other than 1 mg once daily in 2 company sponsored phase I clinical studies (PRP-001 [N=33], MDV3800-13 [N=34][d]) were also assessed (67 patients).

Important Identified Risk: none

Important Potential Risk 1: Myelodysplastic Syndrome/Acute Myeloid Leukaemia

Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in patients who received PARP inhibitors. In the pivotal randomized breast cancer study, MDS/AML was not reported for any patients who received talazoparib and in 1 out of 126 (0.8%) patients who received chemotherapy. Overall, MDS/AML has been reported in 1 out of 561[d] (0.2%) solid tumour patients treated at any dose with talazoparib in clinical studies.

Risk-benefit impact: MDS/AML are serious, life-threatening conditions. Currently, the impact to the overall risk-benefit balance is not known because a causal relationship between talazoparib and MDS/AML has not been established. Cases of MDS/AML reported in the continuing development talazoparib programme and in post-marketing surveillance will be continually reviewed and patient monitoring guidance will be provided to healthcare professionals via the SmPC to mitigate this important potential risk.

Important Potential Risk 2: Second Primary Malignancies (other than MDS/AML)

Potential second primary malignancies (other than MDS/AML) have been reported in 6 patients (7 events) who received talazoparib at the proposed starting dose of 1 mg once daily and no patients who received talazoparib at doses other than 1 mg once daily. In comparison, one case of a potential second primary malignancy (other than MDS/AML) was reported in the PCT arm (N=126) of Study 673-301 (EMBRACA).

Risk-benefit impact: The 7 newly occurring primary malignancies reported amongst 6 patients taking talazoparib included Squamous cell carcinoma of skin (2), Basal cell carcinoma, Glioblastoma multiforme, Intraductal proliferative breast lesion, Neoplasm skin, Ovarian neoplasm (1 each). Other risk factors and/or unlikely temporal relationships were present in most cases and in all cases, the events were considered by Investigators to be unrelated to talazoparib. Although newly occurring malignancies can be serious life-threatening conditions, the impact to the overall risk-benefit balance is not known because a causal relationship with talazoparib has not been established. Cases of second primary malignancies (other than MDS/AML) reported in the continuing development talazoparib programme and in post-marketing surveillance will be continually reviewed and in-vitro and in-vivo clastogenicity testing results will be provided to healthcare professionals via the SmPC to provide information about this important potential risk.

[d] Excludes 3 patients that initiated treatment with talazoparib at 1 mg once daily in the originating study and are also represented in the 1 mg once daily population

Important Potential Risk 3: Reproductive and Developmental Toxicity

Based on findings from animal studies, talazoparib can cause embryo-foetal harm and may compromise male and female fertility. There are no available clinical data on talazoparib use in pregnant women or any clinical effects on fertility to inform a drug-associated risk.

Risk-benefit impact: Currently, the impact to the overall risk-benefit balance is not known because the relationship of reproductive and developmental toxicity to talazoparib treatment has not been identified. The SmPC contains instructions to avoid pregnancy and utilise contraception in male and female patients.

Missing information: Use in Severe Renal Impairment

Pharmacokinetics and safety of talazoparib in patients with severe renal impairment (CrCl < 30 mL/min) or requiring haemodialysis have not been studied. A formal renal impairment study is currently ongoing.

Risk-benefit impact: Currently, the impact to the overall risk-benefit balance is not known because talazoparib pharmacokinetics and safety have not been studied in patients with severe renal impairment.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

There have been no newly identified safety concerns since submission of the initial RMP that are considered to warrant inclusion in this update.

Following completion of renal impairment study MDV3800-01/C3441001, A Phase 1, open-label study to evaluate the PK and safety of daily oral doses of 0.5 mg talazoparib in patients with advanced solid tumours and normal renal function or varying degrees of renal impairment, use in Severe Renal Impairment is no longer considered an area of missing information.

Following the receipt of the CHMP day 120 list of questions related to Procedure No. EMEA/H/C/004674/X/015/G, the important potential risk Myelodysplastic syndrome/Acute myeloid leukaemia is being reclassified as identified risk (not important) and removed from the list of safety concerns.

For the proposed submission in mCRPC, the starting talazoparib dose of 0.5 mg QD in combination with 160 mg QD of enzalutamide maintains a similar talazoparib exposure to that achieved with 1 mg QD monotherapy and a generally similar safety profile.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important identified and potential risks have been determined based on the safety and tolerability of talazoparib in the development programme with the characterization of these risks based on the data from safety data presented in Section SVII.1.2 and patients who

participated in the pivotal TALAPRO-2 (C3441021) study who received talazoparib in combination with enzalutamide.

For each risk, the reported TEAEs for patients in each pooled dataset presented in Section Module SIII were used to characterize the frequency and severity of each risk and the seriousness and outcomes of each important risk. All PTs listed in the AE tables were coded to MedDRA version 25.0.

To further characterize each risk post-authorisation, the MAH's safety database[e] was searched for all talazoparib cases reporting AEs or SAEs from CTs that coded to at least one relevant MedDRA PT (version 25.0) through the PM DLP of 15 October 2022 (refer to Annex 7 for safety database search terms for each risk).

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: none

Important Potential Risk: Second Primary Malignancies (other than MDS/AML)

Potential mechanisms

Talazoparib was clastogenic in *in vitro* chromosomal aberration and *in vivo* micronucleus assays, indicating potential for genotoxicity in humans.

Evidence source and strength of evidence

During the clinical development, amongst patients who received talazoparib monotherapy at the starting dose of 1 mg once daily for solid tumours, there were 12 TEAEs indicative of 6 second primary malignancy adverse events (excluding MDS/AML), and none amongst patients who received talazoparib monotherapy at doses other than 1 mg once daily.

In the pivotal mCRPC study there were 14 events of SPM in patients treated with talazoparib in combination with enzalutamide: 2 in Part 1 of the Study, and 12 in randomized Part 2 of the study. In comparison, 20 events of SPM were observed in Part 2 of mCRPC study in the placebo/enzalutamide arm (see Table 15 for more details).

Overall, as of 16 August 2022, Second Primary Malignancy has been reported in 26 out of 1199[f] (2.1%) solid tumour patients treated at any dose with talazoparib in clinical studies (See Characterization of the risk, below).

[e] The MAH's safety database contains cases of AEs reported spontaneously to the MAH, cases reported by health authorities, cases published in the medical literature, cases from MAH-sponsored marketing programs, cases from non-interventional studies, and cases of SAEs reported from clinical studies (including non-MAH-sponsored CTs) regardless of causality.

[f] Of the participants who initiated treatment in MDV3800-13 at talazoparib doses other than 1 mg/day, 5 initiated treatment with talazoparib 1 mg/day in the originating study and are also represented in the talazoparib 1 mg population in the tables below.

Evidence is confounded by prior exposure to other chemotherapeutic agents that may increase risk, and the inability to rule out the possibility of occurrence of second primary malignancies (other than MDS/AML) unrelated to treatment with talazoparib.

Characterisation of the risk

As of 16 August 2022, there were 26 TEAEs indicative of MDS/AML reported among all participants receiving talazoparib regardless of dose.

Clinical Trial data:

Table 15. Second Primary Malignancies (other than MDS/AML) - *Frequency with 95% CI*

Preferred Terms	Talazoparib 1 mg daily[a] (N= 690)		Talazoparib non 1 mg daily[b] (N=98)		Talazoparib+Enzalutamide[c] (N=416)		
	n	% (95% CI)	n	% (95% CI)		n	% (95% CI)
Number of participants with at least 1 relevant PT	**12**	**1.7% (1.0%, 3.0%)**	**0**	**0.0% (0.0%, 3.6%)**	**Number of participants with at least 1 relevant PT**	**14**	**3.4% (2.0%, 5.6%)**
Basal cell carcinoma	2	0.3% (0.1%, 1.0%)	0	0.0% (0.0%, 3.6%)	Colon cancer	3	0.7% (0.2%, 2.1%)
Squamous cell carcinoma of skin	2	0.3% (0.1%, 1.0%)	0	0.0% (0.0%, 3.6%)	Bladder transitional cell carcinoma	2	0.5% (0.1%, 1.7%)
Breast cancer	1	0.1% (0.0%, 0.8%)	0	0.0% (0.0%, 3.6%)	Lung adenocarcinoma	2	0.5% (0.1%, 1.7%)
Glioblastoma multiforme	1	0.1% (0.0%, 0.8%)	0	0.0% (0.0%, 3.6%)	Lung neoplasm malignant	2	0.5% (0.1%, 1.7%)
Intraductal proliferative breast lesion	1	0.1% (0.0%, 0.8%)	0	0.0% (0.0%, 3.6%)	Bladder cancer	1	0.2% (0.0%, 1.3%)
Lymphangiosis carcinomatosa	1	0.1% (0.0%, 0.8%)	0	0.0% (0.0%, 3.6%)	Gastric cancer	1	0.2% (0.0%, 1.3%)
Neoplasm	1	0.1% (0.0%, 0.8%)	0	0.0% (0.0%, 3.6%)	Lentigo maligna	1	0.2% (0.0%, 1.3%)
Neoplasm skin	1	0.1% (0.0%, 0.8%)	0	0.0% (0.0%, 3.6%)	Rectal neoplasm	1	0.2% (0.0%, 1.3%)
Ovarian neoplasm	1	0.1% (0.0%, 0.8%)	0	0.0% (0.0%, 3.6%)	Small cell lung cancer	1	0.2% (0.0%, 1.3%)
Pancreatic carcinoma	1	0.1% (0.0%, 0.8%)	0	0.0% (0.0%, 3.6%)			
Squamous cell carcinoma	1	0.1% (0.0%, 0.8%)	0	0.0% (0.0%, 3.6%)			

a. Includes all participants enrolled in 673-301, 673-201, PRP-001, MDV3800-14, MDV3800-13 (who completed studies 673-201, PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study), MDV3800-06, and C3441020. Participants who started Studies PRP-001, MDV3800-14, or 673-201 at Talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once.
Final database lock date for 673-301 was 22 March 2021, 673-201 was 31 October 2018, MDV3800-13 was 13 August 2021, C3441006 was 04 September 2020, and C3441020 was 20 November 2020. Date of last participant discontinued study for PRP-001 was 30 January 2017, and MDV3800-14 was 22 June 2017.

Table 15. Second Primary Malignancies (other than MDS/AML) - *Frequency with 95% CI*

Preferred Terms	Talazoparib 1 mg daily[a] (N= 690)		Talazoparib non 1 mg daily[b] (N=98)		Talazoparib+Enzalutamide[c] (N=416)		
	n	% (95% CI)	n	% (95% CI)		n	% (95% CI)
Number of participants with at least 1 relevant PT	**12**	**1.7% (1.0%, 3.0%)**	**0**	**0.0% (0.0%, 3.6%)**	**Number of participants with at least 1 relevant PT**	**14**	**3.4% (2.0%, 5.6%)**

b. Includes all participants enrolled in MDV3800-13 (who completed studies PRP-001, MDV3800-03, MDV3800-04, MDV3800-14, and 673-201, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib other than 1 mg once daily either in the originating or extension study).
Participants who initiated treatment in MDV3800-13 at talazoparib doses other than 1 mg/day, 5 of these participants initiated treatment with talazoparib 1 mg/day in the originating study and are also represented in the Talazoparib 1 mg population.

c. Includes data from Talazoparib C3441021 as of 16 August 2022.
95% Confidence Interval derived using Blaker method.
Participants with multiple events for a given preferred term are counted once only for each preferred term. Events are sorted by decreasing frequency of preferred term in Talazoparib 1 mg/day.
MedDRA Version: 25.0

Table 16. Second Primary Malignancies (other than MDS/AML) – *Seriousness/outcomes*

Important Potential Risk	Talazoparib 1 mg daily[a] (N= 690)		Talazoparib non 1 mg daily[b] (N=98)		Talazoparib+Enzalutamide[c] (N=416)		
	Serious Events (N=226) n (%)	Total (N=690) n (%)	Serious Events (N=43) n (%)	Total (N=98) n (%)		Serious Events (N=166) n (%)	Total (N=416) n (%)
Number of participants with at least one relevant PT	**7 (3.1)**	**12 (1.7)**	**0 (0)**	**0 (0)**	**Number of participants with at least one relevant PT**	**10 (6.0)**	**14 (3.4)**
Basal cell carcinoma	1 (0.4)	2 (0.3)	0 (0)	0 (0)	Colon cancer	2 (1.2)	3 (0.7)
Squamous cell carcinoma of skin	1 (0.4)	2 (0.3)	0 (0)	0 (0)	Bladder transitional cell carcinoma	2 (1.2)	2 (0.5)
Breast cancer	1 (0.4)	1 (0.1)	0 (0)	0 (0)	Lung adenocarcinoma	2 (1.2)	2 (0.5)
Glioblastoma multiforme	1 (0.4)	1 (0.1)	0 (0)	0 (0)	Lung neoplasm malignant	2 (1.2)	2 (0.5)
Intraductal proliferative breast lesion	1 (0.4)	1 (0.1)	0 (0)	0 (0)	Bladder cancer	1 (0.6)	1 (0.2)
Ovarian neoplasm	1 (0.4)	1 (0.1)	0 (0)	0 (0)	Gastric cancer	1 (0.6)	1 (0.2)

Table 16. Second Primary Malignancies (other than MDS/AML) – *Seriousness/outcomes*

Important Potential Risk	Talazoparib 1 mg daily[a] (N= 690)		Talazoparib non 1 mg daily[b] (N=98)		Talazoparib+Enzalutamide[c] (N=416)		
	Serious Events (N=226) n (%)	Total (N=690) n (%)	Serious Events (N=43) n (%)	Total (N=98) n (%)		Serious Events (N=166) n (%)	Total (N=416) n (%)
Number of participants with at least one relevant PT	**7 (3.1)**	**12 (1.7)**	**0 (0)**	**0 (0)**	**Number of participants with at least one relevant PT**	**10 (6.0)**	**14 (3.4)**
Pancreatic carcinoma	1 (0.4)	1 (0.1)	0 (0)	0 (0)	Lentigo maligna	0 (0.0)	1 (0.2)
Lymphangiosis carcinomatosa	0 (0)	1 (0.1)	0 (0)	0 (0)	Rectal neoplasm	0 (0.0)	1 (0.2)
Neoplasm skin	0 (0)	1 (0.1)	0 (0)	0 (0)	Small cell lung cancer	0 (0.0)	1 (0.2)
Neoplasm	0 (0)	1 (0.1)	0 (0)	0 (0)			
Squamous cell carcinoma	0 (0)	1 (0.1)	0 (0)	0 (0)			

a. Includes all participants enrolled in 673-301, 673-201, PRP-001, MDV3800-14, MDV3800-13 (who completed studies 673-201, PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with Talazoparib at 1 mg/day in either the originating or extension study), MDV3800-06, and C3441020. Participants who started Studies PRP-001, MDV3800-14, or 673-201 at Talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once.
Final database lock date for 673-301 was 22 March 2021, 673-201 was 31 October 2018, MDV3800-13 was 13 August 2021, C3441006 was 04 September 2020, and C3441020 was 20 November 2020. Date of last participant discontinued study for PRP-001 was 30 January 2017, and MDV3800-14 was 22 June 2017.

b. Includes all participants enrolled in MDV3800-13 (who completed studies PRP-001, MDV3800-03, MDV3800-04, MDV3800-14, and 673-201, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib other than 1 mg once daily either in the originating or extension study).
Participants who initiated treatment in MDV3800-13 at talazoparib doses other than 1 mg/day, 5 of these participants initiated treatment with talazoparib 1
mg/day in the originating study and are also represented in the Talazoparib 1 mg population.

c. Includes data from Talazoparib C3441021 as of 16 August 2022.
Participants with multiple events for a given preferred term are counted once only for each preferred term. Events are sorted by decreasing frequency of preferred term in Talazoparib 1 mg/day.
MedDRA Version: 25.0

Table 17. Second Primary Malignancies (other than MDS/AML) – *Severity and nature of risk*

		Severity					Total n (%)
		Mild or Grade 1 n (%)	Moderate or Grade 2 n (%)	Severe or Grade 3 n (%)	Life threatening or Grade 4 n (%)	Fatal or Grade 5 n (%)	
Talazoparib 1 mg daily[a] (N= 690)	**Number of participants with at least one relevant PT**	**3 (0.4)**	**4 (0.6)**	**5 (0.7)**	**0 (0.0)**	**0 (0.0)**	**12 (1.7)**
	Basal cell carcinoma	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	**2 (0.3)**
	Squamous cell carcinoma of skin	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	**2 (0.3)**
	Breast cancer*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.1)**
	Glioblastoma multiforme	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	**1 (0.1)**
	Intraductal proliferative breast lesion	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	**1 (0.1)**
	Lymphangiosis carcinomatosa	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	**1 (0.1)**
	Neoplasm	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.1)**
	Neoplasm skin	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.1)**
	Ovarian neoplasm	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	**1 (0.1)**
	Pancreatic carcinoma	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	**1 (0.1)**
	Squamous cell carcinoma	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.1)**
Talazoparib non 1 mg daily[b] (N= 98)	**Number of participants with at least one relevant PT**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**

Table 17. Second Primary Malignancies (other than MDS/AML) – *Severity and nature of risk*

		Severity					Total n (%)
		Mild or Grade 1 n (%)	Moderate or Grade 2 n (%)	Severe or Grade 3 n (%)	Life threatening or Grade 4 n (%)	Fatal or Grade 5 n (%)	
Talazoparib+ Enzalutamide[c] (N=416)	**Number of participants with at least one relevant PT**	3 (0.7)	1 (0.2)	10 (2.4)	0 (0.0)	0 (0.0)	**14 (3.4)**
	Colon cancer	1 (0.2)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	**3 (0.7)**
	Bladder transitional cell carcinoma	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	**2 (0.5)**
	Lung adenocarcinoma	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	**2 (0.5)**
	Lung neoplasm malignant	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	**2 (0.5)**
	Bladder cancer	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.2)**
	Gastric cancer	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	**1 (0.2)**
	Lentigo maligna	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.2)**
	Rectal neoplasm	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.2)**
	Small cell lung cancer	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	**1 (0.2)**

a. Includes all participants enrolled in 673-301, 673-201, PRP-001, MDV3800-14, MDV3800-13 (who completed studies 673-201, PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study), MDV3800-06, and C3441020. Participants who started studies PRP-001, MDV3800-14, or 673-201 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once.
Final database lock date for 673-301 was 22 March 2021, 673-201 was 31 October 2018, MDV3800-13 was 13 August 2021, C3441006 was 04 September 2020, and C3441020 was 20 November 2020. Date of last participant discontinued study for PRP-001 was 30 January 2017, and MDV3800-14 was 22 June 2017.
b. Includes all participants enrolled in MDV3800-13 (who completed studies PRP-001, MDV3800-03, MDV3800-04, MDV3800-14, and 673-201, subsequently enrolled in the open-label extension study MDV3100-13 and initiated treatment with talazoparib other than 1 mg once daily either in the originating or extension study). Date of last participant discontinued study for PRP-01 was 30 January 2017. Final database lock date for MDV3800-13 was 13 August 2021.
c. Includes data from Talazoparib C3441021 as of 16 August 2022.
Participants with multiple events for a given preferred term are counted once only for each preferred term.
Events are sorted by decreasing frequency of preferred term in total column.
Adverse event grades are evaluated based on National Cancer Institute (NCI) - Common Terminology Criteri afor AEs (CTCAE) (version 4.03).
MedDRA Version: 25.0
*Breast cancer is included in total column only as its toxicity grade is missing.

Post-marketing experience:

A cumulative search of the MAH's safety database through 15 October 2022 identified 18 talazoparib cases (15 form CT sources and 3 from PM sources) reporting events indicative of Second primary malignancies (see Annex 7 for search terms). These 18 cases represent a 0.7% reporting proportion of all 2648 talazoparib cases through 15 October 2022. Distribution of event by seriousness and clinical outcome is provided below:

Table 18. Second primary malignancies (other than MDS/MDL)

	No. of Events (% of total PTs)	**No. of Serious Events** (% of PT)	**No. of Events with Criterion of Hospitalisa-tion** (%of PT)	**Fatal**	**Resolved/ resolving**	**Resolved with sequelae**	**Not resolved**	**Unknown /no data**
CT data								
All PTs	**26 (100)**	**26 (100)**	**14 (53.8)**	**3 (11.5)**	**12 (46.2)**	**2 (7.7)**	**9 (34.6)**	**0**
Second primary malignancy	10 (38.5)	10 (100)	6 (60)	1 (10)	4 (40)	1 (10)	4 (40)	0
Basal cell carcinoma	2 (7.7)	2 (100)	0	0	1 (50)	0	1 (50)	0
Pancreatic carcinoma	2 (7.7)	2 (100)	2 (100)	1 (50)	1 (50)	0	0	0
Adenocarcino ma of colon	1 (3.8)	1 (100)	1 (100)	0	1 (100)	0	0	0
Colorectal adenocarcino-ma	1 (3.8)	1 (100)	0	0	0	0	1 (100)	0
Glioblastoma multiforme	1 (3.8)	1 (100)	1 (100)	0	0	1 (100)	0	0
Inflammatory myofibro-blastic tumour	1 (3.8)	1 (100)	1 (100)	0	1 (100)	0	0	0
Intraductal proliferative breast lesion	1 (3.8)	1 (100)	0	0	1 (100)	0	0	0
Lung adenocarcino ma	1 (3.8)	1 (100)	1 (100)	0	0	0	1 (100)	0
Malignant neoplasm of unknown primary site	1 (3.8)	1 (100)	1 (100)	1 (100)	0	0	0	0
Malignant ovarian cyst	1 (3.8)	1 (100)	0	0	1 (100)	0	0	0
Neuroendocrin e carcinoma	1 (3.8)	1 (100)	1 (100)	0	0	0	1 (100)	0
Squamous cell carcinoma	1 (3.8)	1 (100)	0	0	0	0	1 (100)	0
Squamous cell carcinoma of lung	1 (3.8)	1 (100)	0	0	1 (100)	0	0	0
Squamous cell carcinoma of skin	1 (3.8)	1 (100)	0	0	1 (100)	0	0	0

Table 18. Second primary malignancies (other than MDS/MDL)

	No. of Events (% of total PTs)	**No. of Serious Events** (% of PT)	**No. of Events with Criterion of Hospitalisa-tion** (%of PT)	**Fatal**	**Resolved/ resolving**	**Resolved with sequelae**	**Not resolved**	**Unknown /no data**
PM data								
All PTs	**6 (100)**	**6 (100)**	**0**	**0**	**0**	**0**	**0**	**6 (100)**
Second primary malignancy	3 (50)	3 (100)	0	0	0	0	0	3 (100)
Cervix neoplasm	1 (16.7)	1 (100)	0	0	0	0	0	1 (100)
Malignant melanoma	1 (16.7)	1 (100)	0	0	0	0	0	1 (100)
Ovarian cancer	1 (16.7)	1 (100)	0	0	0	0	0	1 (100)

For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

Risk factors and risk groups and preventability

Potential contributing factors for the development of second primary malignancies (other than MDS/AML) include previous platinum-containing chemotherapy, other DNA damaging agents, or radiotherapy. The incidences of second primary malignancies (other than MDS/AML) after first primary breast cancer are higher than the general population and have been estimated in several cohort studies, where rates range from 0.24 to 0.83 per 100 Patient-Years. Rates may vary due to various factors, including malignancy type definitions, cancer sites included, patient inclusion criteria, treatment patterns, and clinical approaches to follow up.[145] In addition, and underlying increased risk of ovarian cancer may be present in patients with mutated gBRCA.[146]

There are no known specific preventive measures to reduce the risk of second primary malignancies in patients treated with talazoparib. Patients being treated with talazoparib should be monitored for new onset malignancies as per standard clinical practice.

Impact on the risk-benefit balance of the product

Depending on location and type, second primary malignancies (other than MDS/AML) can be serious, life-threatening conditions. Currently, the impact to the overall risk-benefit balance is not known because a causal relationship between talazoparib and second primary malignancies (other than MDS/AML) has not been established. Cases of second primary malignancies (other than MDS/AML) reported in the continuing talazoparib development programme and in post-marketing surveillance will be continually reviewed to determine if guidance to healthcare professionals is warranted.

Public health impact

The expected risk of second primary malignancies due to talazoparib in the post-marketing setting is not known since the relationship between talazoparib administration and second primary malignancies has not been established.

Important Potential Risk: Reproductive and Developmental toxicity

Table 19. Reproductive and Developmental toxicity

Potential mechanisms	Talazoparib was clastogenic in in vitro chromosomal aberration and in vivo micronucleus assays, indicating potential for genotoxicity in humans.
Evidence source and strength of evidence	Based on findings from animal studies, talazoparib can cause embryo-foetal harm and may compromise male and female fertility. There are no available clinical data on talazoparib use in pregnant women or any clinical effects on fertility to inform a drug-associated risk.
Characterisation of the risk	**Clinical Trial data:** As of the data cutoff date of 16 August 2022, there were no relevant AEs suggestive of Reproductive and developmental toxicity[g]. **Post-marketing experience:** As of 15 October 2022, there were no relevant AEs captured from the MAH's safety database suggestive of reproductive and developmental toxicity.[g]
Risk factors and risk groups and preventability	Risk factors and risk groups include women of childbearing potential, pregnant women, and lactating women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving talazoparib. A highly effective method of contraception is required for patients and partners of patients during treatment with talazoparib. Male patients with female partners of reproductive potential or pregnant partners should be advised to use effective contraception (even after vasectomy), during treatment with talazoparib and for at least 4 months after the final dose.
Impact on the risk-benefit balance of the product	Currently, the impact to the overall risk-benefit balance is not known because the relationship of reproductive and developmental toxicity to talazoparib treatment has not been identified. The SmPC contains instructions to avoid pregnancy and utilise contraception in female patients and in male patients with female partners of reproductive potential.

[g] Please note that a total of 11 events were retrieved with the search criteria included in Annex 7 from clinical trials and an additional 7 cases (6 CTs and 1 PM) from the post-marketing safety database, however none of those was assessed as relevant for the risk.

Table 19. Reproductive and Developmental toxicity

Public health impact	The expected risk of reproductive and developmental toxicity due to talazoparib in the post-marketing setting is not known since the relationship between talazoparib administration and reproductive and developmental toxicity has not been established.

SVII.3.2. Presentation of the Missing Information

None.

Module SVIII. Summary of the Safety Concerns

Table 20. Summary of Safety Concerns

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

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

Pregnancy follow-up questionnaires (Exposure During Pregnancy Supplemental Forms) will be utilized to collect further data on reproductive and developmental toxicity.

- **Other forms of routine pharmacovigilance activities for safety concerns:**

Cumulative reviews of adverse events of interest will be provided in Periodic Safety Update Reports.

III.2. Additional Pharmacovigilance Activities

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

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

None.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

PAES: In order to further characterise the long-term efficacy of talazoparib in combination with enzalutamide for the treatment of adult patients with 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.

Table 21. Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
C3441021 (TALAPRO-2) Ongoing	Part 2 Primary Objective: 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 DDR status (Cohort 1) and in patients with	Long term efficacy	Final report	29/11/2024 (Submission to the EMA)

Table 21. Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
	mCRPC harbouring DDR deficiencies (Cohort 2). Part 2 key 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 DDR status (Cohort 1) and in patients with mCRPC harbouring DDR deficiencies (Cohort 2).			
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None	N/A	N/A	N/A	N/A

Abbreviations: BICR = blinded independent central review; DDR= DNA Damage Repair; EMA = European Medicines Agency; mCRPC = metastatic castration-resistant prostate cancer; N/A = Not applicable; OS = overall survival; rPFS = radiographic progression free survival.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 22. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks	
None.	None.
Important Potential Risks	
Second primary malignancies (other than MDS/AML)	Routine risk communication: SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Reproductive and developmental toxicity	Routine risk communication: - SmPC Section 4.4, 4.6 - PL section 2 What you need to know before you take Talzenna: Pregnancy and, breast-feeding and fertility. Routine risk minimisation activities recommending specific clinical measures to address the risk: Use of contraception in male and female patients and in male patients with female partners of reproductive potential. Other routine risk minimisation measures beyond the Product Information: None
Missing Information	
None.	None.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Table 23. 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.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Talzenna (talazoparib)

This is a summary of the Risk Management Plan (RMP) for Talzenna. The RMP details important risks of Talzenna, how these risks can be minimised, and how more information will be obtained about Talzenna's risks and uncertainties (missing information).

Talzenna's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how talazoparib should be used.

I. The Medicine and What It Is Used For

Talzenna monotherapy is authorised for the treatment of adult patients with germline BRCA mutated HER2-negative locally advanced or metastatic breast cancer (see SmPC for the full indication). The recommended dose of talazoparib monotherapy is 1 mg capsule taken orally once daily, for which 1 mg hard capsules are available. Talzenna is also available as 0.25 mg hard capsules to allow dose reductions to 0.75 mg, 0.5 mg, and 0.25 mg Talzenna.

Talzenna is proposed to be used 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 recommended dose of Talzenna when used in combination with enzalutamide is 0.5 mg.

Further information about the evaluation of Talzenna's benefits can be found in Talzenna's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Talzenna, together with measures to minimise such risks and the proposed studies for learning more about Talzenna's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of Talzenna is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Talzenna are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of talazoparib. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

Table 24. List of important risks and missing information

Important identified risks	None
Important Potential Risks	Second primary malignancies (other than MDS/AML)
	Reproductive and developmental toxicity
Missing Information	None

II.B Summary of Important Risks

Table 25. Important Potential Risk 1: Second Primary Malignancies (other than MDS/AML)

Evidence source and strength of evidence	During the clinical development, amongst patients who received Talzenna at the proposed starting dose of 1 mg once daily, there were 6 patients who experienced 7 second primary malignancy adverse events (excluding MDS/AML), and none amongst patients who received Talzenna at doses other than 1 mg once daily. In comparison, 1 case of second primary malignancy (Malignant melanoma) was reported in the PCT arm (N=126; 0.8%) of pivotal study 673-301 (EMBRACA). In the pivotal mCRPC study there were 14 events of SPM in patients treated with talazoparib in combination with enzalutamide: two (2) in part 1 of the study, and 12 in randomized part 2 of the study. In comparison, 20 events of SMP were observed in part 2 of mCRPC study in the placebo/enzalutamide arm. Overall, as of 16 August 2022, Second primary malignancy has been reported in 26 out of 1199[h] (2.1%) solid tumour patients treated at any dose with Talzenna in clinical studies. Evidence is confounded by prior exposure to other chemotherapeutic agents that may increase risk, and the inability to rule out the possibility of occurrence of

[h] Of the participants who initiated treatment in MDV3800-13 at Talzenna doses other than 1 mg/day, 5 initiated treatment with Talzenna 1 mg/day in the originating study and are also represented in the talazoparib 1 mg population.

Table 25. Important Potential Risk 1: Second Primary Malignancies (other than MDS/AML)

	second primary malignancies (other than MDS/AML) unrelated to treatment with Talzenna.
Risk factors and risk groups	Potential contributing factors for the development of second primary malignancies (other than MDS/AML) include previous platinum-containing chemotherapy, other DNA damaging agents, or radiotherapy. The incidences of second primary malignancies (other than MDS/AML) after first primary breast cancer are higher than the general population and have been estimated in several cohort studies, where rates range from 0.24 to 0.83 per 100 Patient-Years. Rates may vary due to various factors, including malignancy type definitions, cancer sites included, patient inclusion criteria, treatment patterns, and clinical approaches to follow up.[54] There are no known specific preventive measures to reduce the risk of second primary malignancies (other than MDS/AML) in patients treated with Talzenna. Patients being treated with talazoparib should be monitored for new onset malignancies as per standard clinical practice.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3 which provides in-vitro and in-vivo mutagenesis results Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

Table 26. Important Potential Risk 2: Reproductive and Developmental Toxicity

Evidence source and strength of evidence	Based on findings from animal studies, Talzenna can cause embryo-foetal harm and may compromise male and female fertility. There are no available clinical data on Talzenna use in pregnant women or any clinical effects on fertility to inform a drug-associated risk.
Risk factors and risk groups	Risk factors and risk groups include women of childbearing potential, pregnant women, and lactating women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving Talzenna. A highly effective method of contraception is required for patients and partners of patients during treatment with Talzenna.
Risk minimisation measures	Routine risk minimisation measures: - SmPC Section 4.4, 4.6 where advice is given regarding use of contraception in male and female patients as well as in male patients with female partners of reproductive potential or pregnant partners. - Package leaflet Section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	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

II.C Post-Authorisation Development Plan

Not applicable.

II.C.1 Studies which are Conditions of the Marketing Authorisation

The following study is condition of the marketing authorisation (obligation to conduct post-authorisation measures):

- Study C3441021 (TALAPRO-2): A Phase 3, Randomized, Double Blind, Placebo Controlled Study of Talazoparib With Enzalutamide in Metastatic Castration Resistant Prostate Cancer.

  Purpose of the study: 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 DDR status (Cohort 1) and in patients with mCRPC harbouring DDR deficiencies (Cohort 2).

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Talzenna.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 1 – EudraVigilance Interface – Not Applicable

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents – not applicable.

Follow-up forms – Exposure During Pregnancy (EDP) Supplemental Form.

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)									

For Pfizer internal use only	
Local #	Date Reported to Pfizer

PROTOCOL # **SUBJECT #**

Complete whenever an embryo or fetus has been exposed to study drug. Send as soon as EDP has been diagnosed, together with the SAE Report Form with the appropriate fields completed. If more space is needed, use additional copies of this page.

Pregnancy

First Day of Last Menstrual Period (DD-MMM-YYYY)

Estimated Date of Delivery (DD-MMM-YYYY)

Number of Foetuses

Gestation at time of initial exposure _____ weeks **Or, if number of weeks unknown:** ☐ First trimester? ☐ Second trimester? ☐ Third trimester?

Relevant History/Exposure to Products

Risk factors for adverse pregnancy outcomes including environmental or occupational exposures, medical disorder e.g. hypertension, diabetes seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, psychiatric or mental health disorders, sexual transmitted disorders, hepatitis, AIDS, and other predisposing factors for neurodevelopmental disorders. Any treatment for infertility (please specify).Family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

1) Did the mother smoke during this pregnancy? ☐ No ☐ Yes: Number per day? _____

2) Did the mother drink alcohol during this pregnancy? ☐ No ☐ Yes : Frequency? _____

3) Did the mother use illicit drugs during this pregnancy? ☐ No ☐ Yes : Frequency? _____

Obstetrical History *(Check the box if not applicable)*

☐ Not Applicable: No previous pregnancy

Number of previous pregnancies _____ Number of other children _____

Outcome of previous pregnancies (live birth, miscarriage, elective termination with specification of gestational length and context, late fetal death, ectopic pregnancy, molar pregnancy).

Previous maternal pregnancy complications. Previous fetal/neonatal abnormalities and type. History of sub-fertility.

OUTCOME OF PREGNANCY

Complete and send after the end of pregnancy in all cases when an embryo or fetus has been exposed to study drug

Date of outcome of pregnancy DD-MMM-YYYY

Mode of delivery (e.g., natural birth [i.e., vaginal delivery without medication or anesthesia], cesarean section): [_____]

Pregnancy outcome

Check one ☐ Full term live birth ☐ Preterm live birth ☐ Stillbirth* ☐ Spontaneous abortion/miscarriage* ☐ Induced abortion ☐ Unknown

Gestational age at birth in weeks, (if known): _____

Complete also the Serious Adverse Event section of the report

Infant

Check one ☐ Normal ☐ Congenital Malformation/Anomaly** ☐ Other neonatal problem** ☐ Unknown

Other neonatal problem/abnormality (include dysmaturity, neonatal illness, foetal distress, amniotic fluid abnormal, anormal placenta hospitalization, drug therapies) Specify:

Apgar Score 1min _____ 5min _____

☐ Male ☐ Female Birthweight _____ grams ***Or, if birthweight in grams unknown:*** Birthweight ☐ lb ☐ oz

Length at birth: _____ ☐ in ☐ cm Head Circumference at birth: _____ ☐ in ☐ cm

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)									
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For Pfizer internal use only	
Local #	Date Reported to Pfizer
[ ]	[ ]

PROTOCOL # [ ] **SUBJECT #** [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

*****Complete also the Serious Adverse Event section of the report, specifying the diagnosis as the Serious Adverse Event***

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)									

For Pfizer internal use only	
Local #	Date Reported to Pfizer

PROTOCOL # **SUBJECT #**

Paternal Information *(Check the box if not applicable)*

☐ Not Applicable

Date of Birth (dd-Mmm-yyyy) : or **Occupation**

Age (years): or

Age group (e.g., adult):

Relevant History

Risk factors including environmental or occupational exposures, e.g. AIDS, toxins. Family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

Exposure to Products

Where any drugs (e.g., OTC, medical prescription) taken by the father during the mother's pregnancy? ☐ No ☐ Yes, *please specify*

Product	Indication	Start Date \ Stop Date	Reason for stopping	Dose	Formulation	Frequency
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				

Exposure to Products - Recreational Drug Use

1) Did the father smoke during the mother's pregnancy? ☐ No ☐ Yes: Number per day?

2) Did the father drink alcohol during the mother's pregnancy? ☐ No ☐ Yes : Frequency?

3) Did the father use illicit drugs during the mother's pregnancy? ☐ No ☐ Yes : Frequency?

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)									
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For Pfizer internal use only	
Local #	Date Reported to Pfizer
[ ]	[ ]

PROTOCOL # [ ]

SUBJECT #								
[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)									

For Pfizer internal use only	
Local #	Date Reported to Pfizer

PROTOCOL # **SUBJECT #**

Paternal Information *(Check the box if not applicable)*

☐ Not Applicable

Age (years) **Date of Birth** DD-MMM-YYYY **Occupation**

Relevant History

Risk factors including environmental or occupational exposures, e.g. AIDS, toxins. Family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

Exposure to Products

Where any drugs (e.g., OTC, medical prescription) taken by the father during the mother's pregnancy? ☐ No ☐ Yes, *please specify*

Product	Indication	Start Date \ Stop Date	Reason for stopping	Dose	Formulation	Frequency
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				

Exposure to Products - Recreational Drug Use

1) Did the father smoke during the mother's pregnancy? ☐ No ☐ Yes: Number per day?

2) Did the father drink alcohol during the mother's pregnancy? ☐ No ☐ Yes : Frequency?

3) Did the father use illicit drugs during the mother's pregnancy? ☐ No ☐ Yes : Frequency?

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.