26 April 2019
EMA/270498/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Talzenna

nternational non-proprietary name: talazoparib

Procedure No. EMEA/H/C/004674/0000

Note

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

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List of abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BMN 673	BioMarin Pharmaceuticals, Inc. legacy compound number for talazoparib (also known as PF-06944076, MDV3800)
BOR	best overall response
bpm	beats per minute
BRCA	breast cancer susceptibility gene
BRCA1	breast cancer susceptibility gene 1
BRCA2	breast cancer susceptibility gene 2
CA 15.3	cancer antigen 15.3
CA 27.29	cancer antigen 27.29
CBR24	clinical benefit rate at 24 weeks
CDx	companion diagnostic
CHMP	Committee for Medicinal Products for Human Use
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
CR	complete response
CRF	case report forms
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
CV	coefficient of variation
CYP	cytochrome P450
DCT	data collection tools
DMC	data monitoring committee
DFI	disease free interval
DNA	deoxyribonucleic acid
DOE	Design of experiments
DOR	duration of response
EC	ethics committee

ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
EDR	early discrepancy rate
EMA	European Medicines Agency
EORTC QLQ-BR23	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer Module
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
ER	estrogen receptor
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GnRH	gonadotropin-releasing hormone
HDPE	high density polyethylene
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRD	Homologous recombination deficient/deficiency
ICH	International Council for Harmonisation
INR	international normalized ratio
IQR	interquartile range
IRF	independent radiology facility
ITT	intent-to-treat
IXRS	interactive voice and web response system
LDR	late discrepancy rate
MDS	myelodysplastic syndrome
MDV3800	Legacy Medivation, Inc. compound number for talazoparib (also known as PF-06944076, formerly BMN 673)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeat measurement
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
mTOR	mechanistic target of rapamycin
NBCC	National Breast Cancer Coalition
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	objective response rate
PARP	poly ADP-ribose polymerase
PCT	physician's choice treatment
PD	Pharmacodynamics

PFS	progression-free survival
PFS2	progression on post-study anticancer therapy
PK	Pharmacokinetic(s)
P-gp	P-glycoprotein
PgR	progesterone receptor
PR	partial response
PRO	patient-reported outcomes
QoL	quality of life
QSR	Quality System Regulations
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF50	surviving fraction 50%
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TBL	total bilirubin
TNBC	triple-negative breast cancer
TTD	time to deterioration
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
VTE	venous thrombotic event
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 27 April 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Talzenna, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 October 2016.

The applicant applied for the following indication: Talzenna is indicated for the treatment of adult patients with germline breast cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance talazoparib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP on 27 June 2013 (EMEA/H/SA/2545/1/2013/III), 25 March 2015 (EMEA/H/SA/2545/2/2015/I, EMEA/H/SA/2545/1/FU/1/2015/II), and 22 June 2017 (EMEA/H/SA/2545/2/FU/1/2017/I,

EMEA/H/SA/2545/1/FU/2/2017/II). The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:

- Definition of starting materials; dissolution methods to demonstrate comparability across strengths/CMC changes; in vitro analytical comparability for additional manufacturing site; bracketing approach for batch data; stability studies.
- Adequacy of the overall non-clinical toxicology programme to support MAA.
- A multicentre, multinational, randomised, active-controlled phase 3 study with physician's choice as comparator: Proposed study population (patients with locally advanced or metastatic breast cancer with BRCA 1 and/or BRCA 2 mutation); selection of physician's choice comparator arm; progression free survival as primary endpoint; safety assessments and monitoring approach; statistical assumptions and approach to testing primary and secondary endpoints, control of type 1 error, stratification factors.
- Adequacy of the clinical pharmacology package to support MAA.
- Overall registrational strategy: adequacy of the phase 3 study, supported by data from a Phase 2 open label study, and the overall safety database to support full MAA; applicability of a conditional marketing authorisation in the proposed indication.
- Clinical demonstration of comparability between 4 × 0.25 mg and 1 mg capsules.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Kolbeinn Gudmundsson

The application was received by the EMA on	27 April 2018
The procedure started on	24 May 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	14 August 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	13 August 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 August 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 September 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 December 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	6 February 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	28 February 2019

The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 April 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Talzenna on	26 April 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication is for treatment of adult patients with germline breast cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Breast cancer is the 2nd most common cause of cancer deaths in women, despite improvements in screening and treatment regimens. According to the World Health Organization, in 2012, 1.7 million women were diagnosed with breast cancer and over 522,000 women died due to the disease[1]. In Europe in 2018 approximately 522,513 subjects were diagnosed with breast cancer and approximately 137,707 subjects died due to the disease[2].

2.1.3. Biologic features

Breast cancer is a biologically diverse and genetically heterogeneous disease but approximately 20 - 25% of hereditary breast cancers and 5 - 10% of all breast cancers are associated with mutations in breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2)[3], which are key components in the repair pathway for DNA double-strand breaks. In the United States (US) and Europe, women in the general population have a 12% lifetime risk of developing breast cancer[4,5]. In contrast, 55% to 65% of women who inherit a BRCA1 mutation and approximately 45% of women who inherit a BRCA2 mutation will develop breast cancer by age 70[6, 7, 8]. Poly (ADP-ribose) polymerase-1 (PARP1) is an enzyme with essential role in recognition and repair of single-strand DNA breaks through base excision repair process.

Approximately 70% of BRCA1 mutated breast cancers present as triple negative breast cancer (TNBC). In contrast, breast cancer patients carrying mutations in the BRCA2 gene are more likely to be positive for expression of the estrogen receptor (ER) and progesterone receptor (PgR) and only approximately 20% have TNBC[9].

[1] World Health Organization. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. International Agency for Research on Cancer (IARC), World Health Organization (WHO). Available: http://globocan.iarc.fr/Default.aspx
[2] The Global Cancer Observatory, March, 2019.
[3] Easton DF. How many more breast cancer predisposition genes are there? Breast Cancer Res 1999;1(1):14-7.
[4] Howlader N, Noone AM, Krapcho M, et al. (editors). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
[5] Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Ann Oncol 2005;16:481-8.
[6] Balmana J, Diez O, Rubio I, et al. BRCA in breast cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2010;21(Suppl 5):v20-2.
[7] Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25(11):1329-33.
[8] Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: A combined analysis of 22 studies. Am J Hum Genet 2003;72(5):1117-30
[9] Mavaddat et al 2012

Deleterious gBRCA mutations increase the risk of breast (and ovarian) cancer through homologous repair deficiency which develops as a consequence of haplo-insufficiency or locus-specific loss of heterozygosity, i.e. the wild type BRCA allele is no longer sufficiently active to achieve homologous repair of DNA breaks.

gBRCA may be known in the individual patient prior to the onset of cancer of the breast or ovary, but the cancer may manifest itself in ways not different from non-BRCA related disease.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging, and confirmed by pathological assessment. Disease stage is assessed according to the TNM system[10].

Well-known prognostic and predictive factors for breast cancer include hormone receptor and HER2 expression. Estrogen receptor-negative, PgR-negative, HER2-negative tumours, known as TNBC, are associated with a poor prognosis.

Metastatic TNBC has the worst prognosis of all breast cancer subtypes, with a median PFS of 3 to 5 months and a median overall survival of <12 months with currently available therapies[11, 12, 13, 14, 15].

2.1.5. Management

Prophylactic surgery in gBRCA carriers is one way to reduce the lifetime risk of cancer.

The choice of treatment is informed by tumour receptor and HER2 status at the time of initiation, as tumour characteristics can evolve over time. A variety of treatments are approved or recommended for hormone receptor-positive HER2-negative disease and TNBC without specification of BRCA mutation status.

Initial therapy of gBRCA positive breast cancer still follows the standards of therapy in breast cancer, but early treatment with platinum compounds in e.g. triple negative breast cancer has emerged as an alternative in the standard of care in the present decade. The results of the olaparib, another PARPi, study in recurrent HER2 negative, gBRCA positive breast cancer has influenced clinical practice[16].

Treatment of patients with advanced or metastatic breast cancer is palliative and the aim of the treatment is to reduce symptoms and prolong life with preservation of quality of life. Treatment of advanced or metastatic breast cancer can include surgery, radiotherapy, interventional radiology and systemic palliative treatment with number of different anti-neoplastic agents including anti-hormonal drugs, biologicals, targeted treatments and cytotoxic agents. In case of palliative treatment, the use of systemic treatments is generally sequential, mainly monotherapy, based on patient characteristics, patient previous medical history, previous treatments, disease biology, disease burden and both the patient and physician preferences and experience.

[10] 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)
[11] Kast K, Link T, Friedrich K, et al. Impact of breast cancer subtypes and patterns of metastasis on outcome. Breast Cancer Res Treat 2015;150(3):621-9.
[12] Chacón RD, Costanzo MV. Triple-negative breast cancer. Breast Cancer Res 2010;12(Suppl 2):S3.
[13] Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol 2007;25(33):5210-7.
[14] von Minckwitz G, Puglisi F, Cortes J, et al. Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15(11):1269-78.
[15] Gerratana L, Fanotto V, Bonotto M, et al. Pattern of metastasis and outcome in patients with breast cancer. Clin Exp Metastasis 2015;32(2):125-33.
[16] Robson M, Im S-A, SenKus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 2017;377(6):523-33.

For patients with progressive germline BRCA mutated, HER2 negative, locally advanced or metastatic breast cancer and indication for new anti-neoplastic treatment, after exhaustion of anti-hormonal agents and anti-CDK4/6 agents if indicated, treatment with PARP inhibitors or next line palliative chemotherapy, including capecitabine, eribulin and platinum containing cytotoxic agents, can be considered as next treatment option[10,17].

Regardless of the available treatment options, the disease condition remains incurable with limited life expectancy and near continuous need for palliative systemic treatment with the side effects that generally follow cytotoxic treatments, including fatigue and general health deterioration, and intermittently progressive disease with increasing disease related symptoms. There is an unmet medical need for patients with advanced or metastatic HER2 negative breast cancer.

About the product

Talazoparib (PF-06944076, formerly BMN 673 or MDV3800) is a PARP inhibitor. The chemical name of talazoparib free base is (8*S*,9*R*) 5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3*H*-pyrido[4,3,2-*de*]phthalazin-3-one. Talazoparib is provided as the 4 methyl-benzenesulfonate (tosylate) salt.

Talazoparib is an inhibitor of PARP enzymes, PARP1, and PARP2. PARP enzymes are involved in cellular DNA damage response signalling pathways such as DNA repair, gene transcription, 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, thereby resulting in apoptosis and/or cell death. Treatment of cancer cell lines that are harbouring defects in DNA repair genes with talazoparib single agent leads to increased levels of γH2AX, a marker of double stranded DNA breaks, and results in decreased cell proliferation and increased apoptosis. Talazoparib anti-tumour activity was also observed in a patient-derived xenograft (PDX) BRCA mutant breast cancer model where the patient was previously treated with a platinum-based regimen. In this PDX model talazoparib decreased tumour growth and increased γH2AX level and apoptosis in the tumours (see SmPC section 5.1).

The applicant applied for the following indication: Talzenna is indicated for the treatment of adult patients with germline breast cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer.

The recommended indication is as follows: Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2 mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments (see section 5.1). Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.

The recommended dose is 1 mg talazoparib once daily. Patients should be treated until disease progression or unacceptable toxicity occurs.

Talzenna is available as hard capsules (0.25 mg and 1 mg).

[17] NCCN 2018

Treatment with Talzenna should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Patients should be selected for the treatment of breast cancer with Talzenna based on the presence of deleterious or suspected deleterious germline BRCA mutations determined by an experienced laboratory using a validated test method.

Genetic counselling for patients with BRCA mutations should be performed according to local regulations, as applicable (see SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 0.36 mg or 1.45 mg talazoparib tosylate, (equivalent to 0.25 mg or 1 mg of talazoparib free base, respectively).

Other ingredient is silicified microcrystalline cellulose (sMCC). The capsule shells contain hypromellose (HPMC), titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (E172).

The printing ink consists of shellac, propylene glycol, ammonium hydroxide, black iron oxide and potassium hydroxide.

The product is available in High-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat induction seal (HIS) liner and in polyvinyl chloride / polyvinylidene chloride (PVC/PVdC) blister with an aluminum peel off foil lidding in cartons, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of talazoparib tosylate is (8*S*,9*R*)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3*H*-pyrido[4,3,2-de]phthalazin-3-one 4-methylbenzenesulfonate (1:1) corresponding to the molecular formula $C_{26}H_{22}F_2N_6O_4S$ (tosylate salt) or $C_{19}H_{14}F_2N_6O$ (free base). It has a relative molecular mass 552.56 g/mol (tosylate salt) or 380.35 g/mol (free base) and has the structure shown in Figure 1.

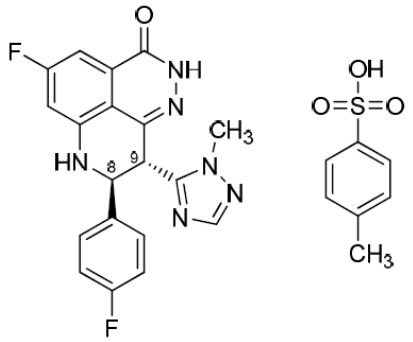


Figure 1 Structure of talazoparib tosylate

The structure of the active substance (AS) was elucidated by a combination of NMR (^{1}H, ^{13}C and ^{19}F; 1D and 2D experiments), mass spectrometry (ESI+ and MSMS), IR spectroscopy and UV spectrometry. The obtained

spectra are in agreement with the assigned structure. Additionally, investigations on the polymorphic form were conducted by X-ray powder diffraction (P-XRD).

Talazoparib tosylate appears as a white to yellow solid non-hygroscopic crystalline powder with a low solubility.

Talazoparib has two asymmetric centres, giving four possible stereoisomers. The absolute configuration at the 8-position is the *S* optical isomer. The absolute configuration at the 9-position is the *R* optical isomer.

Talazoparib tosylate exists as a single crystal form and no other polymorphs have been observed through extensive screening studies during development including conditions covering the solvent compositions used in the final isolation process.

Manufacture, characterisation and process controls

The manufacturing process of talazoparib tosylate comprises eight consecutive manufacturing steps, of which three are true chemical transformations as defined in ICH Q11 (Steps 1, 2 and 5). The remaining steps are purification and salt-formation steps. The proposed starting materials are consistent with the general principles outlined in ICH Q11 and are controlled by sufficient specifications. Potential and actual impurities were well discussed with regards to their origin and characterised. The impurities present in the starting materials have been studied with fate and purge studies and this data, along with batch history, have been used to develop appropriate starting material specifications that, along with the talazoparib tosylate manufacturing process, ensure control of talazoparib tosylate quality. Specifications were established for selected isolated intermediates.
An enhanced development program was executed to define the commercial manufacturing process of talazoparib tosylate. Critical quality attributes of the active substance, process knowledge and sound scientific judgement have been used to perform a preliminary assessment of the potentially significant process parameters. These parameters were evaluated in Design of Experiments (DOEs). Multivariate and univariate experiments have then been undertaken to deduce the final critical process parameters and IPC tests. No design space has been claimed. The control strategy applied in the manufacturing process is satisfactory and is considered sufficient to guarantee the quality of the final active substance.

The active substance is packaged in a a container which is suitable for pharmaceutical or “in contact with food” use and complies with the EU Regulation 10/2011 and amendments, as well as Ph. Eur. 3.1.3. Satisfactory specifications for the packaging materials are included in this section.

Specification

Talazoparib tosylate active substance specification includes appropriate tests and limits for appearance (visual), particle size (laser diffraction), identification (IR, chiral HPLC), enantiomeric purity (chiral HPLC), assay (UPLC), counter ion (Ph. Eur.), residual solvents (HS-GC), residue on ignition (Ph. Eur.), water content (Karl-Fischer) and organic impurities (UPLC, HPLC).

The specifications for the active substance are based on batch analyses of several batches of talazoparib tosylate manufactured by the commercial process, and batches used for clinical and toxicological, stability data as well as ICH recommended Guidelines (Q3A, Q3C, Q3D, Q6A and S9). The maximum daily dose (MDD) for talazoparib tosylate is 1.45 mg/day (corresponding to 1 mg of talazoparib base). As talazoparib tosylate is indicted for late stage cancer, the applicant’s proposal to control impurities at acceptance criteria higher than the ICH Q3A recommended thresholds is acceptable.

The analytical procedures used in the control of the active substance have been satisfactorily described and non-compendial methods have been validated in accordance with the ICH guidelines. Information regarding the reference standards used in the analytical testing is satisfactory.

Batch analysis results and certificates of analysis of a sufficient number of commercial scale batches of the active substance manufactured at the proposed manufacturing site have been presented. The results met the specification criteria and confirm consistency of the manufacturing process from batch to batch.

Stability

Stability data on three production scale batches of active substance stored in the intended commercial packaging for up to 24 months under long term conditions (25 °C / 60 % RH), and for up to 6 months under accelerated conditions (40 °C / 75 % RH) was provided according to the ICH guidelines.

Samples were tested for appearance, water content, related substances, enantiomeric purity, assay and solid form. The test methods were the same as for release and are stability indicating. No significant changes to any of the measured parameters were observed under long term and accelerated conditions and all remained within specification.

Supportive stability data are also available through 36 months and 6 months at 25°C/60% RH and 40°C/75% RH, respectively. No significant change were observed in any of the monitored parameters through 36 months and 6 months at 25°C/60% RH and 40°C/75% RH respectively, compared to the initial values.

Photostability was investigated as per ICH Q1B on one commercial scale batch. The active substance did show slight signs of degradation after exposure to light without the protection of the primary packaging material and is hence considered to be photosensitive. This is mitigated by the use of an aluminium pouch as part of the container closure system.

Stress testing was conducted in solution (acidic, alkaline and oxidizing conditions), as well as solid state (heat and light). Degradation was observed under acidic, peroxide oxidation and light exposed conditions; the highest degradation occurred under alkaline conditions. Results from mass balance demonstrate that the method for assay and related substances is stability indicating.

Based on the presented stability data, the proposed re-test period of 36 months is considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Talzenna is provided as an immediate release 0.25 mg and 1 mg strengths hard hypromellose (HPMC), opaque capsules for oral administration. The strengths are differentiated by capsule shell colour and printing. The 0.25 mg strength capsules are size 4, (white body/ivory cap) of which the body is printed with “TLZ 0.25” and the cap printed with “Pfizer” in black. The 1 mg strength capsules are size 4, (white body/light red cap) of which the body is printed with “TLZ 1” and the cap printed with “Pfizer” in black ink.
The two capsule strengths are dose proportional with respect to the active substance (AS) content; the amount of filler is changed to account for the change in AS within the meaning of condition c i) and iii) of the bioequivalence guideline. The excipients and container closure system are common for this type of dosage form. Silicified microcrystalline cellulose NF (sMCC) is a co-processed material consisting of microcrystalline cellulose particles and colloidal silicon dioxide.

Compatibility of the AS with silicified microcrystalline cellulose was investigated by exposing capsules of both strengths under open dish conditions.

The goal for formulation development across different drug product generations (DP Gen) was to improve capsule manufacturability and scalability suitable for each stage of clinical development, while minimising the potential impact on finished product performance. This was accomplished by maintaining essentially the same qualitative formulation composition, but modifying the level and grade of sMCC, active susbtance loading, and the capsule fill weight.
The manufacturing processes for DP Gen 2.0 and DP Gen 3.1 have similar manufacturing processes that include processing steps for screening, mixing, and encapsulation; DP Gen 3.1 has an additional blending step after the mixing step. A detailed description of the formulation used in clinical studies throughout the development of talazoparib was provided.
The applicant applied Quality by design (QbD) concepts to develop Talzenna hard capsules. The quality target product profile (QTPP), was defined based on the formulation developed for clinical studies, manufacturing process considerations and the properties of the active substance.

Identification of product critical quality attributes (CQAs) was based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attribute of the finished product. Pharmaceutical development focused on those CQAs that could be impacted by a realistic change to the finished product formulation or manufacturing process. The CQAs were selected based on prior information and knowledge gained from pharmaceutical development studies of the same or similar types of formulations.

Attributes and parameters have been categorised as either critical or non-critical, based on their impact to the product quality. Where a quality attribute has been designated as critical (CQA), associated elements of the control strategy have been explained in detail. Ranges where acceptable product can be made have been identified for process parameters. The control strategy encompasses finished product specifications, compendial tests and GMP controls to ensure that the manufacturing process will consistently produce a finished product which fulfils all the quality attributes listed in the QTPP.

The process understanding developed for each unit operation was used to define the proposed commercial manufacturing process. The process consists of manufacturing a simple binary dry mix of the API with the excipient silicified microcrystalline cellulose, followed by encapsulation. A series of experiments was conducted to study the influence of the selected process parameters on the critical quality attributes of the drug product. Based on these experiments, process target values and acceptable ranges were established. Experiments were conducted on full commercial scale. No design space is claimed.

Talazoparib capsules are immediate release (IR) products designed to disintegrate and dissolve rapidly under the physiological conditions in the stomach. The solubility of talazoparib tosylate is low across the physiological pH range at 37 °C. The highest dose strength/clinical dose for talazoparib (1 mg), however, is soluble in less than 250 mL of aqueous media. Hence, talazoparib absorption is expected to be neither solubility-limited nor reliant on dissolution performance.

A dissolution method was developed and validated for the release and stability testing of talazoparib capsules. Given the solubility of the active substance and the simplicity of the formulation as well as the tightening of the dissolution specification it is deemed that there is no need for further investigation of the discriminatory properties of the dissolution method.
Two container closure systems are proposed for Talzenna 0.25 mg and 1 mg hard capsules:

- High-density polyethylene (HDPE) bottles and polypropylene (PP) closures with heat induction (HIS) seal liners

- Polyvinyl chloride/polyvinylidene chloride (PVC/PVdC) blisters with aluminum peel off foil lidding

Specifications and analytical procedures for control of the packaging material were provided in the dossier. The HDPE containers, the PP caps and the PVC/PVdC duplex film comply with EU Regulation 10/2011, as well as Ph.Eur. 3.1.3 and 3.2.2. Compliance of the aluminium foil (sealing film) with EU Regulation 10/2011 and Directive 94/62/EC has also been stated.

Manufacture of the product and process controls

Talazoparib immediate release capsules are manufactured by a conventional manufacturing process which includes dry mixing/blending and encapsulation. Because of the low active substance load of both strengths (< 2%), the manufacturing process is regarded as non-standard process (Guideline on Process Validation for Finished Products - Information and Data to be Provided in Regulatory Submissions, EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1).

Critical process parameters have been identified and suitable in-proces controls are put in place.
Talazoparib tosylate is a clastogenic agent therefore the manufacture and development of the capsules has to be performed within high containment facilities.

The manufacturing process has been validated on three commercial scale batches of each strength. Process validation results comply with set acceptance criteria.

It has been demonstrated that the manufacturing process is sufficiently robust to provide assurance that hard capsules of consistent quality, complying with the designated specification, are produced.

Product specification

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

The finished product is released on the market through traditional final product release testing.

The maximum daily dose (MDD) for Talzenna is 1.45 mg/day (corresponding to 1 mg of talazoparib base). The proposed limits for specified and unspecified impurities are in line with ICHQ3B and hence acceptable.

A risk assessment on elemental impurities was performed on the talazoparib finished product as per ICH Q3D (Option 1). Based on the outcome, no controls or acceptance criteria for individual elemental impurities are proposed for talazoparib finished product, as the risk of elemental impurities being present at levels above the oral PDEs has been established to be negligible.

Chiral purity of talazoparib tosylate active substance is controlled via the active substance specification and this was considered sufficient based on the information that was presented. All impurities, including chiral, are appropriately controlled via the drug substance and drug product specifications.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis results for historical batches of both strengths used in the clinical program, as well as results of the most recent commercial scale batches for both strengths were provided in the dossier. All parameters are

within the specified limits. Impurities are well controlled. It is concluded that the process is well controlled and that the finished product can be manufactured with consistent quality and meeting its specifications.

Stability of the product

Stability data of 12 commercial scale batches of Talzenna (three batches of each strength and container closure system) were stored under long term conditions (25°C±2°C / 60%±5% RH) and intermediate conditions (30°C±2°C / 75%±5% RH) for up to 12 months and for up to 6 months under accelerated conditions (40°C±2°C / 75%±5% RH) according to the ICH guidelines were provided. The stability batches were with two different batches of active substance. The primary packaging was representative of the one proposed for marketing.

The following parameters have been investigated: appearance, assay, related substances, water content, dissolution and microbial quality. The methods used were the same as for release testing and are stability indicating.

The product is generally very stable in both proposed container packaging systems and only slight signs of degradation are observable at higher temperatures and humidity. The results showed no general trends for degradation. At accelerated and intermediate conditions, an increase of impurities is noticeable over time. Furthermore, a gradual increase in water content can be observed. No change in dissolution and assay is noticed for the time-frame covered so far under all storage conditions.

Forced degradation studies were performed. The protocol included degradation in the solid state by heat (70°C), humidity (70°C/75%RH) and light (ICH Option 1). Results from mass balance demonstrate that the method for assay and related substances is stability indicating.

A photostability study has been performed on unprotected Talzenna 0.25 mg and 1.0 mg hard capsules, as well as protected by the primary packaging (blisters and HDPE container). The conditions of the study were selected according to ICH Q1B. The samples were tested for appearance, degradation products, assay, dissolution and water content. The drug product did show signs of degradation after exposure to light without the protection of the respective primary packaging materials. The degradation is far more pronounced for the lower strength. All other tested quality attributes remain unchanged, except for a slight decrease in assay which balances the increase in total impurities. No degradation trends were observed when the capsules were protected by the respective primary packaging material. As no significant changes were observed during the photostability studies, the finished product was concluded to be stable against light.

Based on the provided stability data, the proposed shelf life of 2 years without special storage conditions, as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

None of the excipients used in the manufacture of talazoparib capsules are of human or animal origin

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical primary and secondary pharmacodynamic studies and safety pharmacology studies were submitted. All pivotal studies (general toxicity, developmental and reproductive toxicity, genetic toxicity, phototoxicity, hERG and safety pharmacology) were conducted in compliance with GLP. For *in vitro* assessment of DNA damage and cytotoxicity markers, non-GLP studies were provided. Talazoparib is also referred to as PF 06944076, MDV3800, BMN 673, LT-00673 in some of these studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro

Talazoparib activity was assessed with a panel of 13 PARP enzymes using a biochemical assay that measured incorporation of biotin-NAD^+ in ADP-ribose polymers onto histone proteins. IC50 values for talazoparib were determined for all enzymes in the PARP panel and are summarized in the following table:

Table 1: Selectivity of PARP Inhibition in an Enzymatic Assay

IC50 (nM)	
PARP Enzyme	**Talazoparib (PF-06944076)**
PARP1	0.7
PARP2	0.3
PARP3	22.0
TNKS1	13.5
TNKS2	4.7
PARP6	574
PARP8	225
PARP11	517
PARP12	9600
PARP7, PARP10, PARP 14, PARP15	>10000

IC50 values for PARP inhibition by various PARP inhibitors from a single experiment where each value was determined from an 11-point dose response curve performed in duplicate. All 22 data points were fit with a single curve to generate the IC50 value.
IC50 = 50% inhibitive concentration; PARP = poly(adenosine diphosphate [ADP]-ribose) polymerase.
Source: Study PF-06944076_02Nov17_092045

Talazoparib Cytotoxic Activity in Cell Lines with DNA Repair Deficiencies

Talazoparib was assessed for cytotoxic activity in cancer cell lines harboring defects in DNA repair pathways. A CellTiter-Glo Luminescent cell viability assay was conducted after 5 days of treatment for PC-3 and HCT-116, or 12 days of treatment for all other cell lines, which were incubated with test compounds at 0.128 nM to 10,000 nM.

Table 2: Summary of Key Pharmacological Properties of Talazoparib

Talazoparib Cytotoxicity			
Human Cell line	**Cancer Type**	**Mutation**	**IC50**
Capan-1	Pancreatic	BRCA-2	5.0 nM
MX-1	Breast	BRCA-1	0.3 nM
MDA-MB-468	Breast	PTEN	3.7 nM
LNCaP	Prostate	PTEN	4.3 nM
PC-3	Prostate	PTEN	4.4 nM
HCT-116	Colorectal	MLH-1	10.6 nM
MRC-5	Normal primary cells	No reported DNA repair mutations	306.0 nM
MDA-MB-231	Breast	No reported DNA repair mutations	261.8 nM
LoVo	Colorectal	No reported DNA repair mutations	257.7 nM
A549	Adenocarcinoma alveolar basal epithelial cells	No reported DNA repair mutations	>1000 nM

Assay was conducted in triplicate at final compound concentrations of 10000, 2000, 400, 80, 16, 3.2, 0.64[a], and 0.128 nM. Curve fit for IC50 was generated using GraphPad Prism 5 software. IC50 = Half maximal inhibitory concentration.
a. Corrected mathematical error in original report. Source: Study BMN673-10-093

Effect of Talazoparib on PARP Trapping

The potency to trap PARP–DNA complexes varies widely across the different PARPi and is not correlated with the potency of their PARP catalytic inhibition (Murai et al, 2012). The varying cytotoxicity profile of PARPi was proposed to be correlated with the PARP trapping potency and not the catalytic activity (Shen et al, 2013).

Table 3: Potency of Talazoparib and Other PARP Inhibitors in In Vitro Assays of PARP Inhibition and Cytotoxicity

PARP Inhibitor	**PARP1 Enzyme Inhibition[a] (IC50, nM)**	**Cellular PAR Synthesis[b] (EC50, nM)**	**Cytotoxicity[c] (IC50, nM)**
Veliparib	4.73	5.9	>10,000
Rucaparib	1.98	4.7	609
Olaparib	1.94	3.6	259
Talazoparib	0.57	2.5	5

EC50 = 50% effective concentration; IC50 = 50% inhibitory concentration; PAR = poly(ADP-ribose); PARP = poly(ADP-ribose) polymerase
a. IC50 values were calculated for inhibition of PARP1 enzyme activity in cell-free PARP enzyme biochemical assays.
b. EC50 values were calculated for inhibition of cellular PAR synthesis in LoVo cells, a human colon adenocarcinoma cell line.
c. IC50 values were calculated for cytotoxicity in Capan-1 (BRCA2 -/-) cells, a pancreatic adenocarcinoma cell line.
Source: Adapted from Table 1 in Shen et al, 2013.

PARP trapping was originally assessed in an assay of chromatin-bound PARP1 and PARP2 levels in damaged DNA in the prostate cancer DU145 cell line treated with 0.1% methyl methane sulfonate (MMS, a DNA alkylating agent that stimulates ssDNA breaks and potentiates PARP trapping) in the presence or absence of talazoparib, olaparib, or rucaparib. Treatment with PARPi (talazoparib, olaparib, or rucaparib) was associated with a concentration-dependent increases in the levels of both PARP1 and PARP2 bound chromatin complexes.

Table 4: Cytotoxicity and PARylation IC50 and IC90 Values and Fold PARP Trapping following Talazoparib Treatment of Breast Cancer Cells + 0.01% MMS

BC cell lines	Talazoparib + 0.01 %MMS				
	Cytotoxicity (nM)		PARylation (nM)		Fold Trapping @ ~PARylation IC90[b]
	IC50 (n = 1)	IC90 (n = 1)	IC50[a] (n = 3)	IC90 (n = 3)	
MDA-MB-436	1	16	15 ± 6	104 ± 44	36x
HCC1954	32	677	6 ± 4	89 ± 33	12x
JIMT1	34	180	9 ± 3	61 ± 16	45x
HCC1143	119	2298	9 ± 1	75 ± 26	46x

BC = Breast Cancer; IC50 = 50% inhibitive concentration; IC90 = 90% inhibitive concentration; MMS = Methyl methane sulfonate; PAR = PARylation.
a. IC50 is means ± standard deviation
b. The PARP trapping fold at the approximate PARylation was determined by normalizing to Histone H3 and then drug treatment trapping was divided by no drug control.

Multiparametric DDR assays in the BRCA2 mutated DU145 prostate cancer cell line were conducted using a range of clinically relevant talazoparib concentrations in the presence and absence of the DNA alkylating agent temozolomide (TMZ), which is used as a tool to further evaluate the functional effects of talazoparib (see Table 10).

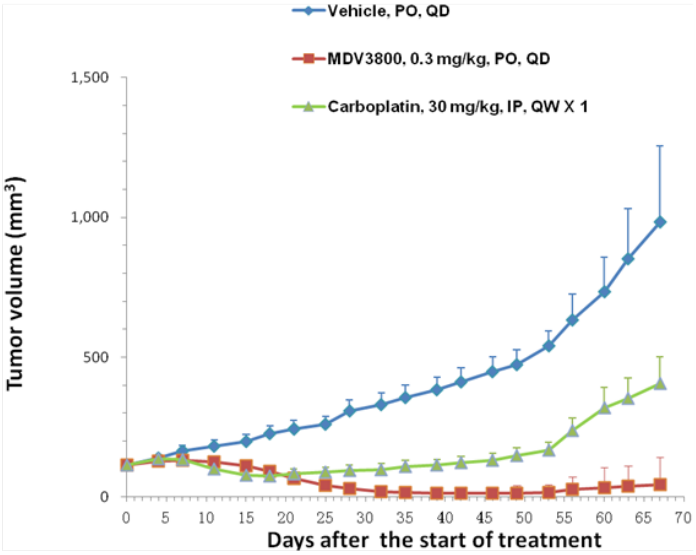
Table 5: ACC Values (μM) at 24 Hour Post Treatment

Endpoint	Talazoparib		
	0	43μM TMZ	128 μM TMZ
DNA breaks[a]	0.87	0.002	0.0005
DNA breaks in S phase[a]	0.20	0.008	0.0003
S phase accumulation[b]	2.5	0.02	0.002
Early Apoptosis[c]	3.84	0.009	0.0016
Decrease in Growth[d]	0.0005	0.0022	0.0004

N/A = Not Active; Each end point value represents the point of departure concentration (ACC; Activity Concentration at Cut-off) derived from statistical dose-response modeling. Values represent data from a single experiment.
a. DNA breaks: γH2AX Alexa 647 fluorescence
b. S phase accumulation values were not derived from dose-response modeling and represent the lowest concentration that is at least 2x higher than negative control.
c. Early apoptosis: Cleaved Caspase 3 Alexa488 Fluorescence
d. Cell growth: % cell count relative to control.

In vivo

Talazoparib was evaluated for anti-tumour efficacy as a single agent compared to carboplatin in the BR-05-0028 breast cancer PDX model in female BALB/c nude mice.



Talazoparib (MDV3800) antitumour activity in BR-05-0028 breast cancer PDX model. Balb/c nude mice (n = 7/group) bearing BR-05-0028 xenografts were dosed with vehicle, talazoparib (PO, 0.3 mg/kg QD), or carboplatin (IP, 30 mg/kg QWx1). The study was terminated on Day 67. Data are presented as the mean ± SEM. PO = oral administration; QD = Once daily; QW x 1 = Once weekly; SEM = Standard error of the mean.

Figure 2: Antitumour Efficacy of Talazoparib vs Carboplatin

Five patient-derived xenograft (PDX) triple negative breast cancer models were evaluated with a single agent dosing regimen of talazoparib at 0.07 mg/kg and 0.15 mg/kg. The 5 models tested were the BRCA1-mutated T168 PDX model, BRCA2-mutated HBC-x10 PDX model, and 3 PDX models that are wild type for BRCA1/2, HBC-x6, HBC-x9, and HBC-x12B.

Table 6: Talazoparib Anti-tumour Activity in Breast Cancer Patient-derived Xenograft Models

Model	BRCA Status	N/ Group	Talazoparib (mg/kg)	TGI (T/C%; Statistical Significance vs Vehicle)	Unbound C_{av} (nM)[a]	AUC_6 (ng•h/mL)
T168	BRCA1 Mutant	10	0.07	T/C% = 1.26% D18; p <0.001 from D14	1.14	58.8
		10	0.15	T/C% = 0.39% D18; p <0.001 from D11	2.48	128.0
HBCx-10	BRCA2 Mutant	10	0.07	T/C% 34.27% D24; p <0.001 D24 to D28	0.92	47.5
		10	0.15	T/C% = 3.48% D24; P <0.001 D14 to D28	1.89	97.4
HBCx-6	Wild Type BRCA1/2	10	0.07	T/C% = 1.63% D35; p <0.001 D17 to D35	0.84	43.6
		10	0.15	T/C% = 0.32% D35; p <0.001 D14 to D35	1.50	77.5
HBCx-12B	Wild Type BRCA1/2	8	0.07	T/C% = 44.4% D31; p<0.05 D28 to D35;	ND	ND
		8	0.15	T/C% = 26.6% D31 p <0.01 D28 to D35	ND	ND
HBCx-9	Wild Type	10	0.07	T/C% = 73.8% D25	0.509	26.3

Model	BRCA Status	N/ Group	Talazoparib (mg/kg)	TGI (T/C%; Statistical Significance vs Vehicle)	Unbound C_{av} (nM)[a]	AUC_6 (ng•h/mL)
	BRCA1/2	10	0.15	T/C% = 46.25% D25; p <0.01 from D18	1.55	79.8

AUC_6 = area-under-the-concentration-time-curve from pre-dose to last measureable concentration at 6 hours. D = Day; ND = Not determined; T/C% = Percentage ratio between the mean tumour volume of a treated group (T) and the mean tumour volume of the control group (C); TGI = Tumour growth inhibition.
a.

In addition to antitumour efficacy, samples were taken pre- and post-dose on the final day of dosing for pharmacokinetic (PK) analysis.

Table 7: Total and Unbound Exposures to Talazoparib in Breast Cancer Patient-derived Xenograft Models

Model	BRCA Status	Talazoparib (mg/kg)	Total C_{min} (nM)	C_{min} Unbound (nM)	Total C_{max} (nM)	Unbound C_{max} (nM)	Total C_{av} (nM)	Unbound C_{av} (nM)
T168	BRCA1 Mutant	0.07	0.815	0.0360	44.7	1.98	25.8	1.14
		0.15	1.74	0.0767	97.8	4.32	56.1	2.48
HBCx-10	BRCA2 Mutant	0.07	0.973	0.0430	32.6	1.44	20.8	0.92
		0.15	1.157	0.0511	69.7	3.08	42.7	1.89
HBC-x6	Wild Type BRCA1/2	0.07	0.973	0.0430	28.7	1.27	19.1	0.84
		0.15	0.815	0.0360	43.9	1.94	34.0	1.50
HBC-x12B	Wild Type BRCA1/2	0.07	1.43	0.0632	21.9	0.969	ND	ND
		0.15	1.30	0.0575	56.5	2.50	ND	ND
HBC-x9	Wild Type BRCA1/2	0.07	1.72	0.0760	18.8	0.832	11.5	0.509
		0.15	1.18	0.0522	61.3	2.71	35.0	1.55
Mean values		0.07	1.18	0.0522	29.3	1.298	19.3	0.852
		0.15	1.24	0.0547	65.8	2.91	42.0	1.86

C_{av} = AUC_6 /6 hr; C_{max} = maximal plasma concentrations; C_{min} = Predose plasma concentrations on Day 34 or 35; ND = Not Determined. Unbound concentrations = C x Fu, where Fu = 0.0442 in mouse plasma. Talazoparib MW = 380.35.

Secondary pharmacodynamic studies

Talazoparib was profiled *in vitro* against a broad panel of over 70 receptors, enzymes and ion channels at a single concentration of 10 μM. Less than 50% inhibition of binding or enzyme activity was observed against all targets (Studies AA86818 and AA87288).

Safety pharmacology programme

A battery of safety pharmacology studies was conducted with Talazoparib to examine potential effects on the cardiovascular, respiratory and the central, peripheral and autonomic nervous systems. These studies were conducted in accordance with the ICH Guidelines on Safety Pharmacology (ICH S7A, ICH S7B). All of these studies were conducted in compliance with GLP.

CNS

To evaluate potential effects on the central nervous system, talazoparib was administered as a single oral dose to male rats at 0, 0.3, 1 and 3 mg/kg, and were subjected to a modified Irwin battery to detect potential effects on central and peripheral nervous systems. There were no talazoparib-related effects on the parameters evaluated in modified Irwin battery of neurological assessments. Toxicokinetic parameters were not measured in this study, but based on the 5-day rat study (8227540), maximum mean unbound plasma concentration at 3 mg/kg/day was 62.6 ng/kg and was 11.4x the observed unbound human Cmax concentration at the 1 mg/dayclinical dose (5.46 ng/mL).

Respiratory

Talazoparib was administered as a single oral dose to male rats at 0, 0.3, 1 or 3 mg/kg to assess potential effects on the respiratory system (Study 8229153) over a 5.5-hour period using whole body plethysmography at baseline and then starting at 0.5 and 24 hours post dose. Tidal volume was decreased as much as 12% (relative to control) in all dose groups administered talazoparib. These generally non-dose dependent decreases in tidal volume were offset by the non-statistically significant increases in respiration rate so that there was no overall change in minute volume. Toxicokinetic parameters were not measured in this study, but based on the 5-day rat study (8227540), maximum mean unbound plasma concentration at 3 mg/kg (the highest dose tested) was 62.6 ng/mL and was 11.4x the observed unbound human Cmax concentration at the 1 mg daily clinical dose (5.46 ng/mL).

Cardiovascular

Talazoparib was evaluated for its effect on binding to the hERG (human ether- à -go-go gene) potassium channel stably expressed in human embryonic kidney (HEK-293) cells (Study 8229172). Talazoparib inhibited the hERG current 6.7%, 14.2% and 33.4% at concentrations of 10, 30 and 100 μM. Due to solubility limitations the highest dose that could be tested was 100 μM and an IC50 could not be calculated since 50% inhibition was not achieved at the concentrations tested. Thus the IC50 for hERG inhibition is considered >100 μM (38000 ng/mL) and is approximately >6996-fold above the observed unbound human clinical exposure at 1 mg daily human dose based on mean unbound steady state C_{max} of 5.46 ng/mL.

To further evaluate the potential for talazoparib to affect the cardiovascular system in vivo, electrocardiogram (ECG) assessments were added on to the repeat GLP dog studies (8227539, 8227532, 8279298). No effects on ECG's were noted at doses of up to the highest dose tested (0.1 mg/kg) with mean unbound plasma exposures corresponding to 3.5x above human clinical exposure at 1 mg daily dose based on mean unbound steady state C_{max} of 5.46 ng/mL.

Pharmacodynamic drug interactions

Pharmacodynamics drug interaction studies were not submitted.

2.3.3. Pharmacokinetics

Methods of analysis

High-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) methods were developed for the quantitation of talazoparib in mouse, rat, and dog plasma for the determination of pharmacokinetic parameters.

Single dose pharmacokinetics

The PK of talazoparib were characterized in rats, and dogs as having low plasma clearance relative to hepatic blood flow, moderate V_{ss} that approximated or exceeded total body water, and moderate to high oral bioavailability. These results are summarized in the following tables:

Table 8: Pharmacokinetic Parameters of Talazoparib in Male and Female Rats, and Dogs Following Single Intravenous Administration

Species (Sex)[a]	Dose[b] (mg/kg)	C_{5min} (ng/mL)	$t_{½}$ (h)	AUC_{inf} (ng•h/mL)	CL (mL/h/kg)	V_{ss} (mL/kg)
Rat (M)	0.1	312	21.6	753	133	700
Rat (F)	0.1	250	29.7	833	120	586
Dog (M)	0.025	20.4	45.7	289	96.3	3543
Dog (F)	0.025	20.6	51.3	260	96.9	3835

Note: Data are Mean of 3/sex (dog) or 12/sex (rat).
AUC_{inf} = Area under the concentration-time curve from time 0 to infinity; C_{5min} = Concentration at 5 minutes; CL = Total plasma clearance; IV = Intravenous; h = Hour; $t_{½}$ = Apparent terminal elimination half-life; V_{ss} = Apparent volume of distribution at steady state.
a. M = Male, F = Female.
b. Vehicle: a dimethylacetamide: polyethoxylated castor oil (Solutol HS15):PBS, pH 7.4 10:5:85 (v/v/v) solution

Table 9: Pharmacokinetic Parameters of Talazoparib in Male and Female Rats, and Dogs Following Single Oral Administration

Species (Sex)[a]	Dose[b] (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (ng•h/mL)	$t_{1/2}$ (h)	F[c](%)
Rat (M)	0.015	6.35	4.0	48.0	25.6	42.6
Rat (F)	0.015	4.92	4.0	62.3	27.7	49.9
Rat (M)	0.1	89.6	3.0	490	37.9	65.1
Rat (F)	0.1	88.0	2.0	569	28.0	68.3
Rat (M)	1	894	3.0	4039	36.8	53.7
Rat (F)	1	1154	3.0	6106	49.6	73.3
Dog (M)	0.0015	0.182	1.1	10.3	72.9	59.6
Dog (F)	0.0015	0.227	1.2	13.5	89.3	86.7
Dog (M)	0.01	2.51	0.6	72.0	69.7	62.4
Dog (F)	0.01	2.21	0.8	68.7	65.2	66.1
Dog (M)	0.1	54.9	3.3	590	54.5	51.1
Dog (F)	0.1	76.0	3.0	746	58.0	71.8

AUC_{inf} = Area under the concentration-time curve from time 0 to infinity; C_{max} = Maximum plasma concentration; F = Systemic bioavailability; h = Hour; T_{max} = Time to reach C_{max}; $t_{½}$ = Apparent terminal elimination half-life.
a. M = Male, F = Female.
b. Vehicle: 0.5% carboxymethylcellulose suspension in water.
c. F(%) = ([AUC(Oral) x Dose(IV)]/[AUC(IV) x Dose(Oral)]) x 100

Multiple dose pharmacokinetics

Dogs

In study 8227539, after 5 daily doses, from 0.003 to 0.1 mg/kg/day in beagle dogs. Increases in mean Cmax and AUC0-24 were observed that were greater than dose proportional. Sex differences were less than 2-fold in Talazoparib mean Cmax and AUC0-24 values.

In study 8227532, after 28 daily doses, Cmax in male and female dogs seem to reach a steady state in the 0.0015 & 0.005 mg/kg/day groups with similar Cmax levels recorded at Day 15 and Day 28. However, at 28 days, a higher dose of 0.01 mg/kg/day did not achieve a Steady State Cmax value and a 1/3 higher Cmax values were recorded at Day 28 as compared to Day 15. Similar trends were observed for the exposure (AUC(0-24)) of Talazoparib. A clear relationship between Cmax and dose was observed for the<0.01 mg/kg/day dose.

In study 8279298, after 13 weeks of daily dosing in dogs, accumulation of Talazoparib in plasma was observed with accumulation ratios generally similar for Cmax and AUC0-24 on Day 29 (range 1.98 to 4.25 and 2.30 to 4.63 for Cmax and AUC0-24, respectively) and Day 91 (range 2.09 to 4.36 and 2.55 to 4.15 for Cmax and AUC0-24, respectively). Differences in mean Cmax and AUC0-24 were less than 2-fold between males and females with the exception of the Group 4 M/F ratio for Cmax on Day 1 (0.49). The remainder of the M/F ratios in Cmax and AUC0-24 ranged from 0.58 to 1.36.

Rats

In study 8227540, after 5 daily doses, from 0.3 to 3.0 mg/kg/day in rats. Increases in mean Cmax and AUC0-24 were observed that were greater than dose proportional on Day 5. Sex differences were less than 2-fold in Talazoparib mean Cmax and AUC0-24 values. No accumulation of Talazoparib was observed after multiple dosing of Talazoparib in rats.

In the rat study 8227533, after 28 single daily oral doses, exposure to Talazoparib increased with the dose level from 0.005 to 0.05 mg/kg/day. The increases in mean Cmax for males and females were greater than dose proportional, while increases in mean AUC0-24 were roughly dose proportional. Sex differences were less than 2-fold in Talazoparib mean Cmax and AUC0-24 values. Similarly to study 8227532, higher than expected Cmax and Exposure (AUC0-24) values were recorded at the high dose level at Day 28.

In study 8279299, after 13 weeks of daily dosing in rats, exposure to Talazoparib increased with increase in dose from 0.005 to 0.050 mg/kg/day. Increases in Cmax were generally greater than proportional to increase in dose on Days 1, 29 and 91, while increases in AUC0-24 were generally greater than proportional to increase in on dose on Day 1, and proportional to increase in dose on Day 29 and Day 91. With repeat daily dosing, accumulation of Talazoparib in plasma was observed with accumulation ratios generally greater for Cmax and AUC0-24 on Day 91 (range 3.81 to 4.98 and 3.52 to 4.10 for Cmax and AUC0-24, respectively) compared to Day 29 (range 1.86 to 3.77 and 1.36 to 2.57 for Cmax and AUC0-24, respectively).

Distribution

Brain penetration in mice

The pharmacokinetics and the ability of talazoparib to distribute to brain tissue were evaluated in male FVB/NTac wild type mice and the multi-drug resistant and breast cancer resistance protein (Mdr1a/b-Bcrp; FVB) constitutive triple knockout mice (n=4/sex/time point) after a single oral dose of 0.5 mg/kg (BMN673-14-043). Plasma and dilution corrected whole brain homogenate exposure (AUC_{24}) to talazoparib in the Mdr1a/b-Bcrp knockout mice were 1.9x and 15x higher, respectively, to those observed in the wild-type mice. The K_p values, based brain to plasma ratio (AUC_{brain} to AUC_{plasma}), were 0.225 in the Mdr1a/b-Bcrp knockout mice and 0.0294 in the wild-type mice. These results further confirm that talazoparib is a substrate of the efflux transporters in rodent as well as the human MDR1 and BCRP isoforms.

Tissue distribution in male rats

Following oral administration of [^{14}C]talazoparib to the male S-D rat, measurable concentrations of radioequivalents were observed in blood from 1 to 12 hours after dosing, with C_{max} occurring at 1 hour. [^{14}C]talazoparib-related radioequivalents were widely distributed to tissues. Drug-related radioequivalents were present in approximately 41 tissues in the S-D rat at concentrations that were at least 0.1x to 14x their respective plasma values between 1 and 24 hours postdose. Excluding the gastrointestinal (GI) tract, the tissues with the highest [^{14}C]talazoparib-related radioequivalents were mainly the organs of elimination, including liver, kidney medulla, kidney, kidney cortex, and adrenal gland. By 48 hours after dosing

[^{14}C]talazoparib-related radioequivalents were completely eliminated from most, but not all tissues in the S-D rat.

In pigmented male LE rats, the same initial distribution pattern was observed. Drug-related radioequivalents were eliminated from all tissues by 72 hours postdose, with the exception of GI contents, uveal tract, lymph nodes, pigmented and non-pigmented skin, and spleen. The uptake and retention of [^{14}C]talazoparib-related radioactivity was prominent with measureable concentrations in the pigmented uveal tract of the eye for up to 72 hours after dosing, suggestive of talazoparib binding to melanin. However, by 168 hours [^{14}C]talazoparib-related radioequivalents was fully eliminated from all tissues, including the uveal tract, indicating that melanin association was reversible.

Drug-related radioequivalents were generally below the limit of quantitation (BLQ; 30.6 ng equivalents ^{14}C-talazoparib/g) in the tissues of the CNS in both the S-D and LE rats. Radioactivity was only detected at low levels in the choroid plexus, external to the CNS, for the first hour only in LE rats and up to 4 hours in the S-D rat.

In vitro protein binding

The binding of talazoparib to proteins in plasma from CD1 mice, S-D rats, beagle dogs, cynomolgus monkey and humans was assessed in vitro at nominal plasma concentrations of 0.01, 0.1 and 1 µM at approximately 37°C using the rapid equilibrium dialysis method (MDV3800P005). Talazoparib was highly protein bound in mouse and rat plasma, and moderately bound in dog, monkey, and human plasma with mean unbound fractions (f_u) of 0.0442, 0.101, 0.365, 0.329, and 0.260 in these respective species. There was no marked change in the f_u for talazoparib over the evaluated concentration range in the respective species.

Red blood cell partitioning

The mean C_b/C_p of talazoparib in rats, dogs, and humans were 0.572, 0.931, and 1.05, respectively, suggesting that talazoparib showed a negligible preferential distribution into the red blood cells in rats and was evenly distributed between red blood cells and plasma in dog and human whole blood.

Metabolism

In vitro

The in vitro metabolism of talazoparib was investigated after incubation with liver microsomes from rats, dogs and humans. There was negligible turnover of talazoparib when incubated with liver microsomes in all of the species evaluated. The percent of parent remaining at 120 min in rat, dog and human microsomes was, 91.5%, 100% and 100%, respectively. Minor amounts of the *N*-demethylated (M9, PF-07052922) and the dehydrogenated (M1, PF-07052386) metabolites, were observed in mouse hepatocytes after incubating for 240 min, accounting for 1.16% and 1.33%

In vivo

In vivo metabolism of [^{14}C]talazoparib was evaluated in rats, dogs, and humans following oral administration. In general, metabolism was a minor clearance pathway (<2% of the dose in rats and <20% of the dose in dogs) in the nonclinical species and humans (<15% of the dose) with talazoparib primarily eliminated from the body by excretion of unchanged drug in the urine and feces. The minor metabolites observed mainly involved hydroxylation and dehydrogenation. All minor oxidative metabolites observed in humans have also been observed in rats and/or dogs.

[8S, 9R]-talazoparib was the only stereoisomer circulating in the plasma of rats. Plasma concentrations of the [8R, 9S]-enantiomer (PF-07052027, MDV10244, LT-000674) were below the limit of quantitation and support that talazoparib did not undergo chiral inversion in the rat following oral administration. Similar observations were made when studying samples from the human mass balance study.

Talazoparib was the only circulating drug-related product identified in humans after oral administration of a single 1 mg (100 μCi) dose of [^{14}C]talazoparib

Excretion

In rats, the recovery of radioactivity was essentially complete by 240 hours (10-days) postdose with 95.1 and 97.6%, of the dose collected in the excreta from bile-duct intact male and female rats, respectively. The major route of elimination of radioactivity was by fecal excretion, accounting for 73.6% of the dose in male rats and 70.9% of the dose in female rats. Urinary excretion was a minor route of elimination and accounted for 19.4% of the dose in male rat and 25.8% of the dose in female rats. Biliary excretion was low in bile duct cannulated male rats with 3.37% of the dose excreted in the bile over a 120 hour period and 24.2% of the dose in the urine and 64.1% in the feces, for a total recovery of 93.5% of the dose.

In dogs, the recovery of radioactivity was essentially complete by 336 hours (14-days) postdose with 93.1% and 94.0%, of the dose collected in the excreta from males and females respectively. The major route of elimination of radioactivity was by fecal excretion, accounting for 68.0% of the dose in male dogs and 66.6% of the dose in female dogs. Urinary excretion was a minor route of elimination and accounted for 21.1% of the dose in male dogs and 24.4% of the dose in female dogs.

In female human patients with solid tumours, the majority of radioactivity was recovered in the first 168 hours (7-days) post-dose and essentially complete by 504 hours (21-days) postdose with approximately 88.3% of the dose recovered. The major route of elimination of radioactivity was by urinary excretion, which accounted for a mean of 68.7% of the dose with the fecal route as a minor elimination pathways accounting for 19.7% of the dose in humans.

2.3.4. Toxicology

Table 10: Overview of toxicology studies

Study	Study Number (Sponsor Reference)	Concentration or Dose (mg/kg/day)[b]	GLP Status
Repeat-Dose Toxicity			
Non-pivotal			
A 5-Day and 14-Day Oral Gavage Range-Finding Toxicity Study in Sprague-Dawley Rat	VQZ00001 (LT_673_TOX_005)	5 Day: 0.3, 3, 10, 30 14 Day: 0, 1, 0.3, 0.1	Non-GLP
Oral Gavage Dose-Range Finding and 14-Day Tolerability Study in Beagle Dogs	VQZ00002 (LT_673_TOX_006)	5 Day: 0.1, 1 14 Day: 0, 1, 0.3, 0.1	Non-GLP
Pivotal Studies			
5-Day Oral Gavage Toxicity and Toxicokinetic Study Using Daily Administrations of BMN 673ts in Sprague-Dawley Rats with a 28-Day Recovery	8227540 (BMN673-10-050)	0, 0.3, 1, 3	GLP
28-Day Oral Gavage Toxicity and Toxicokinetic Study Using Daily Administrations of BMN 673ts in Sprague-Dawley Rats with a 28-Day Recovery Phase	8227533 (BMN673-10-048)	0, 0.005, 0.015, 0.05	GLP

Study	Study Number (Sponsor Reference)	Concentration or Dose (mg/kg/day)[b]	GLP Status
13-Week Oral Gavage Toxicity and Toxicokinetic Study using Once-Daily Administrations of BMN 673ts in Rats with a 4-Week Recovery Phase	8279299 (BMN673-13-002)	0, 0.005, 0.015, 0.05/0.04	GLP
5-Day Oral Gavage Toxicity and Toxicokinetic Study using Daily Administrations of BMN 673ts in Dogs with a 28-Day Recovery Phase	8227539 (BMN673-10-051)	0, 0.003, 0.01, 0.03, 0.1	GLP
28-Day Oral Gavage Toxicity and Toxicokinetic Study using Daily Administrations of BMN 673ts in Dogs with a 29-Day Recovery Phase	8227532 (BMN673-10-049)	0, 0.0005, 0.0015, 0.005, 0.01	GLP
13-Week Oral Gavage Toxicity and Toxicokinetic Study using Once-Daily Administrations of BMN 673ts in Dogs with a 4-Week Recovery Phase	8279298 (BMN673-13-001)	0, 0.0015, 0.005, 0.01	GLP
Genotoxicity			
In Vitro Studies			
Bacterial Reverse Mutation Assay using BMN 673	AE01MH.502ICH.BTL (BMN673-14-040)	100-5000 µg/plate (with and without activation	GLP
In Vitro Mammalian Chromosome Aberration Assay in Human Peripheral Blood Lymphocytes (HPBL) using BMN 673	AE01MH.341ICH.BTL (BMN673-14-039)	10, 25, 50, 100, 125, 150, 200, 380 µg/mL (non-activated and S9-activated 4-hour exposure groups); 0.25, 0.5, 1, 2.5, 5, 10 µg/mL (non-activated 20-hour exposure group)	GLP
In Vivo Studies			
Definitive Micronucleus Assay with BMN 673 Following Single Oral Doses to Rats	AE01MH.125012ICH.BTL (BMN673-14-038)	0, 150, 300, 600 mg/kg	GLP
Reproductive and Developmental Toxicity			
An Embryo-Fetal Development Study of BMN 673 by Oral Gavage in Rats	20074799 (MDV3800P006)	0, 0.015, 0.5, 0.15	GLP
Other Toxicity Studies			
Neutral Red Uptake Phototoxicity Assay of BMN 673 in BALB/c 3T3 Mouse Fibroblasts	20054208 (BMN673-14-058)	0.6, 1.0, 1.8, 3.2, 5.7, 10.1, 17.9, 31.9	GLP
A Multiple Dose Phototoxicity Study to Determine the Effects of Oral Gavage Administration of PF-06944076 on Eyes and Skin in Pigmented Rats	20116618 (17LJ041)	0, 0.015, 0.05 mg/kg	GLP
Investigative Studies			

In vitro assessment of DNA damage and cytotoxicity markers in human DU145 cells after treatment with PF-06944076 (Talazoparib) compared with three PARP inhibitors	17GR323	0 and 2.4 x 10^{-6} to 20.0 μM[c]	Non-GLP
Mechanistic Investigation of Bone Marrow Suppression with Talazoparib	17LJ085	10 nM to 100 μM	Non-GLP

Single dose toxicity

No single dose acute toxicity studies with talazoparib were submitted.

Repeat dose toxicity

Table 10. Overview of repeat dose toxicity studies

Study Type and Duration (Study Number)	Route of Administration	Species	Dose[a] (Lot No.)	NOEL / NOAEL (mg/kg/day)	Major Findings
Repeat-Dose Toxicity Studies					
5-Day and 14-day repeat-dose Study VQZ00001; Not GLP	Oral Gavage	Rat/SD	5 Days: 0.3, 3.0, 10, 30[c] 14 Days: 0, 0.1, 0.3, 1.0 (Lot CL-PIX-092-A-Daicel)		30 mg/kg/day resulted in the early mortality of 2 animals (M+F) No macroscopic findings were noted at necropsy. Reported findings during the study (Phase 1 & 2) were soft and mucoid feces, hunched posture, lethargy, porphyrin staining, loss of body temperature, pale mucous membranes, swelling of the face and extremities, thinness, bruising, and ulcerations. All hematology parameters were affected by Talazoparib administration, exhibiting a dose-dependent decrease. Changes in mean AST and ALP parameters at all dose levels up to and including 1 mg/kg/day, and changes in mean ALB and mean A:G ratio at 0.3 mg/kg/day (females only). Daily dosing for 14 days at 0.1, 0.3, and 1 mg/kg/day was not well tolerated and resulted in the early death or euthanasia of all 1 mg/kg/day animals.
5-Day repeat-dose Study 8227540; GLP	Oral Gavage	Rat/SD	0, 0.3, 1.0, 3.0 (Lot PT-C09101604-E100002)	highest nonseverely toxic dose (HNSTD) is considered to be 0.3 mg/kg/day	3 mg/kg/day resulted in early deaths of animals. Talazoparib at 1 mg/kg/day induced thin appearance, hunched posture, pale, hypoactive, red porphyrin nasal/eye discharge, rough/stained haircoat, and/or squinted eyes. Liquid faeces observed at 3 mg/kg/day and lower body weight (~10%) when compared with controls recorded at Day 5. Changes in hematology test recorded – decreased: red cell mass; hemoglobin concentration, haematocrit, reticulocyte counts All hematology parameters were affected

Study Type and Duration (Study Number)	Route of Administration	Species	Dose[a] (Lot No.)	NOEL / NOAEL (mg/kg/day)	Major Findings
					by Talazoparib administration, exhibiting a dose-dependent decrease Hematologic changes in animals given 0.3 mg/kg/day either reversed or partially reversed by Day 29 of the recovery phase Clinical chemistry – Decreased K levels; decreased AST and ALT activity recorded Presence of liver necrosis reported
28-Day repeat-dose Study 8227533; GLP	Oral Gavage	Rat/SD	0, 0.005, 0.015, 0.05 (Lot PT-C09101 604-E10002)	highest nonseverely toxic dose (HNSTD) is considered to be 0.05 mg/kg/day	All animals survived to their scheduled necropsy at the end of the dosing or recovery phase. Lower mean body weight recorded in treatment arm vs controls (approximately 5% lower on Day 28 of the dosing phase). Haematology – many parameters affected. lower red blood cell count (down to 45% lower than control), hemoglobin (down to 42% lower), and hematocrit (down to 42% lower); lower absolute reticulocyte count (down to 96% lower than control) at Day 8; higher absolute reticulocyte count (42% higher than control), mean corpuscular volume (14% higher), and mean corpuscular hemoglobin (13% higher) at Day 29. higher platelet count (up to at least 162% higher than control lower white blood cell count (down to 42% lower than control) lower absolute neutrophil count (down to 69% lower than control) test article-related hematology and coagulation test effects exhibited reversibility during the recovery phase. sperm granulomas of the epididymis noted in <0.05 mg/kg day doses
13-Week repeat-dose Study 8279299; GLP	Oral Gavage	Rat/SD	0, 0.005, 0.015, 0.05/0.04 (Lot PT-C09101 604-E10002)	no observed adverse effect level (NOAEL) and the highest non-severely toxic dose (HNSTD) were each considered to be 15 µg/kg/day	Talazoparib was not tolerated at 0.05 mg/kg/day resulting in unscheduled euthanasia of 5 males Hematology findings - decreases in red cell mass (i.e., red blood cell count, hemoglobin, and hematocrit) and absolute reticulocyte count and white blood cells; decrease in all leukocytes, except eosinophils 0.015 mg/kg/day was clinically tolerated No talazoparib-related hematology changes (compared to vehicle) at the low dose (0.005 mg/kg/day).
5-Day and 14-Day repeat-dose Study VQZ00002; Not GLP	Oral Gavage	Dog/Beagle	5 Days: 0, 0.1, 1.0 14 Days: 0, 0.01, 0.03, 0.1[c] (Lot CL-PIX-092-A-Daicel)		1 mg/kg/day resulted in moribund euthanasia of animals. Test article resulted in low food consumption, decreases in body weight, and changes in clinical pathology parameters (hematology, serum chemistry, and coagulation). Macroscopic findings at 1 mg/kg/day included red discoloration of the stomach, duodenum, ileum, rectum, esophagus, jejunum, and uterus and/or dark discoloration of the lung.

Study Type and Duration (Study Number)	Route of Administration	Species	Dose[a] (Lot No.)	NOEL / NOAEL (mg/kg/day)	Major Findings
5-Day repeat-dose Study 8227539; GLP	Oral Gavage	Dog/Beagle	0, 0.003, 0.01, 0.03, 0.1 (Lot PT-C09101604-E10002)	highest non-severely toxic dose (HNSTD) was 0.03 mg/kg/day	Initially 0.003, 0.01, 0.03, or 0.1 mg/kg/day for 5 days well tolerated but resulted in moribundity after 8 days. Decreases in body weight, food consumption, and hematology findings were reported Notable hematology findings include marked pancytopenia and decreased red cell mass. only dogs administered 0.01 mg/kg/day showed complete recovery
28-Day repeat-dose Study 8227532; GLP	Oral Gavage	Dog/Beagle	0, 0.0005, 0.0015, 0.005, 0.01[e,f,g] (Lot PT-C09101604-E10002)	highest nonseverely toxic dose (HNSTD) was 0.01 mg/kg/day.	All animals survived to their scheduled euthanasia. Numerically increased faecal abnormalities (liquid, mucoid etc) in treatment groups vs controls. No changes in PR interval, QRS duration, QT interval, QTc interval, RR interval, or heart rate observed in all dose groups No clinical pathology effects at ≤0.0015 mg/kg/day Bone marrow suppression/toxicity observed at 0.01 mg/kg/day - lower red blood cell count, haemoglobin, and hematocrit; lower absolute reticulocyte count ; lower platelet count; lower white blood cells and absolute neutrophil count; lower absolute lymphocyte basophil counts; Lower absolute monocyte counts. Dose-related increased microscopic findings in the GALT in the ileum, depletion of mandibular lymph node (males) and mesenteric lymph node germinal centers and depletion of splenic germinal center (females). All of the above reversed by the end of the recovery phase
13-Week repeat-dose Study 8279298; GLP	Oral Gavage	Dog/Beagle	0, 0.0015, 0.005, 0.01 (Lot PT-C09101604-E10002)	no observed adverse effect level (NOAEL) is 5 µg/kg/day in males and 10 µg/kg/day in females	0.01 mg/kg/day induced: decreases in red cell mass and white blood cell count and increased MCV and decreased MCHC, and transient decreases in reticulocytes and platelets; increases in the myeloid:erythroid ratio in the bone marrow. 0.01 mg/kg/day induced: lower testicular weight; degeneration/atrophy in the seminiferous epithelium of the testis and related findings in the epididymis. Bone marrow suppression/toxicity observed at 0.01 mg/kg/day - lower red blood cell count, haemoglobin, and hematocrit; lower absolute reticulocyte count ; lower platelet count; lower white blood cells and absolute neutrophil count; lower absolute lymphocyte basophil counts; Lower absolute monocyte counts.

Genotoxicity

Table 11: Overview of genotoxicity studies and results

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria/AE01MH.502ICH.BTL /GLP	Salmonella strains TA98, TA100, TA1535 & TA1537 and *E. Coli* WP2 *uvrA*	0,100, 333, 1000, 3333, 5000 µg/plate+/- S9	Negative
Chromosomal aberrations in vitro human peripheral blood lymphocytes/Study AE01MH.341ICH.BTL /GLP	human peripheral blood lymphocytes	0-380 µg/mL in the non-activated and S9-activated 4-hour exposure groups; and 0.25, 0.5, 1, 2.5, 5, 10 µg/mL in the non-activated 20-hour exposure group)	substantial toxicity was observed at dose levels ≥ 125 µg/mL in the S9-activated 4-hour exposure group and at dose levels ≥ 2.5 µg/mL in the non-activated 20-hour exposure group Significant increases in frequency of chromosomal aberrations at ≥50 µg/ml for the 4 hour non activated exposure groups Significant increases in frequency of chromosomal aberrations at ≥50 µg/ml for the 4 hour S9 activated groups Significant increases in frequency of chromosomal aberrations at ≥0.5 µg/ml for the 20 hour exposure groups
Micronucleus test in vivo/ AE01MH.125012ICH.BTL /GLP	SD rats, micronuclei in bone marrow	Single dose of 0, 150; 300 or 600 mg/kg	Micronucleus assay indicate that Talazoparib induced statistically-significant increases in the incidence of micronucleated polychromatic erythrocytes at all dose levels evaluated.

Mechanistic Studies of Genotoxicity

In standard genotoxicity assays, talazoparib was not mutagenic, but was found to be clastogenic in the in vitro chromosome aberration assay in human peripheral blood lymphocytes (PBL), and in the in vivo rat bone marrow micronucleus assay. Additional investigative work was completed to further characterize the genotoxicity and the mechanism of action for talazoparib when combined with the alkylating agent temozolomide (TMZ), which potentiates the pharmacological activity of talazoparib. The studies were performed in the DNA Damage Response (DDR) deficient, BRCA2 mutant, PSA insensitive DU145 Prostate Cancer Cell line.

Results showed that in DU145 cells, talazoparib alone induced double strand DNA (dsDNA) breaks (measured by γH2AX staining) as well as cell cycle arrest in S phase and inhibited cell growth starting at 0.0005 µM (0.5 nM). Micronucleus induction was assessed as a marker of clastogenicity (genotoxicity) and was observed starting at 0.0007 µM (0.7 nM). When DU145 cells were co-treated with 128 µM of TMZ, inhibition of cell growth and micronuclei formation occurred starting at 0.0004 (0.4 nM) and 0.0001 (0.1 nM) µM, respectively. TMZ alone did not induce either cytotoxicity or clastogenicity in DU145 cells at the concentrations tested in this study (up to 128 µM). However, both the cytotoxicity and clastogenicity of talazoparib was potentiated by TMZ.

Carcinogenicity

No carcinogenicity studies were submitted.

Reproduction Toxicity

Fertility and early embryonic development

No fertility and early embryonic development studies were submitted.

Embryo-fœtal development

Table 12: Embryo-Fetal Development in Female Rats

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg)	NOAEL/HNSTD/STD_{10}
20074799 GLP Gestation day 6-17	Rat(SD) 25F	0, 0.015, 0.05, 0.15	NOAEL: not identified STD_{10}: 0.05 mg/kg

At 0.15 mg/kg/day, 8/25 dams in the main study group were found dead or euthanized early (3 were euthanized due to adverse clinical observations on GD 17 (2 rats) and GD 18, respectively; and 5 were found dead on GD 17, 19, 20 and 21 (2 rats), respectively). Clinical observations prior to mortality or unscheduled euthanasia included dehydration, hunched posture, cold to touch, decreased activity, thin body condition due to reduced food consumption (40.5% reduction between GD 10 and 18), and partially closed and/or pale eyes.

Pregnancy was observed in 24 to 25 of the rats in each dose group. All pregnant dams at ≤0.05 mg/kg/day survived to scheduled euthanasia. Due to the early deaths, the number of pregnant dams evaluated at 0 (vehicle), 0.015, 0.05, and 0.15 mg/kg/day dose groups on GD 21 (scheduled euthanasia) were 24, 25, 25, and 16, respectively. There were no live at ≥0.05 mg/kg/day and at 0.015 mg/kg/day, 90.7% of the fetuses were resorbed in the litters. Fetal body weights (male, female and total) at 0.015 mg/kg/day were reduced (≤28%) compared to the control group values. At 0.015 mg/kg/day, litters with fetal malformations and variations included depressed eye bulge, small eye, misshapen zygomatic arch, incompletely ossified, split or misshapen sternebrae, supernumerary ribs, incompletely ossified, fused and/or misshapen cervical arch.

Toxicokinetic data

Table 13: Overview of toxicokinetic data

Study ID	Daily Dose (mg/kg)	Animal Cmax (ng /ml)	Animal AUC (ng·h/ml)	Exposure margin (Cmax / AUC)
8227540	0.3	12.3	86.5	2.3/1.6
Rat 5 days	1	27.4	261.5	5.0/5.0
	3	62.2	661.1	11.4 / 12.6
8227533	0.005	0.103	1.55	0.02 / 0.03
Rat 28 days	0.015	0.547	5.03	0.1 / 0.1
	0.05	1.97	14.9	0.4 / 0.3
8279299	0.005	0.212	2.80	0.04/0.05
Rat 13 weeks	0.015	0.817	8.43	0.1/0.2
	0.05/0.04	2.80	21.3	0.5/0.4

Study ID	Daily Dose (mg/kg)	Animal Cmax (ng /ml)	Animal AUC (ng·h/ml)	Exposure margin (Cmax / AUC)
8227539	0.003	0.203	3.80	0.04/0.1
Dog 5 days	0.01	1.08	15.9	0.2/0.3
	0.03	4.37	58.8	0.8/1.1
	0.1	19.1	258	3.5/4.9
8227532	0.0005	0.0467	0.836	0.01/0.02
Dog 28 days	0.0015	0.141	2.49	0.03/0.05
	0.005	0.475	8.83	0.1/0.2
	0.001	1.27	15.9	0.2/0.3
8279298	0.0015	0.110	2.06	0.02/0.04
	0.005	0.420	7.86	0.1/0.2
	0.01	0.894	15.7	0.2/0.3

Animal exposure values are shown as unbound values based on f_u in rats of 0.101 and f_u in dogs of 0.365. Total/unbound C_{max} exposure margins calculated based on the respective [$C_{max\ dose\ level}/C_{max\ human\ 1\ mg\ QD}$] where unbound $C_{max\ human\ 1\ mg\ QD}$ value is 5.46 ng /mL based on f_u in humans of 0.260. Total/unbound AUC exposure margins calculated based on the respective [$AUC_{dose\ level}/AUC_{human\ 1\ mg\ QD}$] where unbound $AUC_{human\ 1\ mg\ QD}$ value is 52.5 ng•h/mL based on f_u in humans of 0.260.

Local Tolerance

Local tolerance studies have not been submitted (see discussion on non-clinical aspects).

Other toxicity studies

Phototoxicity

In vitro

The purpose of this study was to evaluate the phototoxicity potential of talazoparib as measured by the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to talazoparib and ultraviolet radiation (+UVR), compared to the viability of fibroblasts exposed to talazoparib in the absence of ultraviolet radiation (-UVR). Promethazine was used as the positive control (Study 20054208). The study design followed the OECD guideline for the testing of chemicals and the ICH S10 Guideline. In this definitive phototoxicity assay, talazoparib tosylate (all doses represent free base equivalents) and promethazine were tested up to the maximum solubility limits of 31.9 and 178 µg/mL

In the DRF assay, the IC50 for phototoxicity (+UVR) was 6.163 µg/mL. In the definitive assays (2 assays), the IC50 for talazoparib-induced phototoxicity (+UVR) was 9.389 µg/mL in assay 1 (PIF >3.408; MPE, 0.345) and 9.015 µg/mL in assay 2 (PIF >3.540; MPE, 0.275) in the absence of cytotoxicity (cell survival was 90% and 86%, respectively). The actual PIF could not be calculated for talazoparib and therefore a ">PIF" was calculated using the highest testable talazoparib concentration (-UVR). It is concluded that talazoparib has phototoxic potential (+UVR) in the absence of cytotoxicity in the BALB/c 3T3 mouse fibroblasts.

In vivo

The objectives of this study are to determine the potential phototoxic effects of talazoparib, when administered by oral gavage once daily for 3 consecutive days, on the eyes and skin of female Crl:LE (Long-Evans, LE) pigmented rats, followed by exposure to ultraviolet B, ultraviolet A and visible light from a xenon lamp (Study 20116618).

The female LE rats (5/dose in the main study, 3/dose for bioanalysis) were administered vehicle control or talazoparib tosylate at 0, 0.015, or 0.05 mg/kg/day once daily for 3 consecutive days. Approximately 3 hours following the last administration on Day 3, the rats were exposed to UVR.

There were no talazoparib-related mortality or clinical observations, and all rats survived to scheduled euthanasia on Day 3. There were no talazoparib-related cutaneous reactions or macroscopic or microscopic ocular findings that were indicative of phototoxicity. The NOAEL for the study is 0.05 mg/kg/day and the C_{max} and AUC_6 exposures on Day 3 are 18.5 (unbound:1.87) ng/mL and 84 (unbound: 8.48) ng•h/mL, respectively. The unbound C_{max} exposure margin at the NOAEL is 0.34x to the unbound observed exposure at the clinical dose of 1 mg daily. Due to limited bioanalysis conducted in the study (up to 6 hours), the AUC_{24} margins could not be determined in the study.

Mechanistic Investigation of Bone Marrow Suppression Associated with Talazoparib

Bone marrow (BM) suppression resulting in hematological toxicity has been identified as the dose-limiting toxicity for talazoparib, in both nonclinical toxicology studies and in clinical trials. The molecular mechanism, cross species sensitivity, and potential for any lineage-specific effects were evaluated in vitro using peripheral blood mononuclear cells. No lineage specific effects on BM cell viability were seen with talazoparib and the outcome was similar among erythroid, myeloid and megakaryocyte lineages.

To explore potential effects of Talazoparib on the bone marrow, a study 17LJ085 (non-GLP) was conducted using human bone marrow mononuclear cells (hBMMNCs, a heterogeneous population that includes hematopoietic lineage cells such as erythrocytes, monocytes, stem cells and progenitor cells) and human bone marrow hematopoietic stem cells (CD34+) as well as human PBMCs from normal human donors. These studies consisted of an in vitro PBMC and hBMMNCs viability assay measured by intracellular ATP content. Cells were exposed to Talazoparib for 24 hours. The results obtained show that up to 100 µM, Talazoparib did not impact on PBMC cell viability. In contrast, positive control, dinaciclib, a CDK inhibitor cytotoxic to PBMCs, affected cell viability dose-dependently. When PBMCs were dosed with talazoparib or talazoparib and temozolomide combination for up to 72 hours, decreased cell viability was observed only at talazoparib concentrations $\geq 10\ \mu$M in combination with temozolomide (a DNA alkylating agent).

Evaluation of BMMNC from human, rat and mouse showed that rat BMMNC was most sensitive to the effect of talazoparib on cell viability (IC50 values were 2.9, 5.4, and 6.9 nM for rat, mouse, and human, respectively).

The functional consequences of PARPi activity were further evaluated in multiparametric DDR assays in bone marrow cells treated with talazoparib. The DNA alkylating agent TMZ was used as a molecular tool to induce DNA damage, including single stranded DNA (ssDNA) breaks, which stimulate a BER response and increase reliance on PARP for DNA repair and cell survival. Induction of apoptosis (caspase activation) and synergistic cytotoxicity were observed when hBMMNCs were treated with talazoparib + TMZ.

2.3.5. Ecotoxicity/environmental risk assessment

Table 14. Summary of main study results

Substance (INN/Invented Name): talazoparib			
CAS-number: 1373431-65-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		N/A	Not a potential PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	Default: 0.005	µg/L	< 0.01 threshold
Other concerns (e.g. chemical class)			Clastogenic Embryotoxic Teratogenic

2.3.6. Discussion on non-clinical aspects

The pharmacological rationale for the PARP inhibitors is to target tumour cell with BRCA gene defects, in which case, the combination of the PARP mediated inhibition of DNA repair and the BRCA gene defect results in synthetic lethality. Tumour selectivity would be achieved by that normal cells, expressing one functional BRCA allele would not be equally sensitive to the effect of the PARP inhibitor.

The idea that essentially all tumour cells in cancers caused by the BRCA mutation have undergone loss of heterozygosity has however been challenged. In a recent paper from Maxwell and co. [18], it is shown that in a set of 160 BRCA1 and BRCA2 germline mutation associated breast and ovarian tumours, retention of the normal BRCA1 or BRCA2 allele was observed in 7% of BRCA ovarian, 16% of BRCA2 ovarian, 10% of BRCA1 breast, and 46% of BRCA2 breast tumours. While acknowledging that there are limitations to the study, the authors propose that the use of a BRCA locus-specific LOH assay could be valuable to predict the response to therapy with platinum or PARP inhibitors. The uncertainty around using LOH as a biomarker for susceptibility to a PARP inhibitor was discussed by the applicant. Most importantly, there is today no practical possibility to apply this biomarker in the clinical practice. It is certain that further characterisation of tumour characteristics could lead to identification of biomarkers which would enable better identification of patients likely to benefit from therapy (see clinical aspects).

Talazoparib has been shown to be a potent inhibitor of PARP1 and PARP2 with relevant activity also at other members of the PARP family. No data was presented on PPARs from rat or dog. However, based on the conserved nature of these proteins and most importantly, the expected toxicity at exposure levels below clinical exposure in the toxicity studies, it can be concluded that findings in rat and dog well reflect the pharmacological activity in humans.

In vitro anti-tumour activity was demonstrated in a number of cell lines. These data show that talazoparib is also active in tumour cells harbouring mutations in other genes involved in DNA repair, such as PTEN and MLH-1, with little activity in tumour cells with no known mutation affecting DNA repair.

The cytotoxic activity of different PARP inhibitors is not directly correlated to the potency for enzyme inhibition. It has been proposed that cytotoxicity is more related to the PARP trapping potency, whereby PARP protein bound to the inhibitor does not readily dissociate from the DNA lesion, thus preventing DNA repair, replication and transcription. The applicant has provided data showing that talazoparib exhibits more potent PARP trapping, relative to PARP enzyme inhibition, in a BRCA1 mutant tumour cell that is sensitive to talazoparib cytotoxicity then in a BRCA1 tumour cell that is less sensitive to talazoparib cytotoxicity. These data give some support to the view that PARP trapping is the more important activity for anti-tumour effect.

In vivo anti-tumour activity has been demonstrated in mouse models with patient derived xenografts (PDX models). In these models talzoparib showed potent anti-tumour activity with xenografts from BRCA1 mutant and BRCA2 mutant breast cancers. Out of three BRCA1/2 wildtype tumours talazoparib showed potent activity in one case. Further data showed that for the BRCA1/2 wt tumour cell responding to talazoparib, BRCA1 methylation was substantially lower than in two other nonresponsive WT cell lines (data not shown). While not

[18] Nature Comm 2017, 8:319

conclusive, these data indicate that BRCA-dependent tumour susceptibility to talazoparib can be present in absence of mutations. To some extent, these data support the concept that further biomarkers predictive for susceptibility to PARP inhibitors could be identified (see discussion on clinical aspects).

A conventional screening assay for activity at a set of receptors, enzymes and ion channels did not show any evidence for a clinically relevant off-target activity (data not shown).

No safety concerns were identified in a standard package of safety pharmacology studies (respiration, CNS and cardiovascular). In the in vivo dog study assessing ECG effects, the Cmax was only 3.5x clinical exposure. However, no effect was seen in the in vitro hERG studies at a concentration ~7000-fold the unbound clinical exposure.

Local tolerance studies have not been submitted as the oral route is the clinical route of administration for Talazoparib which was considered acceptable.

The nonclinical pharmacokinetics data provide evidence for the relevance of rat and dog for the safety studies. In these species and in humans, the parent compound is the dominating circulating form with minimal contribution of metabolites.

Talazoparib derived radioactivity showed some retention in the pigmented uveal tract. This finding contributed to the need for a photosafety evaluation (see below).

In repeat-dose toxicity studies in rats and in dogs, the main findings at subtherapeutic exposures included bone marrow hypocellularity with dose-dependent decrease in haematopoietic cells, depletion of lymphoid tissue in multiple organs and atrophy and/or degenerative changes in testes, epididymis and seminiferous tubules (see SmPC section 5.3).

Haematological toxicity is the main clinical adverse event, and needs to be managed by appropriate monitoring and dose modifications (see discussion on clinical safety).

Mechanistic investigation of bone marrow suppression associated with Talazoparib suggested that the talazoparib-induced hematological toxicities are due to induction of apoptosis and inhibition of cell proliferation in bone marrow cells.

Additional findings at higher exposures included dose-dependent increase in apoptosis/necrosis in the gastrointestinal (GI) tract, liver and ovary. Most of the histopathologic findings were generally reversible while the testes findings were partially reversible after 4 weeks of dosing cessation. These toxicity findings are consistent with the pharmacology of talazoparib and its tissue distribution pattern (see SmPC section 5.3).

Talazoparib was not mutagenic in a bacterial reverse mutation (Ames) test. Talazoparib was clastogenic in an in vitro chromosomal aberration assay in human peripheral blood lymphocytes and in an in vivo micronucleus assay in rats at exposures similar to clinically relevant doses. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of talazoparib, indicating the potential for genotoxicity in humans (see SmPC section 5.3). Talazoparib and may cause foetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus (see SmPC section 4.6). Women of childbearing potential should not become pregnant while receiving Talzenna and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment (see SmPC section 4.4).

In accordance with ICH S9, carcinogenicity studies are not warranted for this indication. The mode of action and the positive findings in genotoxicity studies make it likely that talazoparib treatment is associated with an increased risk for secondary malignancies.

In accordance with ICH S9, a study on fertility and early embryonic development is not warranted for this indication. The testicular findings in repeat dose toxicity studies are suggestive of a risk for male fertility. Section 4.6 of the SmPC reflects that Talzenna may impair fertility in males of reproductive potential (see also discussion on clinical safety).

Talazoparib is a strong embryo-foetal toxicant. Severe embryofoetal lethality and malformations were observed in rat at a dose tolerated by the dam, and at an exposure far below clinical exposure. In particular, in the embryo foetal development study in rats, talazoparib resulted in embryo foetal death, foetal malformation (depressed eye bulge, small eye, split sternebrae, fused cervical vertebral arch) and structural variations in bones at a maternal systemic AUC24 exposure approximately 0.09-fold the relevant human exposure at the recommended dose (see SmPC section 5.3). Appropriate warnings and precautions about contraception have been reflected in section 4.4. and 4.6. of the SmPC (see also discussion on clinical safety).

Reproductive and developmental toxicity is also adequately listed in the list of safety concerns as an important potential risk (see RMP).

Talazoparib absorbs light in the visible region and retention in the pigmented uveal tract was observed in rats. An in vitro 3T3 assay demonstrated a photoxic potential. In an in vivo phototoxicity study in rats, there were no evidence for a phototoxic potential. In this study, the exposure was 0.34x clinical exposure (Cmax). Since higher doses are not readily tolerable, it is concluded that the phototoxicity potential is adequately addressed.

Talazoparib PEC surfacewater value is below the action limit of 0.01 µg/L and it is not a PBT substance as log Kow does not exceed 4.5. Considering the above data, Talazoparib is not expected to pose a risk to the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see SmPC section 6.6). Adequate warnings are also included in the package leaflet.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data package is considered adequate to support the marketing authorisation of talazoparib.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

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

- Tabular overview of clinical studies

Table 15: **Overview of talazoparib clinical studies that provided pharmacokinetic and pharmacodynamic data**

Protocol No.	Study Type	Talazoparib Treatment Groups	N	Talazoparib Formulation Fasted/Fed Conditions	PK Sampling		NCA	POPPK	PK-PD [a]
					Serial	Sparse			

Protocol No.	Study Type	Talazoparib Treatment Groups	N	Talazoparib Formulation Fasted/Fed Conditions	PK Sampling		NCA	POPPK	PK-PD [a]
					Serial	Sparse			
Patients with Cancer: Single-Dose and Multiple-Dose Studies									
PRP-001	Phase 1, open-label safety, efficacy and PK study	Part 1: 0.025 to 1.1 mg QD talazoparib in 28-day cycles	39	DP Gen 1.0/2.0 capsule formulations Fasting approximately 6 hours predose and 1 hour postdose	X	X	X	X	X
		Part 2: 1.0 mg QD talazoparib in 28-day cycles	71		X	X	X	X	X
PRP-002	Phase 1, open-label safety, efficacy, and PK study	Arm 1: 0.10, 0.20, 0.30, 0.45, 0.90, 1.35, and 2.00 mg QD talazoparib Arm 2: 0.10 and 0.90 mg QD talazoparib in 21-day cycles	33	DP Gen 1.0 capsule formulation Fasting approximately 2 hours predose and 1 hour postdose up to Cycle 2. Fasting conditions (6 hours predose and 1 hour post dose) through Cycle 2. Thereafter, talazoparib was administered under fasting conditions for approximately 2 hours predose and 1 hour post dose.	X	X	X	X	
673-201	Phase 2, open-label study	Cohort 1 and 2: 1 mg QD talazoparib in 21-day cycles	84	DP Gen 2.0/3.1 capsule formulations Without regards to food		X		X	X
673-301	Phase 3, open-label, 2-arm, randomized study	1 mg QD talazoparib in 21-day cycles	287	DP Gen 2.0/3.1 capsule formulations Without regards to food		X		X	X
Patients with Cancer: Single-Dose and Multiple-Dose Clinical Pharmacology Studies									
MDV3800-03	Phase 1, open-label, ADME study	^{14}C-talazoparib 1 mg single dose	6	Oral solution After an overnight fast	X		X		
MDV3800-14	Phase 1, open-label, QTc study	1 mg QD talazoparib for 22 days	37	DP Gen 3.1 capsule formulation Fasting approximately 6 hours predose and 2 hours postdose	X		X		X
MDV3800-04	Phase 1, open-label, DDI study	Arm A: two single oral doses of 0.5 mg talazoparib; administered alone (Period 1) or co-administered with multiple doses of the P-gp inhibitor, itraconazole 100 mg twice daily (Period 2). Arm B: two single oral doses of 1 mg talazoparib; administered alone (Period 1) or co-administered with multiple doses of the P-gp inducer, rifampin 600 mg once daily (Period 2).	36	DP Gen 3.1 capsule formulation Fasting approximately 8 hours predose and 2 hours postdose	X		X		

Protocol No.	Study Type	Talazoparib Treatment Groups	N	Talazoparib Formulation Fasted/Fed Conditions	PK Sampling		NCA	POPPK	PK-PD [a]
					Serial	Sparse			
Healthy Subjects: Single-Dose Biopharmaceutic Study									
673-103	Phase 1, randomized crossover, food effect study	0.5 mg talazoparib single dose	18	DP Gen 2.0 capsule formulation Fed or fasting approximately 10 hours predose and 4 hours postdose	X		X		

Source: Study PRP-001 CSR; Study PRP-002 CSR; Study 673-201 CSR; Study 673-301 CSR; Study MDV3800-03 CSR; Study MDV3800-14 CSR; Study MDV3800-04 CSR; Study 673-103 CSR.

Abbreviations: ADME=absorption, distribution, metabolism, excretion; DDI=Drug-drug interaction; DP=drug product; Gen=generation; N=number of enrolled patients in talazoparib treatment arm; NCA=noncompartmental analysis; PD=pharmacodynamics; PK=pharmacokinetics; POPPK=population pharmacokinetics; QD=once daily; QTc=QT interval corrected for heart rate.

a. PK-PD analyses included talazoparib concentration-QT analysis of Study PRP-001 (Study PRP-001 CSR Section 12.5.3), talazoparib concentration-QT analysis of Study MDV3800-14 (Study MDV3800-14 CSR Section 12.5.2.5), and safety and efficacy exposure-response analyses of pooled data from Studies 673-201 and 673-301.

Table 16: Overview of Clinical Studies supporting clinical efficacy

Study Number	673-301 (C3441009)	673-201 (C3441008)	PRP-001 (C3441007)
Study Design	Phase 3 open-label; randomized 2:1 (talazoparib:PCT)	Phase 2 open-label, nonrandomized 2-stage, 2-cohort	Phase 1, first-in-human, open-label, dose-escalation and dose-expansion
Population	Locally advanced or metastatic breast cancer with gBRCA mutation; locally advanced HER2-negative breast cancer that is not amenable to curative radiation or surgical cure or metastatic disease appropriate for systemic single cytotoxic chemotherapy	Locally advanced or metastatic breast cancer with gBRCA mutation; received prior chemotherapy for metastatic disease	Advanced or recurrent solid tumours. Patients who had measureable disease in patients with gBRCA-mutated BC at baseline and received at least 1 dose of talazoparib 1 mg were included in the SCE (Evaluable BC Population)
Study Drug(s)	Talazoparib 1 mg/day PCT (capecitabine, eribulin, gemcitabine, vinorelbine)	Talazoparib 1 mg/day	Talazoparib 1 mg/day
Number of Study Sites	145 sites in 16 countries across North America, Europe, ROW randomized ≥1 patient	33 sites in the US and Europe	5 sites in the US, 1 site in the UK
Number of Patients Enrolled / Treated	431 total enrolled / 412 treated Talazoparib: 287 enrolled / 286 treated PCT: 144 enrolled / 126 treated	84 total enrolled / 83 treated, 48 in Cohort 1 (platinum pretreated) and 35 in Cohort 2 (≥3 prior cytotoxic chemotherapies)	Patients with locally advanced or metastatic breast cancer with gBRCA mutations: • 14 patients treated with 1 mg/day
Data Cutoff Date for SCE	15 September 2017 (CSR)	01 September 2016 (CSR) 07 April 2017 (subsequent OS analysis	31 March 2015 (CSR)

		update)	
Primary Efficacy Endpoint	PFS by IRF (sensitivity analyses: PFS by investigator, impact of poststudy antineoplastic therapy, and others)	ORR by IRF (sensitivity analysis: impact of postbaseline [poststudy] antineoplastic therapy)	none
Secondary Efficacy Endpoints	ORR by investigator, OS	CBR24, DOR by IRF, PFS by investigator, OS	ORR by investigator, PFS, DOR, duration of stable disease, tumour burden
Exploratory Endpoints	DOR by investigator and QoL (EORTC QLQ-C30/QLQ-BR23)	QoL (EORTC QLQ-C30/QLQ-BR23); ORR, BOR, CBR24, and DOR by investigator; time to response and PFS by IRF; tumour burden; biomarkers	none

Source: 673-301 CSR, 673-201 CSR, PRP-001 CSR.
BOR=best overall response; CBR24=clinical benefit rate at 24 weeks; CSR=clinical study report; DOR=duration of response; EORTC=European Organization for Research and Treatment of Cancer; Evaluable BC=patients who had measureable BC at baseline and received at least 1 dose of talazoparib 1 mg; gBRCA=germline breast cancer susceptibility gene; HER2= human epidermal growth factor receptor 2; IRF=independent radiology facility; SCE=Summary of Clinical Efficacy; ORR=objective response rate; OS=overall survival; PCT=physician's choice treatment; PFS=progression-free survival; QLQ-BR23=Quality of Life Questionnaire – Breast Cancer Module; QLQ-C30=Quality of Life Questionnaire – Core 30; QoL=quality of life; ROW=Rest of World; UK=United Kingdom; US=United States.
a. CBR24 was added as a secondary analysis in the SAP.

2.4.2. Pharmacokinetics

Introduction

Eight clinical studies were submitted (see **Table 20**). The single dose food effect study has been performed in healthy volunteers, whereas all other clinical pharmacology data were collected in patients with advanced cancer. There were also two ongoing studies, in hepatic impairment (Study No MDV3800-02) and in renal impairment (Study No MDV3800-01).

A population PK analysis, an exposure-response (progression-free survival as well as haematological toxicity) as well as QTc modelling was also provided.

A full *in vitro* package characterising *in vitro* metabolism, transport, protein binding as well as potential to inhibit or induce enzymes or transporters was also provided.

Methods

Plasma and urine concentrations of talazoparib were determined with LC-MS/MS methods and the pharmacokinetic parameters were calculated with standard non-compartmental analysis.

A population pharmacokinetic analysis was performed, using data from the two phase I studies PRP-001 (rich sampling) and PRP-002 (rich sampling), the phase 2 study 673- 201 (sparse sampling) and the phase 3 study 673-301 (sparse sampling). PK data from 490 patients who received dose levels from 0.25 to 2 mg once daily, were included in the final population pharmacokinetic analysis. A linear two-compartment model with first-order absorption and a lag time for absorption was used. Covariate effects included in the final model were age, race

and Clcrea on Cl/F, body weight on V2/F, food and formulation on ka and strong Pgp-inhibitors (PGPINH1) on F1. The parameter estimates of the final model is shown in **Table 20**.

Table 17. Parameter estimates for the final population PK model

	Final Model (Model #6 OFV= 2064.00)			
Parameter	Estimate	SE	RSE (%)	Shrinkage (%)
CL/F (L/hr)	6.37	0.125	1.96	23.84
V_2/F (L)	162	6.43	3.97	89.36
Q /F (L/hr)	6.24	0.85	13.62	51.01
V_3/F (L)	223	18.3	8.21	53.19
k_a (1/hr)	1.22	0.209	17.13	15.78
Lag (hr)	0.243	0.00139	0.57	--
F_1 (fixed)	1	--	--	--
Age effect on CL/F	-0.00124	0.00178	-143.55	--
RACEN effect on CL/F	0.237	0.0584	24.64	--
BCCL effect on CL/F	0.289	0.059	20.42	--
BWT effect on V_2/F	1.21	0.128	10.58	--
FOOD1 effect on k_a	-0.496	0.116	-23.39	--
FOOD2 effect on k_a	-0.451	0.174	-38.58	--
FORM2 effect on k_a	0.576	0.301	52.26	--
FORM3 effect on k_a	3.96	3.54	89.39	--
FORM4 effect on k_a	1.36	0.808	59.41	--
PGPINH1 effect on F_1	0.447	0.202	45.19	--
CL/F ω^2 (%CV)	0.0725 (26.93%)	0.00977	13.48	--
V_2/F ω^2 (%CV)	0.00243 (4.93%)	0.0183	753.09	--
Q/F ω^2 (%CV)	3.17 (178.04%)	0.236	7.45	--
V_3/F ω^2 (%CV)	0.903 (95.03%)	0.271	30.01	--
k_a ω^2 (%CV)	2.72 (164.92%)	0.258	9.49	--
Thetarized Sigma	0.611	0.0173	2.83	7.22

Source Data: ePharmacology step ID=693446.
BCCL=baseline creatinine clearance; BWT=baseline body weight; CL/F=apparent oral clearance; CV=coefficient of variation; F_1=relative bioavailability; FOOD1=fed condition; FOOD2=unknown; FORM2=0.25 mg capsule formulation; FORM3=0.05 mg capsule formulation; FORM4=mixture of 0.05 mg and 0.25 mg capsules formulation; hr=hour; k_a=absorption rate constant; Lag=lag time; OFV=objective function value; PGPINH1=strong P-glycoprotein inhibitor; Q/F=apparent intercompartmental clearance; RACEN=Asian versus Non-Asian race; RSE=relative standard error; SE=standard error; V_2/F=apparent volume of distribution of central compartment; V_3/F=apparent volume of distribution of peripheral compartment.

Absorption

Following oral administration of talazoparib, the median time to Cmax (Tmax) generally ranged from 1 to 2 hours after single and multiple 1 mg oral dosing of talazoparib capsules in patients. The absolute bioavailability study has not been conducted in humans. However, based on urinary excretion data the absolute bioavailability is at least 41% with fraction absorbed of at least 69%. No significant effect of acid-reducing agents on talazoparib exposure is expected, given sufficient solubility of talazoparib at all pHs between 1 and 6.8. Twenty-eight percent (28%) of the patients in the pivotal study were taking acid-reducing agents, mainly proton pump inhibitors.

Bioequivalence

The two tablet strengths for marketing have not been formally compared in a PK study.

Food interaction

Administration of a high-fat, high-calorie meal delayed the absorption of talazoparib relative to administration under overnight fasting conditions. The median t_{max} was delayed with approximately 3 hours. The C_{max} was approximately 46% lower under fed conditions compared to fasting conditions. The total plasma exposure (AUC_{0-t} and $AUC_{0-\infty}$) was comparable following fasted and fed conditions. The excretion of unchanged talazoparib in urine following administration of a single 0.5 mg oral dose was similar under fed and fasting conditions. The plasma results from the food interaction study are presented below in **Table 23**, **Table 24** and **Figure 3**.

Table 18: **Summary of Plasma Talazoparib Pharmacokinetic Parameters Following a Single 0.5-mg Oral Dose of Talazoparib Under Fasted and Fed Conditions (Study 673-103)**

Parameters (Units)	Parameter Summary Statistics[a] by Treatment	
	Treatment A: Fasting	Treatment B: Fed
N, n	18, 18	18, 18
AUC_{inf} (pg·h/mL)	62551 (18)	61065 (19)
AUC_{last} (pg·h/mL)	59694 (19)	58215 (19)
C_{max} (pg/mL)	1849 (41)	996 (22)
T_{max} (hr)	1.00 (0.50-1.52)	4.00 (0.75-5.00)
$t_{½}$ (hr)	116.7 (± 38.3)	113.6 (± 31.9)
CL/F (L/h)	7.99 (18)	8.19 (19)
V_z/F (L)	1289 (33)	1302 (25)

Treatment A: 0.5-mg talazoparib administered as two 0.25-mg capsules after an overnight fast of at least 10 hours.
Treatment B: 0.5-mg talazoparib administered as two 0.25-mg capsules after a high-fat, high-calorie breakfast.

[a] Geometric mean (geometric %CV) is shown for all PK parameters except median (range) for T_{max} and arithmetic mean (±SD) for $t_{½}$.

Table 19 Statistical Summary of Talazoparib Plasma Pharmacokinetic Parameters Under Fed and Fasting Conditions (Study 673-103)

Parameter (Units)	GLSM		GLSM Ratio[a]	90% CI[a]
	Fed (Test)	Fasting (Reference)		
AUC_{inf} (pg·h/mL)	61065	62551	97.62	92.48-103.05
AUC_{last} (pg·h/mL)	58215	59694	97.52	92.18-103.18
C_{max} (pg/mL)	996.3	1849	53.88	48.12-60.34
	Median			
Parameter (Units)	Fed (Test)	Fasting (Reference)	Treatment Difference Median	90% CI
T_{max}, (hr)	4	1	2.63	2.13-3.13

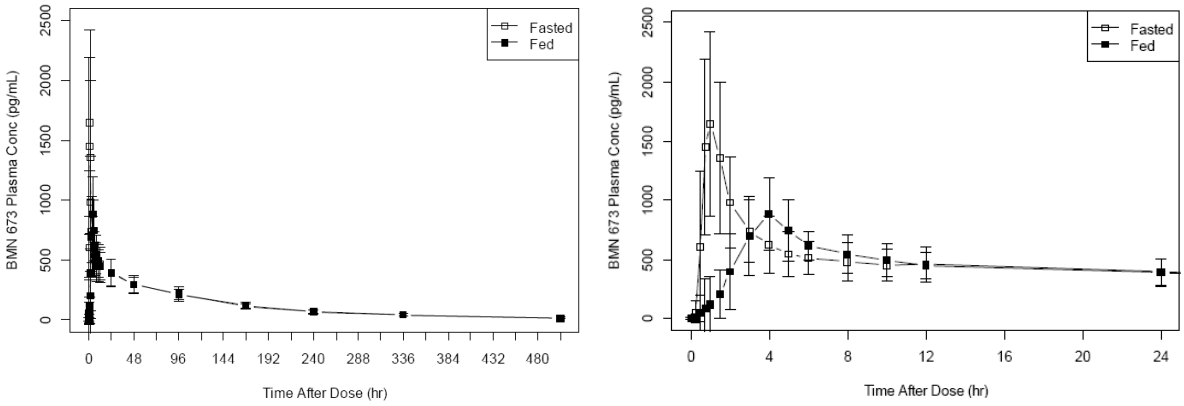


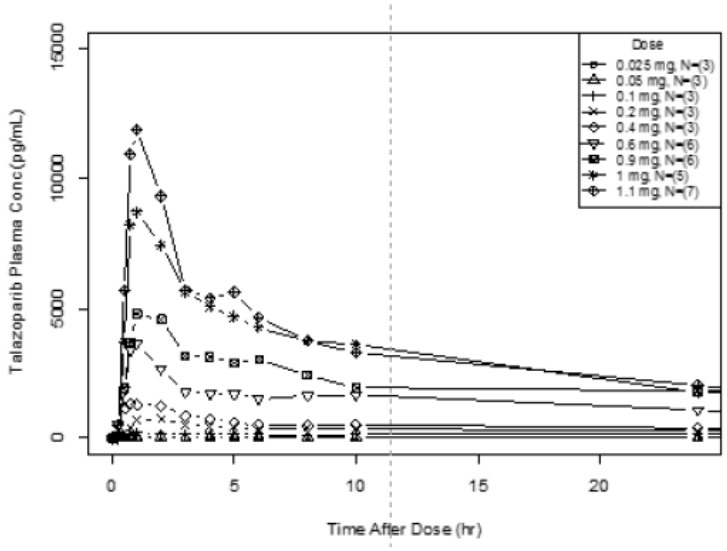
Figure 3: **Overlaid Mean Plasma Talazoparib Concentration-Time Profiles Following a Single 0.5-mg Oral Dose of Talazoparib Under Fasted and Fed Conditions – Complete PK collection interval (left) and Initial 24 Hours Post-Dose (right)**

Dose proportionality

A dose-proportionality analysis was performed with multiple-dose data from both study PRP-001 and PRP-002. The estimated slope values for the Cmax and AUC24 were 1.06 (90% CI: 0.97, 1.15) and 0.92 (90% CI: 0.81, 1.02), respectively thus indicating no major deviation from dose-proportionality in the dose range 0.025 to 2 mg.

Data from the single-dose part of the phase 1 study PRP-001 is shown in **Figure 4**, and the dose-proportionality analysis did not indicate deviations from dose-proportional increase in AUC with dose.

Figure 4. Mean plasma-concentration time profiles of talazoparib single doses in the range 0.025-1.1 mg in study PRP-001.



Distribution

In the population PK analysis, the population mean apparent volume of distribution (Vss/F) of talazoparib was 420 L.

In vitro, talazoparib is approximately 74% bound to plasma proteins with no concentration dependence over the concentration range of 0.01 µM to 1 µM.

The blood/plasma ratio was evaluated in human blood samples from the mass balance study MDV3800-03 and equal partitioning of ^{14}C-Talazoparib was observed between the plasma and red blood cells compartments with a blood to plasma concentration ratio of 1.05.

Elimination

In vitro

There was negligible turnover of talazoparib when incubated with human liver microsomes or hepatocytes. The percent of parent remaining at 120 min in human microsomes was 100%. Consistent with the metabolic stability in liver microsomes, there was no turnover of [14C]talazoparib in freshly isolated or cryopreserved human hepatocytes over 240 min incubations at 1 and 10 µM.

In vivo

In the pooled plasma samples for metabolic profiling from the mass balance study, talazoparib was the only detectable circulating radioactive component.

No metabolites that individually represented more than 10% of the administered dose were recovered in the urine or faeces in the mass balance study. The percent of dose identified in urine and faeces is illustrated in **Figure 5**.

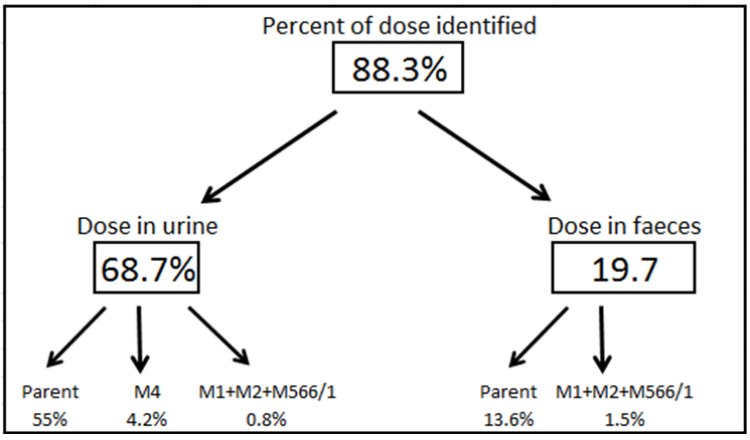


Figure 5. Mean % of dose identified in urine and faeces following administration of 14C-talazoparib (Study MDV3800-03).

Elimination

The mean (±standard deviation) terminal plasma half-life of talazoparib was 90 (±58) hours and the population mean (inter-subject variability) apparent oral clearance (CL/F) was 6.5 (31%) L/h in cancer patients. The

results from the mass balance study showed that approximately 88% were recovered in excreta within 21 days. The mean cumulative recovery of 14C-radioactivity of all 6 patients given a single oral dose of [^{14}C]talazoparib in urine was 68.7% (SD 8.59%), and in faeces 19.7% (SD 5.49%), see **Figure 6**.

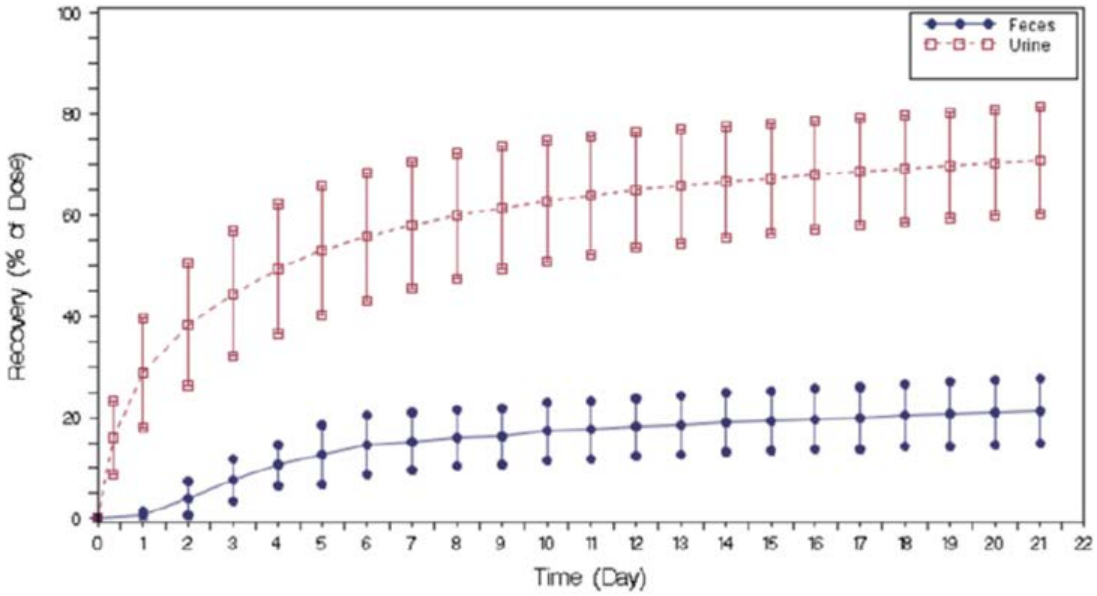


Figure 6. Mean (±SD) Cumulative Recovery of Radioactivity in Urine and Faeces Following Administration of 14C Talazoparib (Study MDV3800-03).

The urinary excretion of unchanged talazoparib was the major route of elimination with a mean recovery in urine of 40.9% of the administered dose based on the liquid chromatography with tandem mass spectrometry (LC-MS/MS) data (**Table 25**). The geometric mean CLr of talazoparib was 3.44 L/hr (arithmetic mean 3.81 L/hr).

Table 20. Summary of Urine Talazoparib Pharmacokinetic Parameter Values (Study MDV3800-03).

Parameter Summary Statistics[a]	
Parameter	**Urine Talazoparib**
N	6
Ae (μg)	366 (12)
Ae%	40.9 (11)
CL_r (L/hr)	3.44 (51)

Source: Study MDV3800-03 CSR Tables 14.2.3.3, 14.2.3.4, and 16.2.6.3.2.
Abbreviations: Ae=amount of drug excreted in urine over the sampling period; Ae%=amount of drug excreted in urine over the sampling period expressed as percentage of administered dose; CL_r=renal clearance; %CV=percent coefficient of variation, N=total number of patients in the treatment arm.
a. Geometric mean (geometric %CV) is shown for CL_r and arithmetic mean (%CV) is shown for Ae and Ae%.

The applicant has made an assessment of the contribution of active renal clearance determined from the difference between the total renal clearance of 3.81 L/h, and the passive renal clearance of 1.95 L/h, estimated from the fraction of unbound talazoparib that is subjected to glomerular filtration (Fu,p x GFR = 0.26 x 7.5 L/h). Active renal clearance of talazoparib in humans was determined to be 1.86 L/h. This value is approximately 29% of the steady-state total apparent clearance in humans (6.37 L/h, PopPK) following a 1 mg/day, and suggests that talazoparib is both actively and passively cleared by the kidneys.

The plasma pharmacokinetics of total radioactivity and talazoparib was characterised in the mass balance study MDV3800-03, see **Table 26** and **Table 27**.

Table 21. Summary of Talazoparib Pharmacokinetic Parameters- Plasma.

Statistic	C_{max}♯ (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}last}$♯ (hr*ng/mL)	$AUC_{0\text{-}inf}$♯ (hr*ng/mL)	%AUC (%)	CL/F (L/hr)	V_d/F (L)	$t_{1/2}$ (hr)	λ_z (1/hr)
N	6	6	6	6	6	6	6	6	6
Mean	8.4	0.5	118.9	129.9	8.6	8.39	922.6	89.8	0.011
SD	3.8	0	65.4	70.4	4.5	3.7	445.8	57.6	0.006
CV%	45.0	0	55.0	54.0	53.0	44	48	64	60
Min	4.7	0.5	54.2	60.4	4.4	3.83	525.7	32.4	0.004
Median	7.6	0.5	112.4	126.1	6.8	7.42	803.9	70.3	0.01
Max	12.7	0.5	237.9	256.5	17.0	14.05	1732.5	188.9	0.021
GeoMean	7.7	0.5	105.7	115.8	7.8	7.71	847.4	76.1	0.009
GeoSD	1.60	1	1.69	1.69	1.6	1.58	1.55	1.88	1.88
GeoCV%	50	0	56	56	50	48	46	70	70

N: total number of patients; SD: standard deviation; CV%: coefficient of variation in percent; Min: minimum; Max: maximum; "Geo": geometric
♯ Values for C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ were changed manually from pg/mL and hr*pg/mL in the source to ng/mL and hr*ng/mL in this table.
Source: Table 14.2.3.1

Table 22. Summary of 14C Pharmacokinetic Parameters- Plasma.

Statistic	C_{max} (ng eq/mL)	T_{max} (hr)	$AUC_{0\text{-}last}$ (hr*ng eq/mL)	$AUC_{0\text{-}inf}$ (hr*ng eq/mL)	%AUC (%)	CL/F (L/hr)	V_d/F (L)	$t_{1/2}$ (hr)	λ_z (1/hr)
N	6	6	6	6	6	6	6	6	6
Mean	12.1	0.5	199.3	222.9	11.0	5.35	655.8	96.2	0.010
SD	5.8	0.0	101.9	108.8	4.8	2.35	338.1	55.1	0.006
CV%	48	0	51	49	43	44	52	57	59
Min	5.8	0.5	95.6	111.7	5.2	2.37	325.3	36.7	0.004
Median	11.7	0.5	186.3	217.6	10.0	4.60	613.1	91.3	0.008
Max	19	0.5	388.7	421.6	18.6	8.96	1199.3	180.2	0.019
GeoMean	10.9	0.5	180.8	203.5	10.2	4.91	587.0	82.8	0.008
GeoSD	1.7	1.0	1.6	1.6	1.6	1.59	1.7	1.8	1.8
GeoCV%	55	0	50	49	47	49	55	68	68

N: total number of patients; SD: standard deviation; CV%: coefficient of variation in percent; Min: minimum; Max: maximum; "Geo": geometric
Source: Table 14.2.4.1

Geometric mean Cmax and AUC0–inf of unchanged talazoparib in plasma were approximately 70% and 60% of those for total 14C-radioactivity in plasma, respectively. The mean terminal elimination half-life (t1/2) was similar for plasma talazoparib and total 14C-radioactivity in plasma with values of 89.8 and 96.2 hours, respectively.

Dose proportionality and time dependencies

Talazoparib exposure generally increased proportionally with dose across the range of 0.025 mg to 2 mg after daily administration of multiple doses. Following repeated daily dosing of 1 mg talazoparib to patients, the geometric mean (% coefficient of variation [CV%]) area under the plasma concentration-time curve (AUC) and maximum observed plasma concentration (Cmax) of talazoparib at steady-state was in the range of 126 (107) ng•hr/mL to 208 (37) ng•hr/mL and 11 (90) ng/mL to 19 (27) ng/mL, respectively. Following repeated daily dosing, plasma talazoparib concentrations reached steady-state within 2 to 3 weeks.

In studies PRP-001, PRP-002 and MDV3800-14 (QT-study), where multiple doses of 1 mg talazoparib was administered, the median accumulation ratio of talazoparib following repeated oral administration of 1 mg once daily was estimated to 2.33, 5.15 and 3.98, respectively.

In study PRP-001 the average AUCinf after a single dose (196 ng•h/ml) was similar to the estimated average AUCT at day 35 (181 ng•h/ml), indicating no major time dependency in pharmacokinetics. In the same study, the estimated half-life was similar after a single dose (62 h) and multiple dosing (58 h) in the same study.

Special populations

The effect of gender, race, weight and age were evaluated in the popPK model.

Impaired renal function

Based on a population PK analysis that included 490 patients, where 132 patients had mild renal impairment (60 mL/min ≤ CrCL < 90 mL/min), 33 patients had moderate renal impairment (30 mL/min ≤ CrCL < 60 mL/min), and 1 patient had severe renal impairment (CrCL < 30 mL/min), talazoparib CL/F was decreased by 14% and 37% in patients with mild and moderate renal impairment, respectively, when compared to patients with normal renal function (CrCL ≥ 90 mL/min).

Impaired hepatic function

Based on a population PK analysis that included 490 patients, where 118 patients had mild hepatic impairment (total bilirubin ≤ 1.0 × ULN and AST > ULN, or total bilirubin > 1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the PK of talazoparib. The PK of talazoparib have not been studied in patients with moderate (total bilirubin > 1.5 to 3.0 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3.0 × ULN and any AST).

Other special populations

Age, sex, and body weight

A population PK analysis was conducted using data from 490 patients with cancer to evaluate the impact of age (ranging from 18 to 88 years), sex (53 males and 437 females), and body weight (ranging from 35.7 kg to 162 kg) on the PK of talazoparib. The results have shown that age, sex, and body weight had no clinically relevant effect on the PK of talazoparib.

Table 23: Number of patients aged ≥ 65 years old included in the PK trials

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials (N=609)	95 (15.6%)	30 (4.93%)	6 (0.99%)

Table 24: Summary of Number of Subjects Contributing to Pharmacokinetic Data by Age Group in Clinical Studies

Age (Yrs)	PRP-001 N=110	PRP-002 N=33	MDV3800-03 N=6	MDV3800-14 N=37	673-103 N=18	673-201 N=83	673-301 N=286	MDV3800-04 N=36	Total N =609
<65	78 (70.91%)	9 (27.27%)	5 (83.33%)	19 (51.35%)	18 (100%)	69 (83.13%)	257 (89.86%)	23 (63.89%)	478 (78.49%)
65-74	23 (20.91%)	16 (48.48%)	0 (0.00%)	12 (32.43%)	0 (0.00%)	12 (14.46%)	23 (8.04%)	9 (25%)	95 (15.6%)
75-84	8 (7.27%)	7 (21.21%)	1 (16.67%)	2 (5.41%)	0 (0.00%)	2 (2.41%)	6 (2.1%)	4 (11.11%)	30 (4.93%)
≥85	1 (0.91%)	1 (3.03%)	0 (0.00%)	4 (10.81%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (0.99%)

Source: Data on File. ePharmacology artifact ID= 16145065
Study 673-103 was conducted in healthy subjects. All other studies were conducted in cancer patients.

Race

Based on a population PK analysis that included 490 patients, where 41 patients were Asian and 449 patients were Non-Asian (361 White, 16 Black, 9 Others, and 63 Not reported), talazoparib CL/F was higher in Asian patients compared to Non-Asian patients, corresponding to 19% lower exposure (AUC) in Asian patients.

Pharmacokinetic interaction studies

In vitro

Enzyme and transporter inhibitory potential

In vitro CYP inhibition (Study BMN673-14-004)

The ability of talazoparib to inhibit the catalytic activity of 7 major human CYP enzymes was evaluated in NADPH supplemented pooled human liver microsomes (HLM) with and without preincubation and specific CYP probe substrates. Specific inhibitors were used as positive controls. Results showed that talazoparib did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 up to the highest concentration of 10 µM, therefore the inhibitory concentration at 50% of the maximum value (IC50) values for CYP inhibition were estimated to be >10 µM, see Table 30. In addition, talazoparib did not show time-dependent inhibition (TDI) or metabolism-dependent inhibition (MDI) against these evaluated CYPs in HLM.

Table 25: Inhibition of CYP enzymes

Type of Study	In vitro cytochrome P450 inhibition
Method	In vitro incubation with human liver microsomes and individual substrates of CYP enzymes in the presence of NADPH-regenerating system with or without preincubation
Analytical Method	LC/MS/MS
Concentrations of Talazoparib	0, 0.01, 0.03, 0.1, 0.3, 1, 3 and 10 µM

CYP	Enzyme Reaction	0-Minute Preincubation			30-Minute Preincubation without NADPH			30-Minute Preincubation with NADPH			Potential for TDI[b,c] (NADPH-Independent)	Potential for MDI[b,c] (Time-& NADPH-Dependent)
		IC_{50} (µM)	Inhibition at 10 µM (%)[a]	r^2	IC_{50} (µM)	Inhibition at 10 µM (%)[a]	r^2	IC_{50} (µM)	Inhibition at 10 µM (%)[a]	r^2		
1A2	Phenacetin *O*-dealkylation	> 10	NA	NC	> 10	NA	NC	> 10	2.1	NC	No	No
2B6	Efavirenz 8-hydroxylation	> 10	NA	NC	> 10	NA	NC	> 10	1.5	NC	No	No
2C8	Amodiaquine *N*-dealkylation	> 10	NA	NC	> 10	0.6	NC	> 10	6.3	NC	No	No
2C9	Diclofenac 4′-hydroxylation	> 10	NA	NC	> 10	4.6	NC	> 10	3.9	NC	No	No
2C19	*S*-Mephenytoin 4′-hydroxylation	> 10	2.7	NC	> 10	9.9	NC	> 10	6.9	NC	No	No
2D6	Dextromethorphan *O*-demethylation	> 10	5.7	NC	> 10	9.9	NC	> 10	7.4	NC	No	No
3A4/5	Testosterone 6β-hydroxylation	> 10	NA	NC	> 10	NA	NC	> 10	2.4	NC	No	No
3A4/5	Midazolam 1′-hydroxylation	> 10	NA	NC	> 10	1.3	NC	> 10	1.6	NC	No	No

CYP = Cytochrome P450; IC_{50} = 50% inhibitory concentration; LC/MS/MS = Liquid chromatography/tandem mass spectrometry; MDI = Metabolism-dependent inhibition; NC = Not calculated; NADPH = Reduced form of nicotinamide adenine dinucleotide phosphate; r^2 = Regression coefficient; TDI = Time-dependent inhibition.
a. Inhibition observed (%) = 100% − Percent solvent control at 10 µM talazoparib.
b. Potential for TDI and MDI was determined by comparison of IC_{50} values both with and without preincubation and with and without NADPH-generating system present. In the cases where a number is listed, this number represents the fold shift of the IC_{50} value to a lower number after preincubation.

In vitro UGT inhibition (Study PF-06944076_18Aug17_035822)

The potential of talazoparib to inhibit the catalytic activity of 6 major human UGT enzymes was evaluated in UDPGA supplemented pooled human liver microsomes with and without 2% BSA and specific UGT probe substrates. Results showed that talazoparib did not inhibit UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and/or UGT2B15 up to the highest concentration of 10 µM, regardless of the presence of BSA, therefore the IC50 values were estimated to be >10 µM, see Table 31.

Table 26: Inhibition of UGT enzymes

Type of Study: Evaluation of UGT Inhibition by Talazoparib.
Method: In vitro incubation with HLM and individual substrates of UGT enzymes in the presence of UDPGA ± 2% BSA.
Analytical Method: LC-MS/MS
Concentration of Talazoparib: 0, 0.1, 0.3, 0.6, 1, 3, 6 and 10 µM

UGT Enzyme	Enzyme Reaction	Talazoparib[a]				
		Without 2% BSA[b]		With 2% BSA		
		IC_{50} (µM)	Inhibition at 10 µM (%)[c]	IC_{50} (µM)	Unbound IC_{50} (µM)	Inhibition at 10 µM (%)[c]
1A1	β-Estradiol-3-Glucuronidation	>10	9.8	>10	NC	8.4
1A4	Trifluorperazine-N-Glucuronidation	>10	5.6	>10	NC	10.7
1A6	5-Hydroxytryptophol-O-Glucuronidation	>10	6.4	>10	NC	7.1
1A9	Propofol-O-Glucuronidation	>10	3.9	>10	NC	3.4
2B7	Zidovudine-5′-Glucuronidation	>10	14.1	>10	NC	12.9
2B15	S-Oxazepam-Glucuronidation	>10	7.6	>10	NC	10.3

BSA = Bovine serum albumin; DDI = Drug-drug interaction; f_u = Fraction unbound; HLM = Human liver microsome; IC_{50} = 50% inhibitory concentration; LC-MS/MS = Liquid chromatography-tandem mass spectrometry; NC = Not calculated, IC_{50} >100 µM; UDPGA = Uridine diphosphate-glucuronic acid; UGT = Uridine diphosphate-glucuronosyltransferase.
a. An assessment of risk for in vivo DDI between Talazoparib and coadministered substrates of these UGT enzymes, based on the 2017 FDA and EMA guidances, are provided in Tabulated Summaries 2.6.5.15I and 2.6.5.15J, respectively.
b. Incubations without 2% BSA, Talazoparib f_u assumed to be 1 due to minimal amount of protein (0.025 mg/mL) present.
c. Inhibition observed (%) is calculated with the following formula (rounded to 2 significant figures): Inhibition observed (%) = 100% − Percent solvent control.

In vitro transporter inhibition (Studies BMN673-13-070 and PF-06944076_19Oct17_051609)

The potential for talazoparib to inhibit various intestinal, hepatic and renal transporters were evaluated *in vitro*. Overall, based on the *in vitro* results, talazoparib showed a low potential to cause DDI by inhibiting P-gp and BCRP both intestinally and systemically or inhibiting OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, BSEP, MATE1 and MATE2-K systemically at clinically relevant concentrations, see Table 32.

Table 27: Transporter inhibition by talazoparib

Summary Results: Talazoparib as an Inhibitor of Human Transporters In Vitro						
Transporter	**Report Numbers**	**Test System**	**Probe Substrate**	**IC_{50} (µM)**	**% Inhibition at Highest Concentration Tested[a]**	**Inhibitor (Yes/No)[b]**
P-gp	BMN673-13-070	MDCK-MDR1	[^{3}H]digoxin	>1	2.29	No
BCRP		Caco-2 cells	[^{3}H]genistein	>1	2.73	No
OATP1B1		Transfected MDCK-II cells	[^{3}H]E17G	>1	4.84	No
OATP1B3		Transfected MDCK-II cells	[^{3}H]CCK-8	>1	6.43	No
OCT1		Transfected MDCK-II cells	[^{14}C]MPP+	>1	NI	No
OCT2		Transfected MDCK-II cells	[^{14}C]metformin	>1	1.86	No
OAT1		Transfected MDCK-II cells	[^{3}H]p-aminohippuric acid	>1	3.62	No
OAT3		Transfected MDCK-II cells	[^{3}H]p-aminohippuric acid	>1	NI	No
BSEP		Transfected Sf9 membrane vesicles	[^{3}H]taurocholate	>1	2.73	No
MATE1		Transfected MDCK-II cells	[^{14}C]metformin	>1	NI	No
MATE2-K		Transfected MDCK-II cells	[^{14}C]metformin	>1	31.8	No
P-gp	PF-06944076_19Oct17_051609	MDCK-MDR1	[^{3}H]digoxin	>30	NI	No
BCRP		HEK293-BCRP vesicles	rosuvastatin	>30	43	No

BCRP = Breast cancer resistance protein; BSEP = Bile salt export pump; Caco-2 = Human colon carcinoma cell line; CCK-8 = cholecystokinin); E17G = estradiol-17β-D-glucuronide; IC_{50}= 50% inhibitory concentration; MATE = Multidrug and toxin extrusion protein; MDCK = Madin-Darby canine kidney cells; MDR1 = Multi-drug resistance gene that encodes for P-gp; MPP+ = 1-methyl-4-phenylpyridinium; NI = No inhibition (≤0%); OAT = Organic anion transporter; OATP = Organic anion transporting polypeptide; OCT = Organic cation transporter; P-gp = P-glycoprotein; Sf9 = *Spodoptera frugiperda* insect cells; Talazoparib (PF-06944076).
a. Highest concentration of Talazoparib tested: 1 µM in study BMN-13-070 and 30 µM in study PF-06944076_19Oct16_051609.

In vitro evaluation of the induction potential

In vitro CYP induction (Study BMN673-14-003)

The potential of talazoparib to induce CYP1A2, CYP2B6, and CYP3A4 mRNA expression and enzymatic activities were investigated in vitro in 3 different lots of cryopreserved human hepatocytes cultures with talazoparib concentrations ranging from 0.003 to 10 µM. The positive controls for induction were omeprazole (50 µM) for CYP1A2, phenobarbital (750 µM) for CYP2B6, and rifampin (20 µM) for CYP3A4, while flumazenil (25 µM) was used as a negative control. Following treatment for 3 days with talazoparib, there was little or no change in the hepatocyte cell morphology with talazoparib concentrations up to 10 µM, and little or no release of lactate dehydrogenase (LDH) as a measure of cell toxicity. Talazoparib did not cause induction of CYP1A2, CYP2B6 or CYP3A4 mRNA levels and enzymatic activities at concentration up to 3 µM, see Table 33. However, at 10 µM, a greater than 2-fold change was seen in CYP2B6 mRNA levels for one of three lots of hepatocytes (7% of positive control) and greater than 2-fold change in CYP3A4 mRNA levels for two of three lots of hepatocytes (13% and 39% of positive control, respectively), suggesting that talazoparib may have induced these isoforms in vitro. No increase in enzymatic activity was seen at 10 µM for any isoform, except for CYP3A4/5 activity in one lot of hepatocytes.

Table 28: Induction of CYP enzymes (Study BMN673-14-003)

Type of Study: Evaluation of CYP3A4, CYP2B6, and CYP1A2 induction by Talazoparib
Method: In vitro incubation with cryopreserved human hepatocytes and quantitated by LC-MS/MS and quantitative RT-PCR
Concentrations of CYP Substrates: 30 µM Midazolam, 500 µM Bupropion, 100 µM Phenacetin.

Hepatocyte Lot	Talazoparib Concentration (µM)	CYP3A4 mRNA Fold Induction	CYP2B6 mRNA Fold Induction	CYP1A2 mRNA Fold Induction	CYP3A4 1′-Hydroxymidazolam Activity Fold Induction	CYP2B6 Hydroxybupropion Activity Fold Induction	CYP1A2 Phenacetin O-Dealkylation Activity Fold Induction
HC10-1	0.003	0.942	0.895	0.910	1.02	0.912	1.05
	0.01	0.599	0.690	0.732	0.961	0.843	0.900
	0.03	1.13	0.902	0.930	1.06	1.09	1.03
	0.1	0.558	0.753	0.796	0.995	0.985	0.949
	0.3	0.711	0.601	0.766	0.998	0.958	0.997
	1	0.629	0.544	0.877	1.05	0.924	0.848
	3	0.819	0.614	1.01	1.18	0.984	0.920
	10	0.796	0.532	0.702	0.989	0.936	0.832
HC5-30	0.003	1.30	1.16	1.21	1.03	1.13	1.13
	0.01	1.16	1.09	0.703	0.952	0.930	0.988
	0.03	1.09	1.19	0.579	1.02	1.18	1.10
	0.1	0.970	0.966	0.442	0.944	0.901	0.952
	0.3	0.961	1.17	0.473	1.01	1.18	1.06
	1	1.04	0.976	0.467	0.936	0.785	0.879
	3	1.42	1.35	0.635	0.943	0.944	1.14
	10	2.93	1.40	0.942	1.48	1.21	1.06
HC7-4	0.003	0.926	0.946	1.02	0.999	0.940	1.06
	0.01	0.944	0.930	1.30	0.779	0.891	0.939
	0.03	1.10	1.01	2.47	1.03	1.01	1.04
	0.1	1.07	0.752	2.24	1.01	0.916	0.997
	0.3	1.09	0.779	1.72	0.999	0.881	1.02
	1	1.24	0.867	1.54	0.969	0.753	0.886
	3	1.94	1.37	1.34	1.39	0.918	1.03
	10	3.57	2.05	1.37	2.57	1.41	1.23

Notes: Reported values are a mean of n= 3.
CYP = Cytochrome P450; LC-MS/MS = Liquid chromatography-tandem mass spectrometry; mRNA = Messenger ribonucleic acid; RT-PCR = Reverse transcription-polymerase chain reaction.

In vivo

A drug-drug interaction study (Study No MDV3800-04) between a single dose talazoparib and multiple doses of itraconazole (Pgp inhibitor) and rifampicin (used as Pgp inducer) was performed. Coadministration of multiple daily doses of itraconazole 100 mg twice daily and a single 0.5 mg talazoparib dose increased the AUCinf and Cmax of talazoparib by approximately 56% (ratio 90% CI 1.38-1.77) and 40% (ratio 90% CI 1.13-1.73), respectively, relative to a single 0.5 mg talazoparib dose administered alone. Multiple daily doses of rifampicin 600 mg and a single 1 mg talazoparib dose increased talazoparib Cmax by approximately 37% (ratio 90% CI 1.03-1.81); whereas, AUCinf was not affected ratio (90% CI 0.94-1.11) relative to a single 1 mg talazoparib dose administered alone.

The dataset for the population pharmacokinetics analysis included data from 18 patients taking strong Pgp inhibitors, and a covariate effect of strong Pgp inhibitors on Cl/F was detected. Population pharmacokinetic (PK) analysis has also shown that concomitant use of strong P-gp inhibitors increased talazoparib exposure by 45%, relative to talazoparib given alone.

2.4.3. Pharmacodynamics

Mechanism of action

Talazoparib is an inhibitor of PARP enzymes, PARP1, and PARP2. PARP enzymes are involved in cellular DNA damage response signalling pathways such as DNA repair, gene transcription, 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 apoptosis and/or cell death. Treatment of cancer cell lines that are harbouring defects in DNA repair genes with talazoparib single agent leads to increased levels of γH2AX, a marker of double stranded DNA breaks, and results in decreased cell proliferation and increased

apoptosis. Talazoparib anti-tumour activity was also observed in a patient-derived xenograft (PDX) BRCA mutant breast cancer model where the patient was previously treated with a platinum-based regimen. In this PDX model talazoparib decreased tumour growth and increased γH2AX level and apoptosis in the tumours (see SmPC section 5.1).

Primary and Secondary pharmacology

Exposure-response modelling

AEs associated with dose modifications (dose reductions or interruption) were reported in 62% of the patients at 1 mg/day. Most common were anaemia (33%), neutropenia (16%) or thrombocytopenia (13%). In patients who received 1 mg once daily starting dose, one dose reduction (to 0.75 mg) was performed in 24% of the patients and two reductions (to 0.5 mg) in 16%. Permanent drug discontinuation due to AEs was done in 3.6% of the patients.

Exposure-response analysis were evaluated for efficacy and safety for EMBRACA (pivotal phase III; 301) and ABRAZO (phase 2; 201). Time-to-event models utilizing Cox proportional hazard methodology were used to address the relationship between talazoparib exposure and progression-free survival (PFS) and the safety endpoints anaemia, neutropenia and thrombocytopenia. A multivariate analysis was used to estimate the effect of talazoparib exposure adjusting for other covariates. The exposure metrics evaluated was Cavg,t, defined as the average daily dose intensity up to the time of each event in the study, divided by individual apparent talazoparib clearance from the popPK model.

In the univariate efficacy analysis, several disease and treatment factors were significantly associated with PFS. In subsequent steps, several covariates were removed and in the final model baseline lactate dehydrogenase, visceral disease status and disease free interval were included together with Cavgt (hazard ratio 0.88, CI 0.82-0.95). Capsule strength was not significant.

In the exposure-toxicity modelling, data from both study 201 and 301 were modelled together. The same procedure as in the exposure-PFS modelling was applied. In the final cox proportional hazards models for anaemia and thrombocytopenia, Cavgt of talazoparib was found to be a significant covariate (hazard ratio 1.30 and 1.16, respectively) whereas talazoparib concentration was not a significant predictor of neutropenia.

When comparing drug exposure in patients with and without a toxic event on liver or kidney, no obvious difference was observed. The geometric mean of talazoparib within-subject talazoparib Ctrough in patients with renal toxicity events (3.93 ng/mL [38%]; n=15) was similar to and within the range of that in patients without renal toxicity (3.54 ng/mL [63%]; n=207). In addition, the geometric mean of talazoparib within-subject talazoparib Ctrough in patients with hepatotoxicity events (4.02 ng/mL [49%)]; n=18) was similar to and within the range of that in patients without hepatotoxicity (3.53 ng/mL [63%]; n=204).

Modelling of the effect on cardiac electrophysiology

The effect of talazoparib on cardiac repolarisation was evaluated using time-matched electrocardiograms (ECGs) in assessing the relationship between the change of the QT interval corrected for heart rate (QTc) from baseline and the corresponding plasma talazoparib concentrations in 37 patients with advanced solid tumours receiving 1 mg talazoparib QD. The primary aim of the study was to perform a concentration-response analysis to examine the relationship between the change from baseline in QTcF interval, to classify the risk for cardiac effects of the drug. Time-matched change from baseline in QTcF was also addressed.

The study did not suggest a clinically relevant effect of talazoparib on QT interval. The slopes (95% CI) of QTcF-concentration and QTcB-concentration relationships were -0.14 (-0.78 to 0.50) and -0.24 (-0.88 to 0.41) msec/ng/mL, respectively. These slopes were not statistically different from 0 (p-values were 0.67 and 0.47 for QTcF and QTcB, respectively). At the mean steady-state talazoparib Cmax (17.2 ng/mL), the predicted change from baseline value was 2.44 msec with a 1- sided upper 95% CI of 4.64 msec for QTcF, and was 2.09 msec with a 1-sided upper 95% CI of 4.59 msec for QTcB.

2.4.4. Discussion on clinical pharmacology

The applicant has performed a limited clinical pharmacology program to describe the pharmacokinetics and elimination of talazoparib, and to identify special populations or drug-drug interactions with risks for altered drug exposure.

It appears difficult to define a therapeutic window of talazoparib. Only one dose has been tested and it has been chosen with an MTD principle. The exposure-response analyses performed did also not appear useful to define a therapeutic window. This difficulty is in general expected when modelling an endpoint like PFS when data is limited to a single initial dose level and dose adjustments are made on the basis of tolerability.

A population PK model has been developed to describe the PK of talazoparib in the clinical program, and to estimate the effect of moderate renal impairment on drug exposure. Several limitations with the model were identified, but it was concluded that the model describes the present data sufficiently well and can be used to get a reasonable estimation of the effect of renal impairment.

Talazoparib appears to have a relatively high absorption. Food intake decreased the rate but not the extent of talazoparib absorption. Following a single oral dose of talazoparib with high-fat, high-calorie food (approximately 827 calories, 57% fat), the mean Cmax of talazoparib was decreased by approximately 46%, the median Tmax was delayed from 1 to 4 hours, while the AUCinf was not affected. Based on these results, Talzenna can be administered with or without food (see section 4.2).

Two dose strengths will be marketed, 0.25 and 1 mg, and there is no relative bioavailability study between the strengths. They are however both used in the pivotal phase III trial, and resulted in similar trough concentrations, therefore the lack of comparative bioavailability data is considered acceptable.

A mass balance study was submitted. The total recovery was somewhat low (70-75%) in two of the patients but exceeds 90% in the remaining four, and the recovery and overall study is considered acceptable. A discrepancy was noted between the results from the radioactivity profiling data and the LC-MS/MS analysis, but it was concluded that this difference was not due to any unidentified metabolites but likely due to methodological differences. Data from the LC-MS/MS measurement was considered more reliable and included in the SmPC.

Talazoparib undergoes minimal hepatic metabolism in humans. Following oral administration of a single 1 mg dose of [14C]talazoparib to humans, no major circulating metabolites were identified in plasma, and talazoparib was the only circulating drug-derived entity identified. No metabolites that individually represented more than 10% of the administered dose were recovered in the urine or faeces (see SmPC section 5.2)..

Renal elimination of unchanged drug (passive filtration and active secretion) is the major route of talazoparib elimination. P-gp is likely involved in talazoparib active renal secretion. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 55% of the administered dose, while unchanged talazoparib recovered in the faeces accounted for 14%.

Renal impairment impacts talazoparib clearance. A dedicated renal impairment study (Study MDV3800-01) is ongoing and it is agreed that no dose recommendations can currently be made for patients with severe renal impairment, as Talzenna has not been studied in patients with severe renal impairment (CrCl < 30 mL/min) or patients requiring haemodialysis and insufficient data are available to estimate the impact of severe renal impairment on talazoparib CL/F in this patient population. A markedly decreased talazoparib clearance is expected in this subpopulation. Talzenna is not recommended for use in patients with severe renal impairment or requiring haemodialysis. Talzenna may only be used in patients with severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events (see section 5.2). Study MDV3800-01 is a category 3 in the RMP.

The population PK analysis has been used to estimate an effect of mild and moderate renal impairment on talazoparib clearance, and the estimates (Cl/F decreased 14% in mild RI and 37% in moderate RI) appear reasonable. No dose adjustment is required for patients with mild renal impairment (60 mL/min $\leqslant$ creatinine clearance [CrCl] < 90 mL/min).

Given that patients in phase III suffering from moderate renal impairment who were given a dose of 1 mg appeared to have a higher incidence of haematological toxicity, a modest starting dose reduction in these patients appears reasonable. This group is known to have a higher average plasma exposure to talazoparib (~50% predicted by the population PK analysis). The proposed dose adjustment in patients with moderate renal impairment (-25%) is predicted to result on average in 19% higher exposure levels than in patients with normal renal function. As the 0.75 mg dose is not predicted to result in a lower exposure than given a 1 mg to normal renal function patients, this dose adjustment is considered appropriate from a pharmacokinetic point of view. Therefore, for patients with moderate renal impairment (30 mL/min $\leqslant$ CrCl < 60 mL/min), the recommended starting dose of Talzenna is 0.75 mg once daily.

Given that active renal secretion appears to be involved in Talzenna elimination, an investigation of potential transport proteins involved was performed. Talazoparib is an in vitro substrate for Pgp and BCRP, but not OAT1, OAT3, OCT2, MATE1, and MATE-2K. Given the high abundancy of Pgp in the kidney, it is agreed that Pgp is likely to contribute to the active renal secretion of talazoparib.

The result from the interaction study indicates that the main effect of Pgp inhibition caused by itraconazol is inhibition of Pgp in the gastrointestinal tract, causing increased bioavailability. A somewhat longer half-life was however also observed after co-administration of itraconazol, which may be a sign of inhibition of renal secretion. In line with the above discussion on dose adjustments in patients with moderate renal impairment, Pgp inhibitors, resulting in a similar increase in talazoparib exposure, may also be assumed to increase the risk of toxicity and thus warrant a similar dose reduction. Section 4.2 of the SmPC reflects that strong inhibitors of P-gp may lead to increased talazoparib exposure. Concomitant use of strong P-gp inhibitors (including but not limited to amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, and verapamil) during treatment with talazoparib should be avoided. Co-administration should only be considered after careful evaluation of the potential benefits and risks. If coadministration with a strong P gp inhibitor is unavoidable, the Talzenna dose should be reduced to 0.75 mg once daily. When the strong P-gp inhibitor is discontinued, the Talzenna dose should be increased (after 3–5 half lives of the P-gp inhibitor) to the dose used prior to the initiation of the strong P gp inhibitor (see SmPC sections 4.2 and 4.5).

In addition to renal elimination, limited metabolism as well as possibly limited secretion into faeces contributes to the elimination of talazoparib. The applicant describes an ongoing study in subjects with different degrees of hepatic impairment. This is appreciated, but given that the role of hepatic elimination in the clearance of talazoparib appears limited, this study is not considered a category 3 study but is recommended to be

submitted. Patients with mild hepatic impairment have been included in the pivotal trial and popPK analysis does not suggest an effect on PK. Therefore, no dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ 1 × upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN, or total bilirubin > 1.0 to 1.5 × ULN and any AST). Talzenna has not been studied in patients with moderate (total bilirubin > 1.5 to 3.0 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3.0 × ULN and any AST) (see SmPC sections 4.2 and 5.2). Talzenna may only be used in patients with moderate or severe hepatic impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for hepatic function and adverse events.

Data for other special populations are only available through the popPK model, which has its limitations, but it appears unlikely that gender, race, weight or age would have a clinically significant effect on talazoparib pharmacokinetics apart from the effect through renal function. No dose adjustment is necessary in elderly (≥ 65 years of age) patients (see SmPC sections 4.2 and 5.2). Pharmacokinetics of talazoparib have not been evaluated in patients < 18 years of age (see SmPC section 4.2).

The *in vitro* results show that talazoparib is a substrate of P-gp and BCRP but not of any other enzymes or transporters. Regarding being a perpetrator on CYP-enzymes, no inhibition (neither direct or time-dependent or metabolism-dependent inhibition) was seen for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 up to the highest concentration of 10 µM talazoparib and IC50 values were reported as >10µM.

No induction was seen for CYP1A2 in the investigated concentration range 0.003 to 10 µM. For CYP2B6 and CYP3A4 no induction was seen in the concentration range 0.003 to 3 µM. However at 10 µM, a greater than two-fold change was seen in CYP2B6 mRNA and CYP3A4 mRNA in one of three lots and two of three lots of hepatocytes, respectively. Considering the cut-offs used for evaluation of interaction potential in vivo, the concentrations relevant for induction of systemically (50xCmax,u) and intestinally (0.1xDose/250 mL) expressed enzymes are lower than 3 µM and the potential for clinically relevant drug-drug interaction due to induction are considered low.

The effect of BCRP inhibitors on PK of talazoparib has not been studied in vivo. Co-administration of talazoparib with BCRP inhibitors may increase talazoparib exposure. Concomitant use of strong BCRP inhibitors (including but not limited to curcumin and cyclosporine) should be avoided. If co administration of strong BCRP inhibitors cannot be avoided, patient should be monitored for potential increased adverse reactions.

In vitro results also indicated that talazoparib did not inhibit UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7 or UGT2B15 up to the highest concentration of 10 µM and IC50 values were estimated to >10µM.

Population PK analysis indicates that co-administration of acid-reducing agents including proton pump inhibitors and histamine receptor 2 antagonists (H2RA), or other acid reducing agents had no significant impact on the absorption of talazoparib.

Overall, the in vitro DDI studies appear sufficient and of acceptable quality, and do not indicate any inhibiting or inducing effects of talazoparib on enzymes or transporters.

Given that hormonal contraceptives are not recommended to women with breast cancer, the lack of DDI data with hormonal contraceptives is acceptable. This is adequately reflected in section 4.5 of the SmPC.

Talazoparib has a pH dependent solubility, but as the solubility of the clinical dose is high at all pHs tested between 1.2 and 6.8, and the fraction absorbed is high and independent of food intake, a pharmacokinetic interaction with acid reducing agents appears unlikely.

Data from a drug-drug interaction study in patients with advanced solid tumours indicated that co-administration of single 1 mg talazoparib dose with multiple daily doses of a P-gp inducer, rifampin 600 mg, with rifampin co-administered 30 minutes before talazoparib on the day of talazoparib dosing, increased talazoparib Cmax by approximately 37% whereas AUCinf was not affected relative to a single 1 mg talazoparib dose administered alone. An increase in Cmax is not an expected result of P-gp induction, rather an indication of inhibition. This is probably the net effect of both P-gp induction and inhibition by rifampin under the tested conditions in the drug-drug interaction study. No talazoparib dose adjustments are required when co administered with rifampin. However, the effect of other P-gp inducers on talazoparib exposure has not been studied. Other P-gp inducers (including but not limited to carbamazepine, phenytoin, and St. John's wort) may decrease talazoparib exposure.

Deleterious gBRCA mutations increases the risk for ovarian and breast cancer and to a clearly lesser degree for some other solid tumours. The relationship between different gBRCA1 and 2 mutations, need for loss of heterozygosity (LOH) or haplotype insufficiency and homologous repair deficiency and tumour phenotype is still unclear. gBRCA1 is more related to hormone receptor negative tumours, basal phenotype and younger age, while the reverse is true for gBRCA2. Talazoparib is an inhibitor of PARP1 and PARP2, which play important roles in DNA repair. It is also a lower-potency inhibitor of PARP3, tankyrase 1 (TNKS1, PARP5a), and tankyrase 2 (TNKS2, PARP5b). PARP inhibitors exert cytotoxic effects by at least 2 mechanisms: inhibition of PARP catalytic activity and PARP trapping.

The rationale for using PARP inhibitors for the treatment of breast cancer was originally based on the sensitivity of BRCA1 and BRCA2 mutant tumour cells. After the identification of synthetic lethality, however, it was found that defects in other DNA repair genes commonly found in human cancers also conferred PARPi sensitivity. These observations are considered to support the "BRCAness" hypothesis, i.e. that a subset of cancers in patients without BRCA1/2 mutations display histopathological, molecular and clinical similarities, including drug sensitive phenotypes, with BRCA cancers.

Talazoparib did not have a clinically relevant effect on QTc prolongation at the maximum clinically recommended dose of 1 mg once daily (see SmPC section 5.1).

2.4.5. Conclusions on clinical pharmacology

Available clinical pharmacology data are considered to support the marketing authorisation of Talzenna. Further data in special populations, in particular in patients with renal impairment, are expected to be provided post-authorisation to further characterise the pharmacokinetic profiled of talazoparib (see RMP).

2.5. Clinical efficacy

2.5.1. Dose response studies

PRP-001

This was a two-part, first in human study; Part 1 was a standard MTD study, part 2 a dose expansion cohort aiming at further defining RPIID. First patient treated Jan 2011, completion date Mar 2015.

Part 1 enrolled patients with solid tumours without available standard therapy. Altogether 39 patients received talazoparib 0.025 to 1.1 mg /day in cohorts of 3 to 6 individuals. Three patients each received talazoparib at 1 of the first 5 doses (0.025, 0.05, 0.10, 0.20, or 0.40 mg/day), and 6 patients each received talazoparib at 1 of the next 4 doses (0.60, 0.90, 1.0, and 1.1 mg/day).

PARP activity was assayed in PBMC and showed inhibition (>2 fold lower than baseline) in 3/3 patients at a dose of 0.20 mg/day and 2/6 at 1.1 mg/day and 4/6 at 1.0 mg/day. Technical issues contributed.

Thrombocytopenia was declared dose limiting toxicity (DLT) and was reported by 2/6 at 1.1 mg/day. 1.0 mg/day was therefore used as starting dose in part II.

A total of 71 patients received talazoparib 1.0 mg/day in **part 2**. The median relative dose intensity across all cancer types was 97.2%, and the median daily dose received was 0.96 mg.

Table 29: Dose Reduction for Patients Receiving Talazoparib at the Recommended Phase 2 Dose of 1.0 mg/day

	Breast (N = 14)	Ovarian (N = 14)	Prostate (N = 3)	Pancreatic (N = 10)	Ewing (N = 13)	SCLC (N = 23)	Overall (N = 77) [1]
Patients with dose reduction	7 (50.0%)	8 (57.1%)	0 (0%)	2 (20.0%)	2 (15.4%)	7 (30.4%)	26 (33.8%)
1 reduction	5	2	0	1	2	4	14
2 reductions	2	5	0	1	0	3	11
3 reductions	0	1	0	0	0	0	1
Reason for reduction							
Adverse event	5 (71.4%)	5 (62.5%)	0	2 (100%)	1 (50.0%)	7 (100%)	20 (76.9%)
Other	2 (28.6%)	4 (50.0%)	0	0	1 (50.0%)	1 (14.3%)	8 (30.8%)

Source: Table 14.3.30.4.1

[1] Includes 1 patient in part 1 who received 1 dose at 1.1 mg on day 1 and then received 1.0 mg/day thereafter with further dose reductions.

SCLC, small cell lung cancer.

Table 30: Objective Response Rate Overall and by Cancer Type (Response-Evaluable Population)

Cancer Type	Part 1 (N = 37) OR, n/N (%)	Part 2 (N = 67) OR, n/N (%)	Overall (N = 104) OR, n/N (%) (95% CI)
All cancer types	11/37 (29.7%)	13/67 (19.4%)	24/104 (23.1%)
Breast	2/8 (25.0%)	6/12 (50.0%)	8/20 (40.0%) (19.1, 63.9)
Ovarian	9/21 (42.9%)	3/10 (30.0%)	12/31 (38.7%) (21.8, 57.8)
Prostate	0/1 (0%)	0/0 (ND)	0/1 (0%) (0.0, 97.5)
Pancreatic	0/3 (0%)	2/10 (20.0%)	2/13 (15.4%) (1.9, 45.4)
SCLC	0/0 (ND)	2/23 (8.7%)	2/23 (8.7%) (1.1, 28.0)
Ewing	0/2 (0%)	0/12 (0%)	0/14 (0%) (0.0, 23.2)
Colorectal cancer	0/2 (0%)	0/0 (ND)	0/2 (0%)

Source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.2.1, Table 14.2.2.2, Table 14.2.2.3

Objective response (confirmed) per RECIST 1.1 is defined as CR and PR that persists on repeat documented results with a period of at least 4 weeks between 2 assessments.

CR, complete response; ND, not determined; OR, objective response; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SCLC, small cell lung cancer.

2.5.2. Main study

Study 673-301 (EMBRACA)

EMBRACA (673-301) is a Phase III, Open-Label, Randomized, Parallel, 2-Arm, Multi-Centre Study of Talazoparib (BMN 673) Versus Physician's Choice in Germline BRCA Mutation Subjects With Locally Advanced and/or Metastatic Breast Cancer, Who Have Received Prior Chemotherapy Regimens for Metastatic Disease.

Methods

Study Participants

Main inclusion criteria

- Histologically or cytologically confirmed carcinoma of the breast.
- Locally advanced breast cancer not amenable to curative radiation or surgical cure and/or metastatic disease appropriate for systemic single cytotoxic chemotherapy.
- Documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation from Myriad Genetics or other laboratory approved by the Sponsor; for data obtained regarding a BRCA1/2 mutation from a non-Myriad laboratory, the pathology report was submitted to and approved by the Sponsor and a blood sample was sent to Myriad for analysis before randomization.
- No more than 3 prior chemotherapy-inclusive regimens for locally advanced and/or metastatic disease (no limit on prior hormonal therapies or targeted anticancer therapies such as mechanistic target of rapamycin [mTOR] or CDK4/6 inhibitors, immune-oncology agents, tyrosine kinase inhibitors, or monoclonal antibodies against CTL4 or vascular endothelial growth factor [VEGF]).
- Prior treatment with a taxane and/or anthracycline in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated.
- 18 years of age or older.
- Have measurable or nonmeasurable, evaluable disease by revised RECIST 1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
- Adequate organ function as defined below:

    a. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN); if liver function abnormalities were due to hepatic metastasis, then AST and ALT ≤5 × ULN.

    b. Total serum bilirubin ≤1.5 × ULN (≤3 × ULN for Gilbert's syndrome).

    c. Calculated creatinine clearance ≥30 mL/min by local laboratory or Cockcroft-Gault formula.

    d. Hemoglobin ≥9.0 g/dL with last transfusion at least 14 days before randomization.

    e. Absolute neutrophil count (ANC) ≥1500/mm3.

    f. Platelet count ≥100,000/mm3.

- A female of childbearing potential who was not pregnant and agreed to avoid pregnancy during the study by using a highly effective birth control method from the time of the first dose of study drug through 45 days after the last dose of study drug.
- Male patients agreed to use a condom when having sex with a pregnant woman and when having sex with a woman of childbearing potential from the time of the first dose of study drug through 105 days after the last dose of study drug. Contraception was to be considered for a non-pregnant female partner of childbearing potential.
- Male and female patients agreed not to donate sperm or eggs, respectively, from the first dose of study drug through 105 days (males) and 45 days (females) after the last dose of study drug.
- Females of childbearing potential must have had a negative serum pregnancy test at screening and were willing to have additional pregnancy tests during the study.

Exclusion Criteria

- First-line locally advanced and/or metastatic breast cancer with no prior adjuvant chemotherapy unless the investigator determined that 1 of the 4 cytotoxic chemotherapy agents in the control arm would be otherwise offered to the patient.
- Prior treatment with a PARP inhibitor (not including iniparib).
- Not a candidate for treatment with at least 1 of the treatments of protocol-specified PCTs (capecitabine, eribulin, gemcitabine, vinorelbine).
- Objective disease progression while receiving platinum chemotherapy administered for locally advanced or metastatic disease; patients who received low-dose platinum therapy administered in combination with radiation therapy were allowed.
- Patients who received platinum in the adjuvant or neoadjuvant setting were eligible; however, patients may not have relapsed within 6 months of the last dose of prior platinum therapy.
- Cytotoxic chemotherapy within 14 days before randomization.
- Radiation or antihormonal therapy or other targeted anticancer therapy within 14 days before randomization.
- Had not recovered from the acute toxicities of previous therapy, except treatment-related alopecia or laboratory abnormalities otherwise meeting the inclusion requirements.
- HER2-positive breast cancer.
- Active inflammatory breast cancer.
- CNS metastases:
    - Except adequately treated brain metastases documented by baseline CT or MRI scan that had not progressed since previous scans and that did not require corticosteroids (prednisone ≤5 mg/day or equivalent was allowed) for management of CNS symptoms. A repeat CT or MRI following the identification of CNS metastases (obtained at least 2 weeks after definitive therapy) must have documented adequately treated brain metastases.
    - Patients with leptomeningeal carcinomatosis were excluded.

- Prior malignancy except for any of the following:
    - Prior BRCA-associated cancer with no current evidence of prior cancer.
    - Carcinoma in situ or non-melanoma skin cancer.
    - A cancer diagnosed and definitively treated ≥5 years before randomization with no subsequent evidence of recurrence.
- Known to have been human immunodeficiency virus positive.
- Known active hepatitis C virus, or known active hepatitis B virus.
- Use of any investigational product or investigational medical device within 14 days before randomization.
- Major surgery within 14 days before randomization.
- Myocardial infarction within 6 months before randomization, symptomatic congestive heart failure (New York Heart Association [NYHA] > class 2), unstable angina, or unstable cardiac arrhythmia requiring medication.
- Female patients who were breastfeeding at screening or planning to become pregnant at any time during study participation through 45 days after the last dose of study drug; male patients planning to impregnate a partner at any time during study participation through 105 days after the last dose of study drug.
- Concurrent disease or condition that would interfere with study participation or safety, such as any of the following:
    - Active, clinically significant infection Grade >2 by National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) version 4.03 or requiring the use of parenteral antimicrobial agents within 14 days before randomization.
    - Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders.
- Non-healing wound, ulcer, or bone fracture, not including a pathological bone fracture caused by a pre-existent pathological bone lesion.
- Known hypersensitivity to any of the components of talazoparib.

Treatments

The protocol-specific physician's choice treatment was to be determined prior to randomization for each individual subject. Talzenna 1 mg capsules once daily or chemotherapy at standard doses were given until progression or unacceptable toxicity.

Options for PCT´s included one of the following single-agent chemotherapies:

- Capecitabine: 1250 mg/m^2, oral, twice daily from Day 1 through 14 of 21-day cycles, 30 minutes after meal.
- Eribulin mesylate: 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2), infusion over 2-5 minutes, Days 1 and 8 of 21-day cycles

- Gemcitabine: 1250 mg/m2, infusion over 30 minutes, Day 1 and 8 of 21-day cycles
- Vinorelbine: 30 mg/m2, weekly infusion over 6-10 minutes, Day 1, 8, and 15 of 21-day cycles

Dose selection and dose modifications and reductions for PCT´s were to occur per the package insert and institutional practice unless institution dose and regimen guidelines differed in which case the site may utilize institution guidelines.

Talazoparib was administered as a single agent orally daily for 21 days in repeated 21-day cycles at 1.0 mg/day with provision for dose reductions to 0.75 mg/day and 0.5 mg/day (or lower) in case of toxicity.

Table 31: Talazoparib Dose Modifications Based on Haematologic or Non-haematologic Toxicity

Toxicity	Recommended Dose Modification
Liver test abnormalities	Dose may have been reduced or interrupted for Grade 2 AST or ALT values, depending on the liver test values at screening.
Grade 1 or 2 toxicity (other than liver test abnormalities)	No requirement for dosing interruption or reduction. For Grade 2 toxicities persisting ≥7 days, the dose could be reduced to the next lower dose (e.g., from 1.0 mg/day to 0.75 mg/day) at the discretion of the investigator.
Grade 3 nonhematologic toxicity (other than liver test abnormalities)	Daily dosing was to be interrupted for Grade 3 AEs, considered related to talazoparib. Study drug could resume at the next lower dose when the toxicity resolved to Grade 1 or baseline. Supportive care could be implemented as appropriate (eg, antiemetics, antidiarrheal agents).
Grade 3 hematologic toxicity	Daily dosing was to be interrupted for Grade 3 laboratory abnormalities known to be associated with talazoparib as per the talazoparib IB. Study drug could resume at the next lower dose when the toxicity resolved to Grade 1 or met criteria for study entry. Supportive care could be implemented as appropriate (eg, growth factor support, blood products).
Grade 4 nonhematologic toxicity (other than liver test abnormalities)	Daily dosing was to be interrupted for Grade 4 AEs (regardless of relationship to talazoparib). Study drug could resume at a lower dose (1-2 dose level decrease) when toxicity resolved to Grade 1 or baseline. Supportive care could be implemented as appropriate (eg, antiemetics, antidiarrheal agents).
Grade 4 hematologic toxicity	Daily dosing was to be interrupted for Grade 4 laboratory abnormalities (regardless of relationship to talazoparib). Study drug must resume at a lower dose (1-2 dose level decrease as per investigator's decision) when the toxicity resolved to Grade 1 or met criteria for study entry. Supportive care could be implemented as appropriate (eg, growth factor support, blood products).

Objectives

The main objective of this study was to evaluate the efficacy and safety of continued administration of talazoparib monotherapy in patients with advanced or metastatic gBRCA mutated, HER2 negative breast cancer, following disease progression on prior cytotoxic chemotherapy.

The primary efficacy objective of the study was to compare PFS of patients treated with talazoparib as a monotherapy relative to those treated with protocol-specific physician's choice treatment (PCT´s).

Secondary objectives of the study were the assessment of:

- Objective response rate (ORR)
- Overall survival (OS)
- Safety of talazoparib
- Pharmacokinetics of talazoparib

Exploratory objectives were the following:

- Duration of response (DOR) for objective responders
- Quality of life for all enrolled subjects (European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLC-C30]/ EORTC Quality of Life Questionnaire – Breast Cancer Module [QLQ-BR23])
- Research assessments related to blood and tumour sampling that includes characterization of tumour sensitivity and resistance to talazoparib.

Outcomes/endpoints

Primary Endpoint:

- Radiographic PFS

Primary efficacy endpoint was progression free survival (PFS), defined as time from randomization until the date of radiologic progressive disease per modified RECIST 1.1, as determined by central IRF assessment, or death due to any cause, whichever occurred first. Radiographic disease assessment (CT and/or MRI) were performed within 28 days prior to randomization and patients received radiographic disease assessment every two 21-day cycles or 6 weeks (± 7 days) from the date of randomization for 30 weeks. Thereafter, imaging assessments were performed every 9 weeks (± 7 days) until radiographic progressive disease as determined by the IRF or the time of initiation of a new anti-neoplastic therapy.

Clinical disease progression was verified by radiographic imaging as determined by the IRF before discontinuing study treatment (or the patient was not considered to have a progressive disease event for the purposes of the analysis). Imaging assessments continued according to the schedule of assessments until radiographic progression was observed by the IRF, unless the patient withdrew consent or initiated a new anti-neoplastic therapy.

Secondary Endpoints:

- ORR
- OS
- Safety
    - The incidence of adverse events, including serious adverse events
    - Change in clinical laboratory tests (serum chemistry and hematology)
    - Change in vital signs
    - Concomitant medication use
- PK of talazoparib

The secondary efficacy measures included OS and ORR (RECIST v.1.1 with modifications) as assessed by the investigator. Confirmation of objective response (CR or PR) was not required. The ORR was defined as the proportion of patients with a CR or PR as defined by the modified RECIST 1.1 in the intent-to-treat (ITT) with measurable disease population by investigator. Overall survival was defined as the time from randomization to death due to any cause.

A population PK modelling approach was used to estimate individual values of apparent clearance

(CL/F) and central volume of distribution (Vc/F). Individual CL/F estimates were used to estimate individual area under the concentration time curve over a dosing interval (AUC_T). Blood samples were collected on Day 1 of Cycles 1 through 4 for patients randomly assigned to talazoparib.

Exploratory Endpoints:

- DOR
- Time to End of First Poststudy Therapy
- EORTC QLQ-C30/EORTC QLQ-BR23 QOL measures
- Research assessments related to blood and tumour sampling that includes characterization of tumour sensitivity and resistance to talazoparib

DOR was defined as the time from first radiographic documentation of objective response (CR or PR) until radiographic disease progression by RECIST 1.1 based on investigator assessment, or to death due to any cause, whichever occurred first.

The time to end of first post-study therapy was defined as the time from randomization to the end date of the first post-study antineoplastic therapy after the first documented disease progression by investigator assessment while on study treatment (talazoparib or PCT).

Patient-reported outcomes (PRO) were assessed as an exploratory efficacy endpoint using the EORTC QLQ-C30 and EORTC QLQ-BR23 at baseline, Day 1 of each cycle, and at the end of treatment.

An analysis of TTD in Global Health Status/QoL was conducted based on survival analysis methods. TTD in Global Health Status/QoL was defined as the time from randomization to the first observation with a ≥10 point decrease and no subsequent observations with a <10 point decrease from baseline.

Sample size

For PFS, based on a 2:1 randomization allocation ratio (talazoparib : physician's choice), a total of 288 PFS events were considered necessary to provide 90% power for a 2-sided log-rank test at a 0.05 significance level to detect a hazard ratio [HR] = 0.67. Assuming an exponential distribution of PFS, this should correspond to an increase in median PFS from 4.6 months in control arm to 6.9 months in active arm (from 20 to 30 weeks; a 50% increase in median PFS). Based on the study design, the minimum observed effect that should result in statistical significance for PFS was an 28% improvement in median PFS (HR = 0.78), from 4.6 to 5.9 months (from 20 to 25.6 weeks). Up to 429 patients were planned to be randomly assigned to 1 of 2 treatment groups (talazoparib or PCT) in a 2:1 ratio and followed to observe the targeted number of 288 PFS events.

For OS, approximately 321 death events would provide 80% power for a 2-sided log-rank test at an overall 0.05 significance level to detect a HR = 0.72. Assuming an exponential distribution of OS, this would correspond to an increase in median OS from 20 months in control arm to 27.8 months in active arm.

Randomisation

Patients were randomly assigned (2:1) to talazoparib or PCT. Randomization was central and stratified as follows:

- Number of prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease (0 vs 1, 2, or 3).
- TNBC (ER-negative, PgR-negative, HER2-negative) status based on most recent biopsy (yes vs no).
- History of CNS metastases (yes vs no).

For patients assigned to PCT, the protocol-specified PCT was to be determined prior to randomization.

Blinding (masking)

This was an open label study.

Statistical methods

Primary Efficacy Analysis:

The primary efficacy analysis was the comparison of PFS in subjects treated with talazoparib versus treatments of protocol-specific physician's choice. The primary analysis was to be conducted when at least 288 PFS events had been observed, and performed using the intent-to-treat (ITT) population, defined as all randomized subjects. The primary analysis was to include only radiographic progression events as determined by the central IRF per RECIST v.1.1 with modifications and deaths. Clinical deterioration or radiographic progression determined by investigators were not to be considered progression events for the primary analysis.

A stratified log-rank 2-sided test with a 0.05 level of significance was used to compare treatment groups. The stratification factors were the same as used to stratify the randomization schedule as documented in the interactive voice and Web response system (IXRS). The median PFS and the associated 95% confidence interval (CI) for each treatment arm were estimated using the Kaplan-Meier method. The hazard ratio (HR=λ talazoparib/ λ control) and the associated 95% CI were estimated using a Cox regression model with treatment group as the only main effect and stratifying by the same stratification factors as were used for the log-rank test. An unstratified HR and the associated 95% CI were presented. If the p-value for the stratified log-rank test was statistically significant (< 0.05, two-sided) and the observed HR (λ talazoparib/ λ control) was < 1, the null hypothesis of no difference in PFS was to be rejected and it was to be inferred that PFS was statistically prolonged in the group receiving talazoparib compared with the group receiving protocol-specific physician's choice of therapy.

Secondary Efficacy Analysis:

Secondary efficacy endpoints included ORR and OS. To maintain experiment-wise 2-sided type I error at 0.05, a detailed multiplicity adjusted inferential procedure for the primary and secondary efficacy analysis for OS was provided in the Statistical Analysis Plan (SAP). The primary analysis of ORR was to be performed among the subjects with baseline measurable disease in the ITT population using Investigator assessment. In the analysis of ORR, patients who did not have any post-baseline adequate tumour assessments were to be counted as non-responders. Formal hypothesis testing of ORR was performed using the stratified Cochran-Mantel-Haenszel test. The stratification factors were the same used to stratify the randomization schedule as documented in the

IXRS. The best overall response (BOR) for objective responders was reported separately for the non-measurable disease patients.

OS was to be censored at the date the patient was last known to be alive on or before the data cut-off date. An interim analysis of OS was conducted at a 0.0001 significance level on the ITT population at the time of the primary analysis of PFS. The median OS was estimated for each treatment group using the Kaplan-Meier method and the 95% CIs was calculated using the Brookmeyer-Crowley method. The HR and the 95% CI was estimated using a stratified Cox regression model. No formal hypothesis testing was performed for interim OS.

The final analysis of OS is planned when approximately 321 deaths occur using the stratified 2-sided log-rank test using the ITT population. The stratification factors were the same used to stratify the randomization schedule as documented in the IXRS. At the final OS analysis, median OS will be estimated for each treatment group using the Kaplan-Meier method and the 95% CIs will be calculated. The HR will be estimated using a stratified Cox regression model with treatment group as the only main effect. An un-stratified log-rank test, a stratified Wilcoxon's rank sum test, and the HR and 95% CI from an un-stratified Cox regression model will be presented as sensitivity analyses.

Exploratory analysis:

PRO: No multiplicity adjustments were considered for the PRO analyses. PRO questionnaire completion rates were reported for the ITT population. All other analyses were performed using the PRO-evaluable population, defined as all patients who received any study drug and completed the PRO questionnaire at baseline and at least 1 visit post-baseline.

Multiplicity Adjustment for Efficacy Analyses

To maintain the overall 2-sided type I error rate at 0.05, the primary and secondary efficacy analyses for OS were protected under a multiplicity adjustment schema using gate-keeping methodology. The details of the 3-step testing approach was as follows:

Step 1: Compare PFS for talazoparib versus physician's choice when approximately 288 PFS events by IRF occur. Compute the p-value for the PFS comparison. If the p-value is < 0.05 and the HR (λtalazoparib/ λphysician's choice) is < 1, declare statistical significance for PFS with talazoparib versus physician's choice and proceed to step 2. If the statistical significance for PFS cannot be declared, the formal hypothesis tests for OS will not be performed.

Step 2: At the time of the PFS analysis (targeted 288 PFS events), compare OS for talazoparib versus physician's choice as follows: Conduct an interim analysis of OS at a 0.0001 significance level using Haybittle-Peto boundary (Haybittle, 1971; Peto et al, 1976). Descriptive summaries including the HR and its 95% CIs will be presented for each treatment group. No formal hypothesis testing will be performed for interim OS. Final OS analysis will be performed in Step 3.

Step 3: At the final analysis of OS (targeted 321 death events), compare OS for talazoparib versus physician's choice as follows: If the result of the test specified in step 1 is statistically significant, conduct the OS analysis at a 2-sided 0.0499 significance level. If the p-value of the OS test is < 0.0499 and the HR (λ talazoparib/ λ physician's choice) is < 1, declare superiority of treatment with talazoparib for OS.

No adjustments were planned for multiple testing/comparisons in the secondary and exploratory hypothesis tests except OS.

Safety Analysis:

The analyses of safety included all patients who received any study drug (talazoparib or active control) throughout the study duration. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. The Investigator classified the severity of AEs using the CTCAE v 4.03. A treatment emergent adverse event (TEAE) was defined as any event with an onset date on or after date of first dose of study drug, or any event present before treatment that worsens after treatment. Only TEAEs with an onset date prior to date of last dose + 30 days or the date of initiation of a new antineoplastic therapy (whichever occurs first) were tabulated in summary tables. The number and percentage of patients who experienced AEs were summarized by system organ class, preferred term, relationship to study drug, and severity for each treatment group. A by–patient listing was provided for those patients who experienced an SAE, including death, or experienced an AE associated with discontinuation from study drug. Clinical laboratory data were summarized by the type of laboratory test. (see section on clinical safety).

Study populations:

Intent-to-Treat Population: The intent-to-treat (ITT) analysis population was defined as all randomized patients. The ITT population was analyzed according to the treatment assigned at randomization (not by actual treatment received).

ITT with Measurable Disease Population: The ITT with measurable disease analysis population was defined as all patients in the ITT population who have at least 1 target lesion identified at baseline. For analyses using IRF assessment, patients were included in the measurable disease population if at least 1 IRF reader identified at least 1 target lesion at baseline. For analyses using investigator assessment, patients were included in the measurable disease population if the investigator identified at least 1 target lesion at baseline.

Safety Population: The safety analysis population was defined as all patients who receive any study drug (talazoparib or protocol-specified physician's choice). The safety population was analyzed according to the actual treatment received (not by treatment assigned).

Pharmacokinetics Population: The PK analysis population was defined as all patients who receive at least 1 dose of talazoparib and provide at least 1 evaluable PK assessment.

PRO-Evaluable Population: The PRO-Evaluable Population was defined as all patients who have completed the PRO questionnaire at baseline and at least one visit post baseline.

Sensitivity Analyses

Sensitivity analyses of PFS based on different definitions of progression events and censoring rules were described. These analyses were performed for the ITT population, using the same statistical methods as the primary analysis.

1. Impact of investigator radiographic assessment: To evaluate PFS by investigator assessment of radiographic progression, the PFS analysis included progression events by investigator assessment of radiographic progression or deaths. Clinical deterioration as assessed by investigator or radiographic progression determined by the IRF were not considered progression events.

2. Impact of investigator radiographic and clinical deterioration assessments: To evaluate PFS by investigator assessments, the PFS analysis included progression events of radiographic progression or clinical deterioration as assessed by investigator or death. Clinical deterioration was determined by clinical review of treatment discontinuation reason recorded on the End of Treatment eCRF.

3. Impact of clinical deterioration by investigator: To evaluate clinical deterioration by investigator assessment, the PFS analysis included radiographic progression as determined by IRF, clinical deterioration as assessed by

investigator, or death. Clinical deterioration was determined by clinical review of treatment discontinuation reason recorded on the End of Treatment eCRF.

4. Impact of radiographic progression after study drug discontinuation + 30 days: Patients who had radiographic progression as determined by IRF after 30 days following treatment discontinuation were also considered to have a PFS event. For this analysis, PFS events included radiographic progression as determined by IRF that occurs anytime (on, before, or after 30 days following treatment discontinuation) or death due to any cause.

5. Impact of treatment discontinuation for any reason: Patients who discontinued study treatment before radiographic progression as determined by IRF or death were considered to have a PFS event at the time of the study treatment discontinuation. For this analysis, PFS was defined as the time from randomization until the date of radiographic progression as determined by IRF, study treatment discontinuation for any reason, or death due to any cause, whichever occurs first.

6. Impact of post-baseline antineoplastic therapies: Patients who received any post-baseline antineoplastic therapy will be considered to have a PFS event. For this analysis PFS was defined as the time from randomization until the date of radiographic progression as determined by IRF, initiation of a new antineoplastic therapy, or death due to any cause, whichever occurs first.

7. Impact of on-study radiotherapy: For patients who received any on-study radiotherapy before radiographic progression as determined by IRF, PFS was censored on the date of the last adequate tumour assessment on or before the radiotherapy. Date of on-study radiotherapy will be derived from the Prior and Concomitant Radiation Cancer Treatment eCRF.

8. Impact of deaths after end of treatment + 126 days (2 scheduled scans, every 9 weeks after week 30): For patients who did not have radiographic progression and died more than 126 days following treatment discontinuation, PFS was censored on the date of the last adequate tumour assessment on or before 126 days following treatment discontinuation.

9. Impact of capsule strength: Patients treated with a starting dose of 4 x 0.25 mg capsules were excluded from this analysis. The treatment effect was assessed in patients treated with a starting dose of 1 x 1 mg capsules.

10. Impact of central genetic testing: This PFS by IRF analysis included only the subgroup of patients with a deleterious or suspected deleterious germline BRCA mutation based on the FDA-approved MYRIAD BRACAnalysis assay (QSR assay) or CLIA assay and excluded patients with only a local result available.

11. Impact of assessing eligibility with QSR assay: This PFS by IRF analysis included only the subgroup of patients with a deleterious or suspected deleterious germline BRCA mutation based on the MYRIAD BRACAnalysis assay (QSR assay) result and excluded patients enrolled based on a local test result or a CLIA result. Approximately 70% of the patients randomized in the study were expected to be included in this sensitivity analysis.

Additional Analyses:

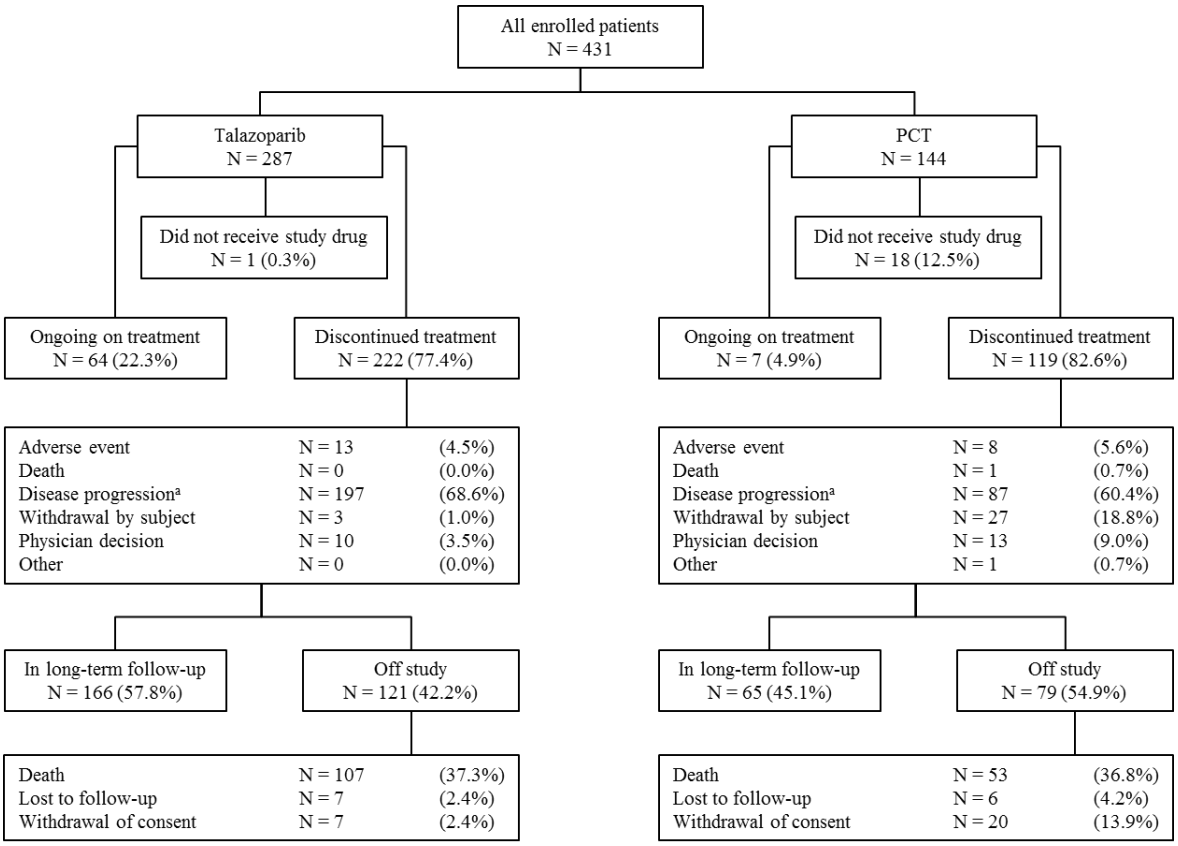
As another analysis for PFS, the HR was estimated using a stratified Cox regression model with treatment group and selected baseline prognostic factors as the main effects, and using the same stratification factors as the primary analysis. The prognostic factors included ECOG score (0 vs > 0), BRCA status (BRCA1 vs BRCA2), prior platinum treatment (yes vs no), and time from initial diagnosis of breast cancer to initial diagnosis of advanced breast cancer (< 12 months vs ≥ 12 months).

Handling of dropouts or missing data

All analyses and descriptive summaries were based on the observed data. Unless otherwise specified, missing data were not imputed. Imputation for partial dates was documented in the SAP. Quality-of-life missing data: for multiple-item scales, missing items were to be imputed based on the mean of the completed items if ≥50% of contributing items were completed. No other adjustment or imputation for missing data was performed.

Results

Participant flow



Source: Table 14.1.2.1
ITT=intent-to-treat; PCT=physician's choice treatment.
a. Disease progression was by local investigator assessment.

Figure 7: Patient Disposition Flow Chart (ITT Population)

Table 32: Patient Disposition (ITT Population)

	Talazoparib (N=287) n (%)	Overall PCT (N=144) n (%)	Total (N=431) n (%)
Did not receive study drug	1 (0.3%)	18 (12.5%)	19 (4.4%)
Treated	286 (99.7%)	126 (87.5%)	412 (95.6%)
Ongoing	64 (22.3%)	7 (4.9%)	71 (16.5%)
Discontinued	222 (77.4%)	119 (82.6%)	341 (79.1%)
Primary reason for discontinuation of study drug			
Adverse event[a]	13 (4.5%)	8 (5.6%)	21 (4.9%)

	Talazoparib (N=287) n (%)	Overall PCT (N=144) n (%)	Total (N=431) n (%)
Death	0 (0.0%)	1 (0.7%)	1 (0.2%)
Disease progression[b]	197 (68.6%)	87 (60.4%)	284 (65.9%)
Withdrawal by patient	3 (1.0%)	27 (18.8%)	30 (7.0%)
Physician decision	10 (3.5%)	13 (9.0%)	23 (5.3%)
Other	0 (0.0%)	1 (0.7%)	1 (0.2%)
Long-term follow-up phase disposition			
Ongoing	166 (57.8%)	65 (45.1%)	231 (53.6%)
Off study	121 (42.2%)	79 (54.9%)	200 (46.4%)
Primary reason for discontinuation of study			
Death	107 (37.3%)	53 (36.8%)	160 (37.1%)
Lost to follow-up	7 (2.4%)	6 (4.2%)	13 (3.0%)
Withdrawal of consent	7 (2.4%)	20 (13.9%)	27 (6.3%)

Source: Table 14.1.2.1, Table 14.3.2.4.2

Percentages are based on the total number of randomized patients in each treatment group and overall.
ITT=intent-to-treat; N=number of evaluable patients; n=number of patients in the category;
PCT=physician's choice treatment.

a. Preferred terms included anaemia, neutropenia, thrombocytopenia, vomiting, fatigue, general physical health deterioration, mucosal inflammation, oedema peripheral, accidental overdose, glioblastoma multiforme, metastases to meninges, cerebral haemorrhage, headache, transient ischaemic attack, dyspnea, obstructive airways disorder, rash, and rash generalized.

b. Disease progression is by local investigator assessment.

Patients in the PCT arm N=126 received either capecitabine (N=55; 44 %), eribulin (N=50; 40 %), gemcitabine (N=12; 10 %), or vinorelbine (N=9; 6 %).

Recruitment

Study Initiation Date: First Subject First Visit (FSFV): 14 October 2013

Primary Completion Date: 15 September 2017

Study Completion Date: Ongoing at data cut-off 15 September 2017 (primary completion date)

Between October 2013 and April 2017, 995 patients were screened for this study and 431 patients were randomized. A total of 145 study sites randomized at least 1 patient: 43 study sites in the US, 74 study sites in Europe (Belgium, France, Germany, Ireland, Italy, Poland, Spain, UK, Russia, Ukraine, and Israel), and 28 study sites in other countries (Australia, Brazil, South Korea, and Taiwan). A total of 156 patients (36.2%) were enrolled in the US, 190 patients (44.1%) in Europe, and 85 patients (19.7%) in the Rest of World.

Conduct of the study

Protocol amendments

The protocol was changed four times by administrative letters #1, #2, #3 and #4, dated respectively 14th of July 2014, 23rd of July 2014, 1st of May 2015 and 09th of February 2017. The original protocol dated 17th July 2013 was amended once (14th December 2015); this amendment incorporated the 3 protocol clarification letters (14th July 2014, 23rd July 2014, and 01st May 2015) previously issued by the initial Sponsor (BioMarin).

Amendment 1 (14 December 2015) was finalized after 184 patients had been randomized. The main purpose of the amendment was to change the Sponsor from BioMarin Pharmaceutical, Inc. to Medivation, Inc. and update

all contact information (including for safety reporting and medical monitor). Other important changes expanded the eligibility criteria, extended safety monitoring (including new liver safety monitoring guidelines for all patients), updated dose modification guidelines based on the type of toxicity, adjusted the secondary efficacy endpoint analyses, and updated study procedures to accommodate study site practices.

The most common stratification error was secondary to incorrect counting of prior therapy (sites were not initially provided with a list of drugs considered to be "cytotoxic" therapy). In addition, the initial randomization form did not use the phrase "for locally advanced/metastatic disease;" therefore, many sites included drugs used in the neoadjuvant/adjuvant setting when they counted cytotoxic drugs. The initial protocol did not clarify that the most recent biopsy data should be used for determination of TNBC or hormone receptor positive breast cancer status for stratification purposes, and sites variably used initial and most recent data; this was clarified in the December 2015 protocol amendment.

Protocol deviations

Table 33: Major Protocol Deviations (ITT Population)

	Talazoparib (N=287) n (%)	Overall PCT (N=144) n (%)	Total (N=431) n (%)
Patients with ≥1 major protocol deviation	65 (22.6)	26 (18.1)	91 (21.1)
Incorrect stratification	19 (6.6)	8 (5.6)	27 (6.3)
Study drug not discontinued or modified per protocol	24 (8.4)	1 (0.7)	25 (5.8)
Imaging assessment not performed	10 (3.5)	9 (6.3)	19 (4.4)
Exclusion criteria met	8 (2.8)	3 (2.1)	11 (2.6)
Inclusion criteria not met	7 (2.4)	3 (2.1)	10 (2.3)
Dosing error	4 (1.4)	1 (0.7)	5 (1.2)
ICF not signed before study procedures conducted	1 (0.3)	2 (1.4)	3 (0.7)
Imaging not submitted to imaging vendor	1 (0.3)	0 (0.0)	1 (0.2)
Imaging performed out of window[a]	1 (0.3)	0 (0.0)	1 (0.2)
Study drug not dispensed per IRT	1 (0.3)	0 (0.0)	1 (0.2)
Study drug not reduced or modified per protocol	1 (0.3)	0 (0.0)	1 (0.2)
Other[b]	0 (0.0)	1 (0.7)	1 (0.2)

Source: Table 14.1.3.1
ICF=informed consent form; IRT=interactive response technology; ITT=intent-to-treat; N=number of evaluable patients; n=number of patients in the category; PCT=physician's choice treatment.
a. One patient was listed as having no tumour assessment performed on Week 24. This deviation should have been captured under the category "Imaging assessment not performed."
b. One patient had an approximate 4 month interruption (07 April 2016-15 August 2016) in eribulin dosing to receive and recover from radiotherapy (26 May 2016-08 July 2016).

Changes in the Planned Analysis

The SAP was finalized on 30 August 2017. Changes to the planned analysis after the finalization of the SAP (Appendix 16.1.9.1) were as follows:

- The primary analysis of PFS performed for the ITT population was to be conducted when approximately 288 PFS events were observed. As of the data cutoff date (15 September 2017), it was estimated that 95% of the total anticipated PFS events would have occurred by database lock, and this would be sufficient to inform the primary analysis.
- The following new PK populations were added:
    - PK population prior to first dose modification: all patients in the PK population prior to a dose reduction or dosing interruption.
    - Dose-compliant PK population: all patients who had received 21 consecutive days of 1 mg talazoparib without dosing interruption prior to sample collection, and who had predose PK samples collected 24 hours ± 10% (2 hours and 24 minutes) after the previous day's dose and no more than 5 minutes after the dose on the day of sample collection. This population was added as an appropriate population to derive the steady state Ctrough.
- Stratified subgroup analyses of PFS and ORR were conducted to further assess the consistency of treatment effects across subgroups.
- Additional analyses were conducted to review the following:
    - Prior therapies for patients with HR+ disease
    - Evaluation of the interaction term for the covariate analysis
    - Analysis of PFS excluding patients who withdrew consent prior to receipt of study drug (1 patient in the talazoparib arm and 18 patients in the PCT arm)
    - Patients who received poststudy PARP inhibitors and/or platinum therapy
    - PK analysis by starting dose capsule strength
    - The SMQ of ‘embolic and thrombotic events, venous’
    - The proportion of patients in the PCT arm who received an adequate starting dose as per NCCN guidelines
    - Evaluation of the hematologic safety profile for patients treated with Generation 3.1 (1 × 1 mg/day capsules) and Generation 2.0 (4 × 0.25 mg/day capsules)

Baseline data

Table 34: Patient Demographics (ITT Population)

Baseline Characteristic	Talazoparib (N=287)	Overall PCT (N=144)	Total (N=431)
Age (years)			
n	287	144	431
Mean (SD)	47.5 (11.61)	49.4 (12.12)	48.1 (11.80)
Median	45.0	50.0	46.0
Minimum, maximum	27.0, 84.0	24.0, 88.0	24.0, 88.0
Age category (years)			
<50	182 (63.4%)	67 (46.5%)	249 (57.8%)
50 to <65	78 (27.2%)	67 (46.5%)	145 (33.6%)
≥65	27 (9.4%)	10 (6.9%)	37 (8.6%)
Gender			
Female	283 (98.6%)	141 (97.9%)	424 (98.4%)
Male	4 (1.4%)	3 (2.1%)	7 (1.6%)
Height (cm)			
n	287	141	428
Mean (SD)	163.2 (7.03)	162.4 (6.82)	162.9 (6.96)
Median	162.5	161.0	162.0
Minimum, maximum	142.0, 188.0	147.0, 180.0	142.0, 188.0
Weight (kg)			
n	287	142	429
Mean (SD)	69.8 (17.24)	68.9 (16.36)	69.5 (16.94)
Median	65.6	66.0	66.0
Minimum, maximum	42.3, 141.2	41.7, 157.8	41.7, 157.8
Body mass index (kg/m^2)			
n	287	141	428
Mean (SD)	26.1 (6.03)	26.1 (5.95)	26.1 (6.00)
Median	24.5	25.3	24.9
Minimum, maximum	17.2, 49.6	17.3, 56.2	17.2, 56.2
Race			
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	31 (10.8%)	16 (11.1%)	47 (10.9%)
Black or African American	12 (4.2%)	1 (0.7%)	13 (3.0%)
Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	192 (66.9%)	108 (75.0%)	300 (69.6%)
Other	5 (1.7%)	1 (0.7%)	6 (1.4%)
Not reported	47 (16.4%)	18 (12.5%)	65 (15.1%)
Ethnicity			
Not Hispanic or Latino	210 (73.2%)	111 (77.1%)	321 (74.5%)
Hispanic or Latino	31 (10.8%)	15 (10.4%)	46 (10.7%)
Not reported	46 (16.0%)	18 (12.5%)	64 (14.8%)
ECOG performance status			
0	153 (53.3%)	84 (58.3%)	237 (55.0%)
1	127 (44.3%)	57 (39.6%)	184 (42.7%)
2	6 (2.1%)	2 (1.4%)	8 (1.9%)
Missing	1 (0.3%)	1 (0.7%)	2 (0.5%)

Source: Table 14.1.4.1.1

ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; SD=standard deviation.

Of the 431 patients randomised in the EMBRACA study, 408 (95%) were centrally confirmed to have a deleterious or suspected deleterious gBRCAm using a clinical trial assay; out of which 354 (82%) were confirmed using the BRACAnalysis CDx. BRCA mutation status (breast cancer susceptibility gene 1 [BRCA1] positive or breast cancer susceptibility gene 2 [BRCA2] positive) was similar across both treatment arms.

Table 35: Hormone Receptor Status and BRCA Mutation Status (ITT Population)

	Talazoparib (N=287)	Overall PCT (N=144)	Total (N=431)
Hormone receptor status[a]			
ER-positive and PR-positive	98 (34.1%)	62 (43.1%)	160 (37.1%)
ER-positive and PR-negative	51 (17.8%)	17 (11.8%)	68 (15.8%)
ER-negative and PR-positive	6 (2.1%)	4 (2.8%)	10 (2.3%)
ER-negative and PR-negative	130 (45.3%)	60 (41.7%)	190 (44.1%)
ER unknown or PR unknown	2 (0.7%)	1 (0.7%)	3 (0.7%)
ER-positive or PR-positive	157 (54.7%)	84 (58.3%)	241 (55.9%)
HER2-negative	287 (100.0%)	144 (100.0%)	431 (100.0%)
HER2-positive	0 (0.0%)	0 (0.0%)	0 (0.0%)
ER and PR and HER2 unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)
Triple-negative[b]	130 (45.3%)	60 (41.7%)	190 (44.1%)
HR-positive (not triple-negative)[b]	157 (54.7%)	84 (58.3%)	241 (55.9%)
BRCA mutation status by central laboratory	270 (94.1%)	138 (95.8%)	408 (94.7%)
BRCA1-positive	123 (45.6%)	60 (43.5%)	183 (44.9%)
BRCA2-positive	147 (54.4%)	78 (56.5%)	225 (55.1%)
BRCA mutation status by local laboratory	17 (5.9%)	6 (4.2%)	23 (5.3%)
BRCA1-positive	10 (58.8%)	3 (50.0%)	13 (56.5%)
BRCA2-positive	7 (41.2%)	3 (50.0%)	10 (43.5%)
Triple-negative status[c]			
Triple-negative	130 (45.3%)	60 (41.7%)	190 (44.1%)
BRCA1-positive	100 (76.9%)	43 (71.7%)	143 (75.3%)
BRCA2-positive	30 (23.1%)	17 (28.3%)	47 (24.7%)
Hormone receptor positive[c]	157 (54.7%)	84 (58.3%)	241 (55.9%)
BRCA1-positive	33 (21.0%)	20 (23.8%)	53 (22.0%)
BRCA2-positive	124 (79.0%)	64 (76.2%)	188 (78.0%)

Source: Table 14.1.4.2.1

BRCA=breast cancer susceptibility gene; CNS=central nervous system; eCRF=electronic case report form; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; ITT=intent-to-treat; PR=progesterone receptor.

a. Based on most recent pathology eCRF.

b. Triple-negative: ER-negative, PR-negative and HER2-negative; HR-positive: any of the ER, PR or HER2 positivity.

c. Determined by either central or local laboratory. If both central and local laboratory results were entered in the database, the central result (if positive) was used. If both central and local laboratory results were entered in the database and the central result was negative, the local result was used.

Table 36: Advanced Breast Cancer Characteristics at Baseline – Investigator Assessment (ITT Population)

	Talazoparib (N=287)	Overall PCT (N=144)	Total (N=431)
Time from initial diagnosis of breast cancer to randomization (years)			
n	287	144	431
Median	3.9	5.0	4.1
Minimum, maximum	0, 35	0, 28	0, 35
Time from initial diagnosis of advanced breast cancer to randomization (years)			
n	286	144	430
Median	1.2	1.4	1.3
Minimum, maximum	0, 30	0, 25	0, 30
Time from the start date of first cytotoxic therapy for advanced breast cancer to randomization (years)			
n	172	85	257
Median	1.0	1.1	1.1
Minimum, maximum	0, 15	0, 6	0, 15
Time from initial diagnosis of breast cancer to diagnosis of advanced breast cancer (years)			
n	286	144	430
Median	1.9	2.7	2.2
Minimum, maximum	0, 22	0, 24	0, 24
Categories for time from initial diagnosis of breast cancer to diagnosis of advanced breast cancer			
<12 months	108 (37.6%)	42 (29.2%)	150 (34.8%)
≥12 months	178 (62.0%)	102 (70.8%)	280 (65.0%)

Source: Table 14.1.4.2.1
ITT=intent-to-treat; PCT=physician's choice treatment.

Table 37: Summary of Prior Therapies for Breast Cancer (Intent-to-Treat Population)

Baseline Characteristics	Talazoparib (N=287)	Overall PCT (N=144)	Total (N=431)
Number of patients who received the following prior therapies	287 (100.0%)	144 (100.0%)	431 (100.0%)
Antineoplastic therapy	286 (99.7%)	144 (100.0%)	430 (99.8%)
Hormonal/aromatase inhibitor treatment	161 (56.1%)	77 (53.5%)	238 (55.2%)
Targeted therapy	83 (28.9%)	43 (29.9%)	126 (29.2%)
Neoadjuvant/adjuvant therapy	238 (82.9%)	121 (84.0%)	359 (83.3%)
Anthracycline	243 (84.7%)	115 (79.9%)	358 (83.1%)
Taxane	262 (91.3%)	130 (90.3%)	392 (91.0%)
Capecitabine	73 (25.4%)	43 (29.9%)	116 (26.9%)
Eribulin	11 (3.8%)	7 (4.9%)	18 (4.2%)
Immunotherapy	2 (0.7%)	1 (0.7%)	3 (0.7%)
Platinumtreatment	46 (16.0%)	30 (20.8%)	76 (17.6%)
Radiotherapy	223 (77.7%)	107 (74.3%)	330 (76.6%)
Cytotoxic treatment	282 (98.3%)	142 (98.6%)	424 (98.4%)
CDK4/6 inhibitors	16 (5.6%)	6 (4.2%)	22 (5.1%)
mTOR inhibitor	21 (7.3%)	14 (9.7%)	35 (8.1%)

The analysis data cutoff date is 15SEP2017.
PCT=Physician's Choice Therapies.
All numbers displayed are based on data from Prior Study Cancer Treatment and Prior and Concomitant Radiation Cancer Treatment CRFs.

Table 38: Number of Prior Therapies for Breast Cancer (Intent-to-Treat Population)

Baseline Characteristics	Talazoparib (N=287)	Overall PCT (N=144)	Total (N=431)
Number of prior cytotoxic chemotherapy regimens for advanced disease derived from eCRF			
0	111 (38.7%)	54 (37.5%)	165 (38.3%)
1	107 (37.3%)	54 (37.5%)	161 (37.4%)
2	57 (19.9%)	28 (19.4%)	85 (19.7%)
3	11 (3.8%)	8 (5.6%)	19 (4.4%)
>=4	1 (0.3%)	0 (0.0%)	1 (0.2%)
Number of prior cytotoxic chemotherapy regimens for advanced disease derived from eCRF summary			
n	287	144	431
Mean (SD)	0.9 (1.01)	0.9 (0.89)	0.9 (0.97)
Median	1.0	1.0	1.0
Min, Max	0, 10	0, 3	0, 10

The analysis data cutoff date is 15SEP2017.
PCT=Physician's Choice Therapies.
All numbers displayed are based on data from Prior Study Cancer Treatment and Prior and Concomitant Radiation Cancer Treatment CRFs.

Table 39: Summary of Prior Taxane and Anthracycline Therapies for Breast Cancer (Intent-to-Treat Population)

	Prior Anthracycline Treatment				
Treatment Arm: Prior Taxane Treatment	(Neo)Adjuvant/ Adjuvant	Advanced	Any Setting	No	Total
Talazoparib:					
(Neo)Adjuvant/Adjuvant	181 (63.1%)	12 (4.2%)	189 (65.9%)	15 (5.2%)	204 (71.1%)
Advanced	57 (19.9%)	29 (10.1%)	84 (29.3%)	24 (8.4%)	108 (37.6%)
Any Setting	196 (68.3%)	37 (12.9%)	225 (78.4%)	37 (12.9%)	262 (91.3%)
No	9 (3.1%)	10 (3.5%)	18 (6.3%)	7 (2.4%)	25 (8.7%)
Total	205 (71.4%)	47 (16.4%)	243 (84.7%)	44 (15.3%)	287 (100%)
Overall PCT:					
(Neo)Adjuvant/Adjuvant	87 (60.4%)	1 (0.7%)	87 (60.4%)	11 (7.6%)	98 (68.1%)
Advanced	31 (21.5%)	12 (8.3%)	43 (29.9%)	14 (9.7%)	57 (39.6%)
Any Setting	95 (66.0%)	13 (9.0%)	106 (73.6%)	24 (16.7%)	130 (90.3%)
No	7 (4.9%)	2 (1.4%)	9 (6.3%)	5 (3.5%)	14 (9.7%)
Total	102 (70.8%)	15 (10.4%)	115 (79.9%)	29 (20.1%)	144 (100%)

The analysis data cutoff date is 15SEP2017.
PCT=Physician's Choice Therapies.
All numbers displayed are based on data from Prior Study Cancer Treatment.
A patient can be counted in more than a category if received the same type of treatment in (neo)adjuvant/adjuvant and in advanced setting.

Table 40: Summary of Stratification Factors (ITT Population)

Stratification Factors	Talazoparib (N=287) n (%)		Overall PCT (N=144) n (%)	
Based on eCRF[a]:	**Based on IXRS:**			
Number of prior cytotoxic chemotherapy regimens for advanced disease	0	>0	0	>0
0	93 (32.4)	18 (6.3)	46 (31.9)	8 (5.6)
>0	2 (0.7)	174 (60.6)	2 (1.4)	88 (61.1)
Triple negative (ER-, PR-, HER2-)	Yes	No	Yes	No
Yes	129 (44.9)	1 (0.3)	60 (41.7)	0 (0.0)
No	2 (0.7)	155 (54.0)	4 (2.8)	80 (55.6)
History of CNS metastasis	Yes	No	Yes	No
Yes	42 (14.6)	1 (0.3)	20 (13.9)	0 (0.0)
No	2 (0.7)	242 (84.3)	1 (0.7)	123 (85.4)

Source: Table 14.1.2.2.2

CNS=central nervous system; eCRF=electronic Case Report Form; ER-=estrogen receptor negative; HER2=human epidermal growth factor receptor 2; ITT=intent-to-treat; IXRS=interactive voice/web response system; N=number of evaluable patients; n=number of patients in the category; PCT=physician's choice treatment; PR-=progesterone receptor negative.

a. Prior cytotoxic chemotherapy regimens for advanced disease: derived from prior study cancer treatment eCRF; Triple negative status: derived from pathology of breast cancer eCRF (most recent biopsy at baseline); History of CNS metastasis: derived from stratification page in eCRF.

Numbers analysed

Table 41: Number of Patients in Each Analysis Population by Treatment Arm

	Talazoparib (N=287) n (%)	Overall PCT (N=144) n (%)	Total (N=431) n (%)
ITT population[a]	287 (100.0%)	144 (100.0%)	431 (100.0%)
ITT with measurable disease population – IRF[b]	217 (75.6%)	94 (65.3%)	311 (72.2%)
ITT with measurable disease population – investigator[c]	219 (76.3%)	114 (79.2%)	333 (77.3%)
Safety population [d]	286 (99.7%)	126 (87.5%)	412 (95.6%)
PK population – talazoparib[e]	286 (99.7%)	0 (0.0%)	286 (66.4%)
PRO-evaluable population[f]	262 (91.3%)	114 (79.2%)	376 (87.2%)

Source: Table 14.1.1.1

IRF=independent review facility; ITT= intent-to-treat; N=number of evaluable patients; n=number of patients in the category; PCT=physician's choice treatment; PK=pharmacokinetic; PRO = patient reported outcomes. Percentages were based on the total number of randomized patients in each treatment group and overall.

a. All patients randomized in the study.
b. All patients in ITT population with ≥1 target lesion identified at baseline by ≥1 IRF reader.
c. All patients in the ITT population with ≥1 target lesion identified at baseline by the investigator.
d. All patients who received any dose of study drug.
e. All patients who received ≥1 dose of talazoparib and provided ≥1 evaluable PK assessment.
f. All patients who completed the PRO questionnaire at baseline and ≥1 postbaseline visit.

Outcomes and estimation

Primary endpoint

- **PFS by IRF**

Table 42: PFS by IRF (ITT Population)

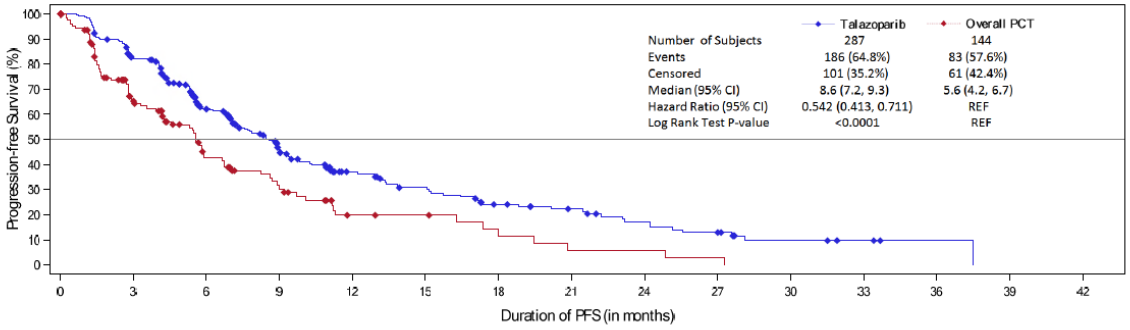
	Talazoparib (N=287)	Overall PCT (N=144)	Treatment Comparison (Talazoparib vs Overall PCT)
Events	186 (64.8%)	83 (57.6%)	-
Radiographic progression	157 (54.7%)	68 (47.2%)	-
Death	29 (10.1%)	15 (10.4%)	-
Censored	101 (35.2%)	61 (42.4%)	-
Discontinued with no adequate postbaseline tumour assessment	1 (0.3%)	19 (13.2%)	-
Withdrew consent	1 (0.3%)	16 (11.1%)	-
Lost to follow-up	0 (0.0%)	1 (0.7%)	-
Other reasons	0 (0.0%)	2 (1.4%)	-
No disease progression or death prior to start of new	28 (9.8%)	29 (20.1%)	-
No disease progression prior to treatment discontinuation + 30	1 (0.3%)	1 (0.7%)	-
Unacceptable gap between last adequate tumour assessment	0 (0.0%)	0(0.0%)	-
Discontinued with no disease progression or death prior to data cutoff date	12 (4.2%)	5 (3.5%)	-
Withdrew consent	2 (0.7%)	1 (0.7%)	-
Lost to follow-up	2 (0.7%)	0 (0.0%)	-
Other reasons	8 (2.8%)	4 (2.8%)	-
In follow-up for disease progression or death (censored at last tumour assessment date)	59 (20.6%)	7 (4.9%)	-
Duration of PFS (months)[a]			
Median (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)	-
Hazard ratio (95% CI): stratified[b]	-	-	0.542 (0.413, 0.711)
P-value: stratified log-rank test[b]	-	-	<0.0001
Hazard ratio (95% CI): unstratified[c]	-	-	0.587 (0.451, 0.764)
P-value: unstratified log-rank test[c]	-	-	<0.0001
PFS probability at month 12 (95% CI)	0.37 (30.66, 43.44)	0.20 (11.30, 29.86)	-

CI=confidence interval; IRF=independent review facility; ITT=intent-to-treat; PCT=physician's choice treatment; PD=progressive disease; PFS=progression-free survival.

a. Based on Kaplan-Meier estimates.

b. P-value for the primary analysis was based on a stratified log-rank test. Hazard ratio was based on

stratified Cox regression model with treatment as the only covariate.
c. P-value for the sensitivity to the analysis method was based on an unstratified log-rank test. Hazard ratio was based on unstratified Cox regression model with treatment as the only covariate and was relative to overall PCT with <1 favoring talazoparib.



Talazoparib: Evt/Cum.	0/0	50/50	53/103	34/137	17/154	9/163	9/172	2/174	5/179	4/183	2/185	0/185	0/185	1/186	0/186
Patients at Risk	287	229	148	91	55	42	29	23	16	12	5	3	1	0	0
Overall PCT: Evt/Cum.	0/0	41/41	20/61	8/69	7/76	0/76	3/79	2/81	0/81	1/82	1/83	0/83	0/83	0/83	0/83
Patients at Risk	144	68	34	22	9	8	4	2	2	1	0	0	0	0	0

Source: Figure 14.2.1.1.2
Primary analysis p-value was based on a stratified log-rank test. Hazard ratio was based on stratified Cox regression model with treatment as the only covariate (stratification factors: number of prior cytotoxic chemotherapy regimens, triple negative status, history of central nervous system) and was relative to overall PCT with <1 favoring talazoparib.
CI=confidence interval; Cum.=cumulative; Evt=event; IRF=independent review facility; ITT=intent-to-treat; PCT=physician's choice treatment; PFS=progression-free survival.

Figure 8: Kaplan-Meier Curves of PFS by IRF (ITT Population)

Secondary endpoints

- **Overall survival**

At the time of the interim overall survival analysis (data cutoff date of 15 September 2017), 163 patients (37.8%) had died, 108 patients (37.6%) in the talazoparib arm and 55 patients (38.2%) in the PCT arm.

Table 43: Overall Survival (Intent-to-Treat Population)

Overall Survival at Data Analysis Cutoff Date	Talazoparib (N=287)	Overall PCT (N=144)	Treatment Comparison (Talazoparib vs. Overall PCT)
Survival status			
Death	108 (37.6%)	55 (38.2%)	
Censored [1]	179 (62.4%)	89 (61.8%)	
Alive at analysis cut-off date	166 (57.8%)	65 (45.1%)	
Lost to follow-up	13 (4.5%)	24 (16.7%)	
Duration of overall survival [1][2] (months)			
n	287	144	
Censored	179 (62.4%)	89 (61.8%)	
25th Percentile	11.8	11.2	
Median (95% CI)	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)	
75th Percentile	37.5	27.3	
Hazard Ratio (95% CI) – Stratified [3]			0.761 (0.547, 1.060)
Hazard Ratio (95% CI) – Unstratified [4]			0.767 (0.553, 1.063)

The analysis data cutoff date is 15SEP2017.
NR=Not Reached. PD=Progressive Disease. PCT=Physician's Choice Therapies
[1] Patients who were not known to have died at the analysis date are censored at the date last known alive or data analysis cutoff date, whichever occurs first.
[2] Based on Kaplan-Meier estimates.
[3] Primary analysis' p-value is based on a stratified log-rank test. Hazard ratio is based on stratified Cox regression model with treatment as the only covariate (stratification factors: number of prior cytotoxic chemotherapy regimens, triple negative status, history of central nervous system) and is relative to overall PCT with <1 favoring Talazoparib.
[4] Sensitivity to the analysis method's p-values are based on an unstratified log-rank test and stratified Wilcoxon's rank sum test. Hazard ratio is based on unstratified Cox regression model with treatment as the only covariate and is relative to overall PCT with <1 favoring Talazoparib.
[5] Probability is estimated from the Kaplan-Meier curve and confidence interval is calculated with product-limit method.

Overall Survival at Data Analysis Cutoff Date	Talazoparib (N=287)	Overall PCT (N=144)	Treatment Comparison (Talazoparib vs. Overall PCT)
Duration of overall survival [1][2] (months)			
P-value – Stratified log-rank test [3]			0.1053
P-value – Unstratified log-rank test [4]			0.1104
P-value – Stratified Wilcoxon's rank sum test [4]			0.0960
Survival probability at month 12 (95% CI) [5]	0.75 (68.58, 79.87)	0.73 (62.89, 80.39)	
Survival probability at month 24 (95% CI) [5]	0.45 (36.74, 53.49)	0.37 (24.07, 49.15)	
Survival probability at month 36 (95% CI) [5]	0.34 (25.28, 43.68)	NR (NR, NR)	

The analysis data cutoff date is 15SEP2017.
NR=Not Reached. PD=Progressive Disease. PCT=Physician's Choice Therapies
[1] Patients who were not known to have died at the analysis date are censored at the date last known alive or data analysis cutoff date, whichever occurs first.
[2] Based on Kaplan-Meier estimates.
[3] Primary analysis' p-value is based on a stratified log-rank test. Hazard ratio is based on stratified Cox regression model with treatment as the only covariate (stratification factors: number of prior cytotoxic chemotherapy regimens, triple negative status, history of central nervous system) and is relative to overall PCT with <1 favoring Talazoparib.
[4] Sensitivity to the analysis method's p-values are based on an unstratified log-rank test and stratified Wilcoxon's rank sum test. Hazard ratio is based on unstratified Cox regression model with treatment as the only covariate and is relative to overall PCT with <1 favoring Talazoparib.
[5] Probability is estimated from the Kaplan-Meier curve and confidence interval is calculated with product-limit method.

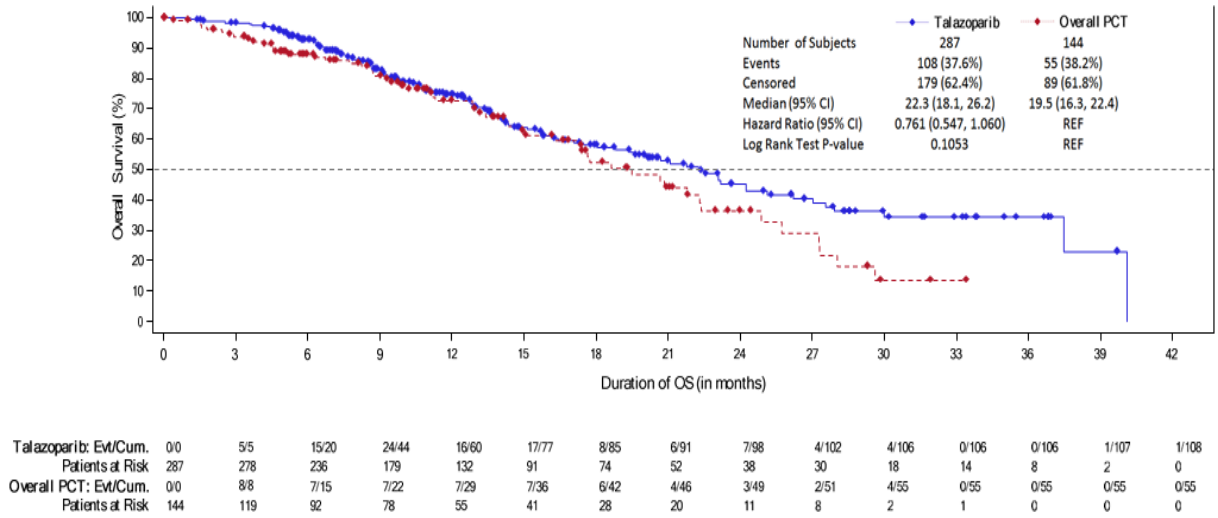


Figure 9: Kaplan-Meier Curves for Overall Survival (Intent-to-Treat Population)

- **ORR**

Table 44: ORR (RECIST 1.1, investigator, confirmation not required for primary analysis)

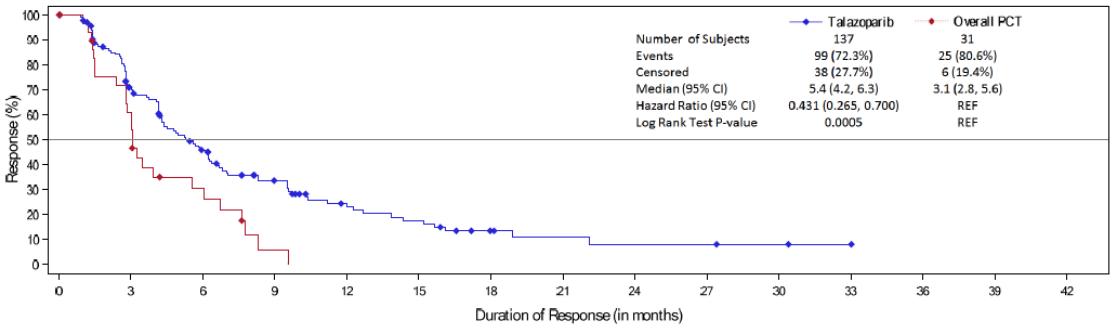
	Talazoparib (N=287)	Overall PCT (N=144)
Number of patients in ITT population with measurable disease at baseline, n (%)	219 (76.3)	114 (79.2)
ORR – unconfirmed (includes confirmed)[a,e], n (%) (95% CI)	137 (62.6) (55.78-68.99)	31 (27.2) (19.28-36.33)
Difference in proportions, % (95% CI)[d]	35.4 (25.0-45.7)	
Odds ratio (95% CI)[c]; p-value[b]	4.99 (2.93-8.83); <0.0001	
ORR – confirmed[a], n (%) (95% CI)	110 (50.2) (43.41-57.04)	21 (18.4) (11.78-26.77)
Difference in proportions, % (95% CI)[d]	31.8 (22.1-41.5)	
Odds ratio (95% CI)[c]; p-value[b]	4.85 (2.69-9.10); <0.0001	
BOR (with unconfirmed [includes confirmed] CR + PR)[a,e]		
Complete response, n (%)	12 (5.5)	0 (0.0)
Partial response, n (%)	125 (57.1)	31 (27.2)
Stable disease, n (%)	46 (21.0)	36 (31.6)
Disease progression, n (%)	32 (14.6)	28 (24.6)
Not evaluable, n (%)	4 (1.8)	19 (16.7)
BOR (with confirmed CR/PR)[a]		
Complete response, n (%)	12 (5.5)	0 (0.0)
Partial response, n (%)	98 (44.7)	21 (18.4)
Stable disease, n (%)	69 (31.5)	45 (39.5)
Disease progression, n (%)	36 (16.4)	29 (25.4)
Non-evaluable, n (%)	4 (1.8)	19 (16.7)

a. For patients in ITT population with measurable disease at baseline.
b. Stratified Cochran-Mantel-Haenszel.
c. Odds ratio of objective response >1 favors treatment with talazoparib.
d. Confidence intervals were calculated using exact methods.

e. Any patient with a PR or CR was considered a responder. The category of unconfirmed response includes all patients who were considered responders, some of whom had a confirmed response.

Exploratory endpoints

- **DOR**



Talazoparib: Evt/Cum.	0/0	38/38	30/68	13/81	9/90	4/94	3/97	1/98	1/99	0/99	0/99	0/99	0/99	0/99	0/99
Patients at Risk	137	88	52	31	17	13	6	4	3	3	2	1	0	0	0
Overall PCT: Evt/Cum.	0/0	11/11	8/19	5/24	1/25	0/25	0/25	0/25	0/25	0/25	0/25	0/25	0/25	0/25	0/25
Patients at Risk	31	17	7	1	0	0	0	0	0	0	0	0	0	0	0

Source: Figure 14.2.4.1.1
Confirmation of CR/PR with a scan ≥4 weeks of first assessment documenting response was not required.
CI=confidence interval; Cum.=cumulative; DOR=duration of response; Evt=event; ITT=intent-to-treat; PCT=physician's choice treatment; REF=reference treatment group.

Figure 10: Kaplan-Meier Curves of DOR by Investigator Assessment (ITT with Measurable Disease Population)

- **Time to the end of the first post study therapy**

As assessed by stratified Cox regression analysis, the HR was 0.678 (95% CI: 0.505, 0.912; p=0.0096) and median time to the end of the first poststudy therapy was 11.9 months (95% CI: 10.7, 14.1) for patients in the talazoparib arm and 10.1 months (95% CI: 8.6, 12.4) for patients in the PCT arm.

- **Patient Reported Outcomes**

Up to Cycle 12, the percentage of eligible patients who completed at least 1 question on the EORTC QLQ-C30 was ≥81% in the talazoparib arm and ≥73% in the PCT arm.

Baseline mean scores for Global Health Status/QoL were similar for the talazoparib and PCT arms, and were moderately high in both treatment arms (61.9 [95% CI: 59.0, 64.7] vs 60.9 [95% CI: 56.9, 64.9], respectively).

Results from the between-treatment comparison of overall Global Health Status/QoL scores from the repeated measures analyses (mixed-effect model) and the same analysis based on change from baseline scores were reported. The difference between the 2 treatment arms in Global Health Status/QoL was 8.4 [95% CI: 4.6, 12.3]; p<0.0001). Based on interpretation from the 95% CIs, the overall change from baseline scores in Global Health Status/QoL was 3.0 [95% CI: 1.2, 4.8] within the talazoparib arm versus -5.4 [95% CI: -8.8, -2.0]) in the control arm.

The median TTD in Global Health Status/QoL was 24.3 months (95% CI: 13.8, NR) in the talazoparib arm compared with 6.3 months (95% CI: 4.9, 12.2) in the PCT arm. The HR was 0.376 (95% CI: 0.26, 0.55; p<0.0001).

Descriptive statistics for the observed means for the EORTC QLQ-C30 scale scores and change from baseline were presented by treatment arm and visit. Baseline scores for all 5 functional scales (EORTC QLQ-C30) were similar between the 2 treatment arms and showed high functional levels in both treatment arms. Mean baseline symptom scale scores (EORTC QLQ-C30) were similar in both treatment arms for all symptoms. Baseline symptom scores indicated low symptom severity in both treatment arms.

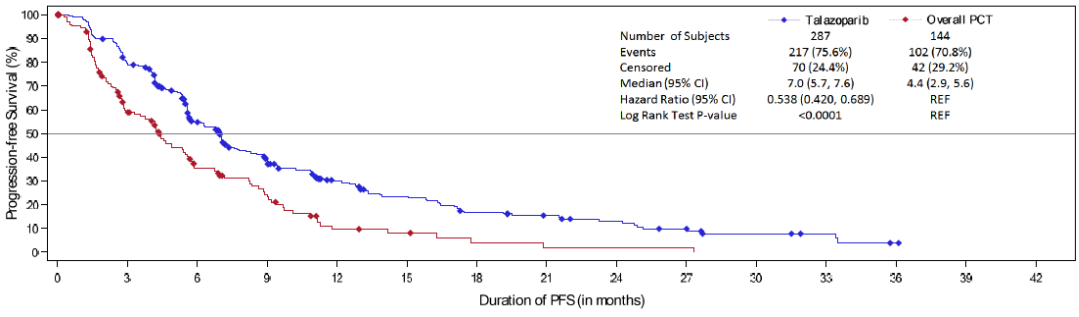
Up to Cycle 12, the percentage of patients completing at least 1 question on the EORTC QLQ-BR23 was ≥81% in the talazoparib arm and ≥73% in the PCT arm. The mean scores for the functional scales (body image, sexual functioning, and future perspective) were generally similar in both treatment arms at baseline except for sexual enjoyment (59.2 in the talazoparib arm vs 48.8 in the PCT arm).

Between-treatment comparisons of breast symptoms scale scores from the repeated measures analyses and analyses based on change from baseline scores were presented. The model estimated difference between the 2 treatment arms in breast symptoms scale scores was -5.0 (95% CI: -8.1, -1.8) favouring talazoparib (p=0.0022). Based on interpretation of the 95% CI, the overall change from baseline for the talazoparib arm was -5.1 [95% CI: -6.7, -3.5].

An analysis of TTD in breast symptoms was conducted based on time-to-event analysis methods. A majority of patients in each treatment arm were censored from the analysis (238 patients [90.8%] in the talazoparib arm and 100 patients [87.7%] in the PCT arm). Talazoparib treatment significantly delayed TTD in breast symptoms compared with PCT. The HR was 0.392 (95% CI: 0.20, 0.78; p=0.0053). The median TTD in the breast symptom scale was not reached for either treatment arm.

Ancillary analyses

PFS by investigator assessment



Talazoparib: Evt/Cum.	0/0	58/58	67/125	38/163	19/182	11/193	11/204	2/206	3/209	4/213	2/215	0/215	2/217	0/217	0/217
Patients at Risk	287	225	140	87	53	39	27	21	15	11	6	4	1	0	0
Overall PCT: Evt/Cum.	0/0	50/50	25/75	10/85	12/97	1/98	2/100	1/101	0/101	0/101	1/102	0/102	0/102	0/102	0/102
Patients at Risk	144	68	35	22	7	5	2	1	1	1	0	0	0	0	0

Source: Figure 14.2.1.2.1
Primary analysis p-value was based on a stratified log-rank test. Hazard ratio was based on stratified Cox regression model with treatment as the only covariate (stratification factors: number of prior cytotoxic chemotherapy regimens, triple negative status, history of central nervous system) and was relative to overall PCT with <1 favoring talazoparib.
CI=confidence interval; Cum.=cumulative; Evt=event; PCT=physician's choice treatment; REF=reference treatment group.

Figure 11: Kaplan-Meier Curves of PFS by investigator assessment (ITT Population)

Table 45: Summary of Radiographic Progression Based on IRF versus Investigator Assessment (ITT Population)

Parameter and Disagreement Type	Talazoparib (N=287)			Overall PCT (N=144)			Difference (%)
	N	n	%	N	n	%	
a1		102			44		
a2		34			21		
a3		16			4		
b		54			26		
c		10			2		
d		71			47		
Total event disagreement rate (c+b)/N	287	64	22.3	144	28	19.4	2.9
Early disagreement rate (b+a3)/(a1+a2+a3+b)	206	70	34.0	95	30	31.6	2.4
Late disagreement rate (c+a2)/(b+c+a2+a3)	114	44	38.6	53	23	43.4	-4.8
Overall disagreement rate (a2+a3+c+b)/N	287	114	39.7	144	53	36.8	2.9

Source: Table 14.2.1.16.2 Parameters are defined as:

a1: Number of agreements on timing and occurrence of PD by both IRF and investigator assessment (within 7-day window).
a2: Number of times investigator declares PD later than IRF (>7 days)
a3: Number of times investigator declares PD earlier than IRF (>7 days)
b: Number of times investigator declares PD but IRF does not.
c: Number of times IRF declares PD; investigator does not.
d: Number of times neither investigator nor IRF declares PD

Sensitivity analysis of PFS

Table 46: Summary of Sensitivity Analyses of PFS (ITT Population)

PFS (months)	Talazoparib (N=287)	Overall PCT (N=144)
PFS by Investigator to Assess the Impact of Radiographic and Clinical Deterioration[a]		
Events, n (%)	220 (76.7)	106 (73.6)
Median (95% CI)[b]	6.9 (5.7, 7.3)	4.2 (2.9, 5.4)
Hazard Ratio (95% CI)[d]; p-value[c]	0.514 (0.402, 0.656); <0.0001	
PFS by IRF to Assess the Impact of Clinical Deterioration by Investigator[e]		
Events, n (%)	188 (65.5)	87 (60.4)
Median (95% CI)[b]	8.5 (7.1, 9.0)	5.6 (3.9, 5.9)
Hazard Ratio (95% CI)[d]; p-value[c]	0.513 (0.392, .0671); <0.0001	
PFS by IRF to Assess the Impact of Radiographic Progression After Study Drug Discontinuation +30 Days[f]		
Events, n (%)	187 (65.2)	84 (58.3)
Median (95% CI)[b]	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard Ratio (95% CI)[d]; p-value[c]	0.545 (0.416, 0.714); <0.0001	
PFS by IRF to Assess the Impact of Treatment Discontinuation for Any Reason[g]		
Events, n (%)	227 (79.1)	121 (84.0)
Median (95% CI)[b]	6.8 (5.6, 7.2)	2.8 (2.3, 3.9)
Hazard Ratio (95% CI)[d]; p-value[c]	0.393 (0.310, 0.497); <0.0001	

PFS (months)	Talazoparib (N=287)	Overall PCT (N=144)
PFS by IRF to Assess the Impact of Postbaseline Antineoplastic Therapies[h]		
Events, n (%)	210 (73.2)	109 (75.7)
Median (95% CI)[b]	7.1 (5.8, 8.1)	3.9 (2.8, 5.3)
Hazard Ratio (95% CI)[d]; p-value[c]	0.462 (0.362, 0.589); <0.0001	
PFS by IRF to Assess the Impact of On-Study Radiotherapy[i]		
Events, n (%)	184 (64.1)	81 (56.3)
Median (95% CI)[b]	8.6 (7.2, 9.4)	5.7 (4.2, 7.1)
Hazard Ratio (95% CI)[d]; p-value[c]	0.581 (0.440, 0.767); 0.0001	
PFS by IRF to Assess the Impact of Deaths After End of Treatment +126 Days[j]		
Events, n (%)	166 (57.8)	74 (51.4)
Median (95% CI)[b]	8.5 (7.1, 9.2)	5.6 (4.2, 5.9)
Hazard Ratio (95% CI)[d]; p-value[c]	0.502 (0.375, 0.671); <0.0001	
PFS by IRF to Assess the Impact of Capsule Strength for Patients Treated with 1 mg Capsules[k]		
Events, n (%)	129 (59.4)	83 (57.6)
Median (95% CI)[b]	8.5 (7.1, 9.0)	5.6 (4.2, 6.7)
Hazard Ratio (95% CI)[d]; p-value[c]	0.568 (0.424, 0.761); 0.0001	
PFS by IRF to Assess the Impact of Central Genetic Testing (All Central Diagnostic Test)[l]		
Events, n (%)	171 (63.3)	82 (59.4)
Median (95% CI)[b]	8.5 (7.1, 9.3)	5.6 (4.2, 6.7)
Hazard Ratio (95% CI)[d]; p-value[c]	0.533 (0.404, 0.703); <0.0001	
PFS by IRF to Assess the Impact of Central Genetic Testing (Commercial Assay Only)[m]		
Events, n (%)	111 (56.3)	51 (52.6)
Median (95% CI)[b]	8.5 (6.9, 9.0)	5.6 (4.2, 8.2)
Hazard Ratio (95% CI)[d]; p-value[c]	0.539 (0.381, 0.765); 0.0004	

a. In this analysis, a PFS event was either radiological progression or clinical progression by the Investigator, or death.
b. Based on Kaplan-Meier estimates.
c. Based on stratified log-rank test.
d. Based on stratified Cox regression model.
e. In this analysis, a PFS event was either radiological progression by the IRF or clinical progression by the Investigator, or death.
f. In this analysis, a PFS event by the IRF could have occurred any time on study, or death.
g. In this analysis, PFS was defined as PD by the IRF. Study drug discontinuation for any reason , or death due to any cause.
h. Patients who received any postbaseline therapy were considered to have had a PD event, as of the start date of new anti-cancer therapy.
i. For patients who received any on-study radiotherapy before PD by the IRF, PFS was censored as of the date of the last adequate tumour assessment on or before radiotherapy.
j. For patients who did not have radiographic PD by the IRF and died more than 126 days following discontinuation, PFS was censored as of the date of the last adequate tumour assessment on or before following treatment discontinuation.
k. N=217 for the talazoparib arm; N=144 for the PCT arm.
l. N=270 for the talazoparib arm; N=138 for the PCT arm.
m. N=197 for the talazoparib arm; N=97 for the PCT arm.

PFS subgroup analysis

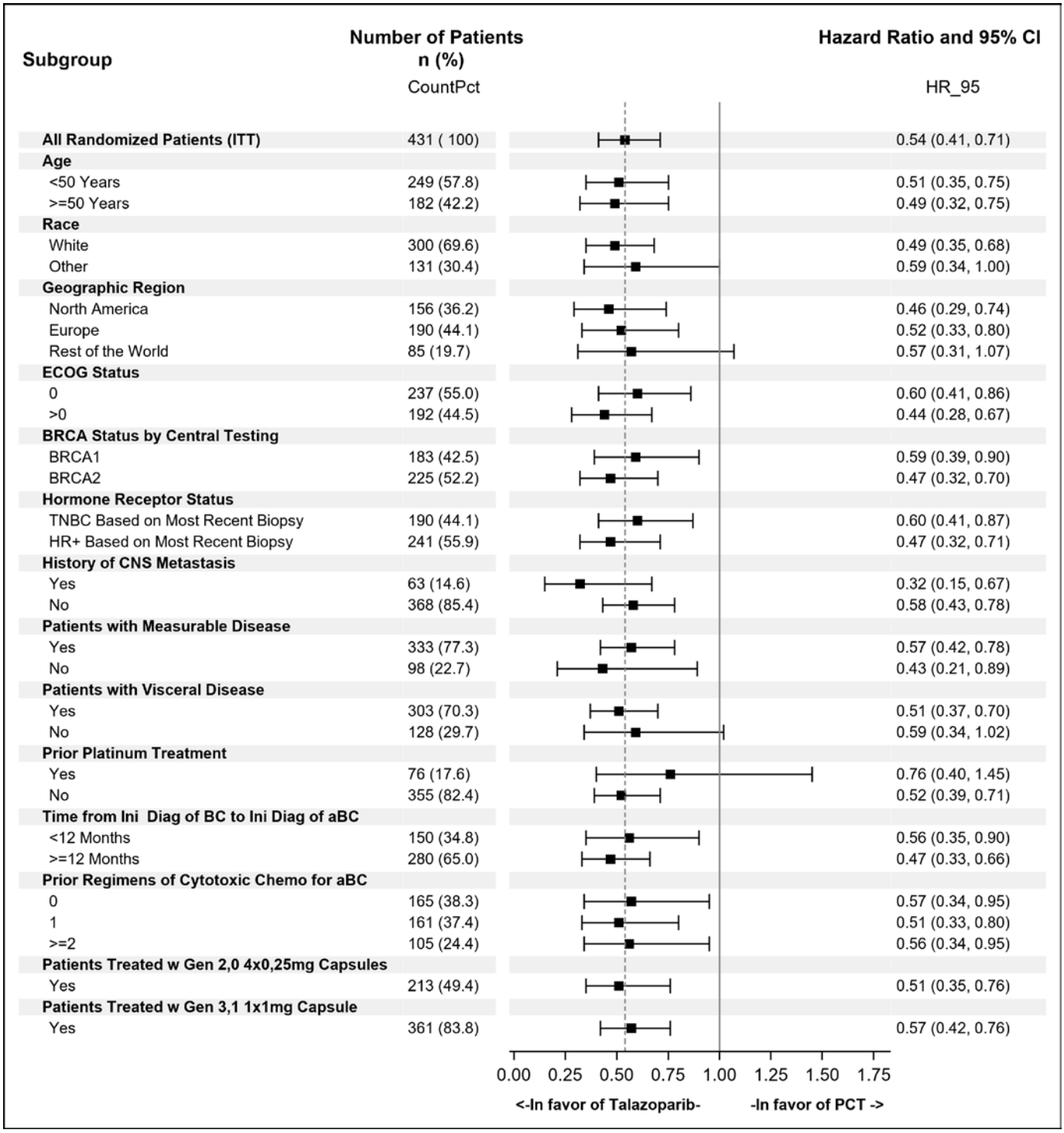


Figure 12: Key Subgroup Analyses of PFS by IRF Assessment – Stratified Analyses (ITT Population)

Post-study antineoplastic therapies

Table 47: Post-study Antineoplastic Therapies by WHO Drug Classification Code Received by ≥5% of Patients in Either Treatment Arm (ITT Population)

ATC Level 2 Description Generic Name	Talazoparib (N=287) n (%)	Overall PCT (N=144) n (%)	Total (N=431) n (%)
Patients who received postbaseline antineoplastic therapy	178 (62.0%)	98 (68.1%)	276 (64.0%)
Antineoplastic agents	171 (59.6%)	96 (66.7%)	267 (61.9%)
Carboplatin	82 (28.6%)	38 (26.4%)	120 (27.8%)
Gemcitabine	54 (18.8%)	26 (18.1%)	80 (18.6%)
Capecitabine	59 (20.6%)	14 (9.7%)	73 (16.9%)
Eribulin	40 (13.9%)	18 (12.5%)	58 (13.5%)
Paclitaxel	25 (8.7%)	10 (6.9%)	35 (8.1%)
Cisplatin	23 (8.0%)	9 (6.3%)	32 (7.4%)
Palbociclib	18 (6.3%)	11 (7.6%)	29 (6.7%)
Cyclophosphamide	19 (6.6%)	8 (5.6%)	27 (6.3%)
Vinorelbine	18 (6.3%)	8 (5.6%)	26 (6.0%)
Olaparib	2 (0.7%)	20 (13.9%)	22 (5.1%)
Methotrexate	15 (5.2%)	3 (2.1%)	18 (4.2%)
Endocrine therapy	41 (14.3%)	22 (15.3%)	63 (14.6%)
Fulvestrant	16 (5.6%)	12 (8.3%)	28 (6.5%)
Letrozole	18 (6.3%)	6 (4.2%)	24 (5.6%)

Poststudy antineoplastic therapies received by ≥5% of patients in either treatment group. For all percentages, the denominator was the number of patients in the ITT population. Therapeutic class was based on the WHO Drug Dictionary. Patients were counted only once at each level of summarization (overall, drug class, and generic name).

ORR subgroup analysis

Table 48: ORR of Unconfirmed CR/PR Based on Investigator Assessment – Stratified Subgroup Analysis (ITT with Measurable Disease Population)

	Talazoparib (N=219)	Overall PCT
Objective response and rate[a], n (%)	137 (62.6)	31 (27.2)
95% CI[b]	(55.78, 68.99)	(19.28, 36.33)
Odds ratio (95% CI)[d]; p-value[c]	4.99 (2.93, 8.83); <0.0001	
ECOG score=0	120	64
ORR, n (%)[a]	77 (64.2)	14 (21.9)
95% CI[b]	(54.90, 72.71)	(12.51, 33.97)
Odds ratio (95% CI) [d]; p-value[c]	6.06 (3.08, 15.07); <0.0001	
ECOG score >0	98	49
ORR, n (%)[a]	60 (61.2)	17 (34.7)
95% CI[b]	(50.85, 70.90)	(21.67, 49.64)
Odds ratio (95% CI) [d]; p-value[c]	3.32 (1.47, 7.37); 0.0014	
BRCA status – BRCA 1	92	50
ORR, n (%)[a]	59 (64.1)	11 (22.0)
95% CI[b]	(53.46, 73.87)	(11.53, 35.96)
Odds ratio (95% CI) [d]; p-value[c]	7.01 (2.99, 19.54); <0.0001	

	Talazoparib (N=219)	**Overall PCT**
BRCA status – BRCA 2	114	60
ORR, n (%)[a]	71 (62.3)	18 (30.0)
95% CI[b]	(52.72, 71.19)	(18.85, 43.21)
Odds ratio (95% CI)[d]; p-value[c]	4.15 (1.90, 8.52); <0.0001	
TNBC status – Yes	102	48
ORR, n (%)[a]	63 (61.8)	6 (12.5)
95% CI[b]	(51.61, 71.21)	(4.73, 25.25)
Odds ratio (95% CI)[d]; p-value[c]	11.89 (4.54, 41.37); <0.0001	
HR+ status on most recent biopsy – Yes	117	66
ORR, n (%)[a]	74 (63.2)	25 (37.9)
95% CI[b]	(53.84, 71.97)	(26.22, 50.66)
Odds ratio (95% CI)[d]; p-value[c]	2.89 (1.43, 5.83); 0.0012	
History of CNS metastasis – Yes	38	19
ORR, n (%)[a]	24 (63.2)	3 (15.8)
95% CI[b]	(45.99, 78.19)	(3.38, 39.58)
Odds ratio (95% CI)[d]; p-value[c]	8.95 (1.86, 52.26); 0.0013	
History of CNS metastasis – No	181	95
ORR, n (%)[a]	113 (62.4)	28 (29.5)
95% CI[b]	(54.94, 69.51)	(20.56, 39.71)
Odds ratio (95% CI)[d]; p-value[c]	4.48 (2.53, 8.43); <0.0001	
Prior platinum treatment – Yes	38	25
ORR, n (%)[a]	19 (50.0)	6 (24.0)
95% CI[b]	(33.38, 66.62)	(9.36, 45.13)
Odds ratio (95% CI)[d]; p-value[c]	3.16 (0.88, 15.67); 0.0456	
Prior platinum treatment – No	181	89
ORR, n (%)[a]	118 (65.2)	25 (28.1)
95% CI[b]	(57.77, 72.11)	(19.07, 38.62)
Odds ratio (95% CI)[d]; p-value[c]	5.36 (2.89, 9.89); <0.0001	
Time from initial diagnosis to initial diagnosis of advanced disease <12 months	90	32
ORR, n (%)[a]	45 (50.0)	6 (18.8)
95% CI[b]	(39.27, 60.73)	(7.21, 36.44)
Odds ratio (95% CI)[d]; p-value[c]	4.86 (1.85, 19.71); 0.0006	
Time from initial diagnosis to initial diagnosis of advanced disease ≥12 months	129	82
ORR, n (%)[a]	92 (71.3)	25 (30.5)
95% CI[b]	(62.70, 78.93)	(20.80, 41.64)
Odds ratio (95% CI)[d]; p-value[c]	6.33 (3.19, 12.49); <0.0001	
Prior regimens of cytotoxic chemotherapy for advanced disease – 0	83	41
ORR, n (%)[a]	66 (79.5)	15 (36.6)
95% CI[b]	(69.24, 87.59)	(22.12, 53.06)
Odds ratio (95% CI)[d]; p-value[c]	6.86 (2.65, 16.81); <0.0001	
Prior regimens of cytotoxic chemotherapy for advanced disease – 1	79	40
ORR, n (%)[a]	45 (57.0)	8 (20.0)
95% CI[b]	(45.33, 68.06)	(9.05, 35.65)
Odds ratio (95% CI)[d]; p-value[c]	5.06 (1.95, 14.18); 0.0002	
Prior regimens of cytotoxic chemotherapy for advanced disease – ≥2	57	33
ORR, n (%)[a]	26 (45.6)	8 (24.2)
95% CI[b]	(32.36, 59.34)	(11.09, 42.26)

	Talazoparib (N=219)	Overall PCT
Odds ratio (95% CI)[d]; p-value[c]	2.66 (0.88, 7.80); 0.0573	
Patients treated with 4 × 0.25 mg capsules (Generation 2.0)	49	114
ORR, n (%)[a]	33 (67.3)	31 (27.2)
95% CI[b]	(52.46, 80.05)	(19.28, 36.33)
Odds ratio (95% CI)[d]; p-value[c]	7.46 (3.19, 20.29); <0.0001	
Patients treated with 1 × 1 mg capsules	169	114
ORR	61.5%	31%
95% CI[b]	(53.76, 68.91)	(19.28, 36.33)
Odds ratio	4.62 (2.62; 8.38)	

BRCA=breast cancer susceptibility gene; CI=confidence interval; CNS=central nervous system; CR=complete response; ECOG=Eastern Cooperative Oncology Group; HR+=hormone receptor positive; ORR=objective response rate; PCT=physician's choice treatment; PR=partial response; RECIST= Response Evaluation Criteria in Solid Tumors; TNBC=triple-negative breast cancer.

a. Patients with an unconfirmed best overall response of PR or CR by investigator assessment at the data cutoff date were considered responders. Percentages were calculated from the total number of patients with measurable disease at baseline.
b. Confidence intervals were calculated using exact methods.
c. Based on stratified Cochran-Mantel-Haenszel method. Stratification factors were the number of prior cytotoxic chemotherapy regimens for advanced breast cancer, triple negative status, and history of CNS metastases.
d. Odds ratio of objective response was based on a stratified procedure; a ratio greater than 1 favored treatment with talazoparib.

Summary of main study

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

Title: A Phase 3, Open-Label, Randomized, Parallel, 2-Arm, Multi-Center Study of Talazoparib (BMN 673) Versus Physician's Choice in Germline BRCA Mutation Subjects With Locally Advanced and/or Metastatic Breast Cancer, Who Have Received Prior Chemotherapy Regimens for Metastatic Disease		
Study identifier	EMBRACA, 673-301	
Design	Randomised, open label, multicentre	
	First patient in Last patient in	14 October 2013 April 2017 Study ongoing
Hypothesis	Superiority	

Treatments groups	Physician's choice treatment (PCT)		N=144 • Capecitabine 1250 mg/m2 orally twice daily (BID) on Days 1 to 14 of each 21-day cycle, 30 minutes after meal. • Eribulin mesylate 1.4 mg/m2 (equivalent to eribulin 1.23 mg/m2), 2- to 5-minute intravenous (IV) infusion on Days 1 and 8 of each 21-day cycle. • Gemcitabine 1250 mg/m2, 30-minute IV infusion on Days 1 and 8 of each 21-day cycle. • Vinorelbine 30 mg/m2, 6- to 10-minute IV infusion weekly on Days 1, 8, and 15 of each 21-day cycle. Treatment until progression or non-acceptable toxicity
	Talazoparib		N=287 Talazoparib 1 mg once daily Treatment until progression or non-acceptable toxicity
Endpoints and definitions	Primary endpoint	PFS IRF	Time from randomization until the date of radiologic progressive disease per modified RECIST 1.1, as determined by central IRF assessment, or death due to any cause, whichever occurred first.
	Secondary endpoint	OS	Time from randomization to death due to any cause (interim analyses)
	Secondary endpoint	ORR	Proportion of patients with a CR or PR as defined by the modified RECIST 1.1 in the intent-to-treat (ITT) with measurable disease population by investigator (no confirmation required)
Data cutoff date	15 September 2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Talazoparib	PCT
	Number of subject	287	144
	PFS IRF		
	PFS events	186 (65%)	83 (58%)
	PD imaging	55%	47%
	Death	10%	10%
	In follow-up for PFS	21%	5%
	Median PFS Months (95% CI)	**8.6 (7; 9)**	**5.6 (4; 7)**

	PFS inv. PFS events Median PFS Months (95% CI)	 217 (76%) 7.0(6; 8)	 102 (71%) 4.4 (3; 6)
	OS Death events Alive at cut-of Lost to follow-up **Median OS months (95% CI)** OS at 2-year	 108 (37.6%) 166 (57.8%) 13 (4.5%) **22.3 (18, 26)** 45%	 55 (38.2%) 65 (45.1%) 24 (16.7%) **19.5 (16, 22)** 37%
	ORR Measurable Disease at baseline **ORR unconfirmed (%)** CR PR Not evaluable ORR confirmed	 219 (76%) **63%** 5.5% 57% 2% 50%	 114 (79%) **27%** 0 27% 17% 18%
	PFS IRF	HR	0.54
		95% CI	(0.4; 0.7)
		P-value	p<0.0001
	PFS inv.	HR	0.54
		95% CI	(0.4; 0.7)
		P-value	p<0.0001
	OS	HR	0.76
		95% CI	(0.5; 1.1)
		P-value	P=0.11
	ORR unconfirmed	Δ	35% (25%; 46%)
		Odds ratio	5
		p-value	p<0.0001

Supportive studies

Study 673-201

Study 673-201 was a Phase 2, open-label, 2-stage, 2-cohort study of talazoparib in patients with locally advanced or metastatic breast cancer with deleterious gBRCA mutations. In July 2015, both cohorts met the criterion to proceed to Stage 2 based on investigator review of the objective responses in Stage 1 (central imaging data were not available at that time).

Further enrolment was discontinued in February 2016 to facilitate enrolment in the Phase 3 Study 673-301, as the eligibility criteria for these 2 studies became overlapping with the issuance of Study 673-301 Protocol Amendment 1 in December 2015.

A total of 84 patients were included in the ITT population (49 patients in Cohort 1 and 35 patients in Cohort 2); 83 of the 84 patients (48 patients in Cohort 1 and 35 patients in Cohort 2) were also included in the tumour-evaluable (by central IRF or investigator assessment), safety, and PK populations (1 patient in Cohort 1 was excluded because the patient did not receive study drug).

Table 49: Patient Disposition (ITT population)

	Cohort 1 (N = 49)	Cohort 2 (N = 35)	Total (N = 84)
Did not receive study drug	1	0	1
Treated	48	35	83
Ongoing	5 (10.2%)	4 (11.4%)	9 (10.7%)
Discontinued	43 (87.8%)	31 (88.6%)	74 (88.1%)
Primary reason for study drug discontinuation			
Physician decision	2 (4.1%)	2 (5.7%)	4 (4.8%)
Withdrew consent to continue treatment	1 (2.0%)	0 (0.0%)	1 (1.2%)
Disease progression	36 (73.5%)	28 (80.0%)	64 (76.2%)
Adverse event	4 (8.2%)	1 (2.9%)	5 (6.0%)
Long-term follow-up phase disposition			
Ongoing	10 (20.4%)	16 (45.7%)	26 (31.0%)
Off study	34 (69.4%)	15 (42.9%)	49 (58.3%)
Primary reason for study discontinuation			
Death	32 (65.3%)	13 (37.1%)	45 (53.6%)
Lost to follow-up	1 (2.0%)	1 (2.9%)	2 (2.4%)
Withdrawal of consent	1 (2.0%)	1 (2.9%)	2 (2.4%)

Table 50: Protocol Deviations

	Cohort 1 (N = 49)	Cohort 2 (N = 35)	Total (N = 84)
Patients with at least 1 major protocol deviation	12 (24.5%)	3 (8.6%)	15 (17.9%)
Major protocol deviation			
Eligibility and entry criteria	8 (16.3%)	2 (5.7%)	10 (11.9%)
IP compliance	4 (8.2%)	1 (2.9%)	5 (6.0%)
Study procedures criteria	1 (2.0%)	0 (0.0%)	1 (1.2%)
Efficacy assessments	1 (2.0%)	0 (0.0%)	1 (1.2%)

In Study 673-201, patient median age was 50.0 years (range: 31.0-75.0 years). The majority of patients were White (72.6%) and approximately 58.3% had ECOG PS 0 and 41.7% had ECOG PS 1. All patients had positive gBRCA status. Further information on patient disease characteristics and prior treatment for breast cancer is presented. Overall, the percentage of patients who had TNBC was 59.2% in Cohort 1 and 17.1% in Cohort 2.

In Cohort 1 and 2, 40.8% and 82.9% of patients, respectively, had hormone-receptor positive disease defined as either ER-positive disease or PR-positive disease. BRCA status results from the central assessment were

presented unless the samples were not available for central assessment, in which case the local assessment was presented.

A history of CNS metastasis was reported for 8 patients (16.3%) in Cohort 1 and for 1 patient (2.9%) in Cohort 2. The median time since the initial diagnosis of breast cancer was longer in Cohort 2 (5.0 years in Cohort 1 and 6.2 years in Cohort 2), as would be expected for the cohort with a higher incidence of hormone-receptor disease. The median time since the start date of first cytotoxic therapy for metastatic disease and the median time since the start date of first antineoplastic therapy for metastatic breast cancer were 1.9 years in Cohort 1 and 3.6 years in Cohort 2, as expected as Cohort 2 patients likely initiated therapy for metastatic disease with hormonal therapy.

All patients in Cohort 1 and all but 1 patient in Cohort 2 (97.1%) had measurable disease by investigator assessment per RECIST 1.1 at baseline. By IRF assessment, measurable disease was reported for 93.9% of patients in Cohort 1 and 91.4% of patients in Cohort 2.

Per local assessment, the majority of patients had visceral disease at baseline as assessed by the investigator (77.6% of Cohort 1 patients and 65.7% of Cohort 2 patients). The most common metastatic disease locations by investigator assessment were lymph nodes (61.2% in Cohort 1 and 57.1% in Cohort 2), bone (53.1% in Cohort 1 and 54.3% in Cohort 2), and liver (46.9% in Cohort 1 and 54.3% in Cohort 2). At baseline, 55.1% of patients in Cohort 1 and 45.8% of patients in Cohort 2 had >2 metastatic sites.

As specified in the protocol, no patients in Cohort 2 had prior treatment with a platinum agent in the metastatic setting. In Cohort 1, 87.8% and 20.4% of patients received prior carboplatin and cisplatin, respectively. Patients in Cohort 1 may have received more than 1 prior platinum treatment. In Cohort 1, the median platinum-free interval was 4.06 months (range, 0.03-49.15 months). As previously noted, the protocol-specified platinum-free interval was 2 months, and enrolment of a patient with a platinum-free interval of <2 months was considered a major protocol violation.

In Cohort 1, patients had a median of 2 cytotoxic regimens (range, 1-10) for advanced breast cancer disease. In Cohort 2, patients had a median of 4 cytotoxic regimens (range, 1-9) for advanced breast disease.

Efficacy results

In Study 673-201, the data cut-off date for all efficacy analyses was 01 September 2016. In addition, an updated analysis of overall survival was performed with a data cutoff date of 07 April 2017. The primary efficacy analysis was ORR by blinded central IRF, and the secondary efficacy endpoints included CBR24 and DOR by IRF, PFS by investigator assessment, and overall survival. Objective response required confirmation of response by imaging obtained at least 4 weeks after the initial observation.

Primary Efficacy Endpoint: ORR by IRF

ORR required confirmation of response. The analysis of the primary efficacy endpoint was based on IRF assessment of response and used the tumour-evaluable population. ORR by IRF was 20.8% (95% CI: 10.47, 34.99) in Cohort 1 and 37.1% (95% CI: 21.47, 55.08) in Cohort 2. For BOR in Cohort 1, 4.2% of patients had CR, 16.7% had PR, 37.5% had stable disease, 37.5% had progressive disease, and 4.2% had scans that were inevaluable.

In Cohort 2, no patients had BOR of confirmed CR, 37.1% had PR, 51.4% had stable disease, and 11.4% had progressive disease.

The sensitivity analysis indicated that post-baseline antineoplastic therapies had a negligible effect on the ORR by IRF assessment in either cohort or overall.

Concordance in Response Assessments Comparing the IRF and Investigator Assessments

In the evaluation of objective response, the concordance between the IRF and the investigator ("assessors") was 78.3% across both cohorts. The concordance between assessors was 81.3% in Cohort 1 and 74.3% in Cohort 2. All discordant results were reviewed by the Sponsor Medical Monitor with the IRF prior to database lock. Overall, there were 17 discordant cases (8 in Cohort 1; 9 in Cohort 2). All discordant cases were re-reviewed by IRF; no change in assessment was made.

Subgroup analyses

Among the subgroups analyzed, a few were identified where the ORR in 1 subgroup was excluded by the 95% CI of the ORR in the opposite subgroup, indicating a possible difference in ORRs. Subgroups with 2 or fewer patients are not discussed.

The following observations were made in the subgroup analyses for Cohort 1:

- A higher proportion of patients who were White had an objective response compared with those who were non-White (White: 26.3% [95% CI: 13.40, 43.10]; non-White: 0% [95% CI: 0.0, 30.85]).
- For subgroups of patients with 1-2 versus ≥ 3 prior antineoplastic chemotherapy regimens, the ORRs were 30.8% (95% CI: 14.33, 51.79) and 9.1% (95% CI: 1.12, 29.16), respectively.
- A lower proportion of patients with visceral disease had an objective response (13.5% [95% CI: 4.54, 28.77]) compared with patients without visceral disease (45.5% [95% CI: 16.75, 76.62]).
- A lower proportion of patients who received prior anthracycline, taxane, or eribulin treatment had an objective response compared with patients who did not receive those prior treatments. For patients who received prior anthracycline, the ORR was 17.5% (95% CI: 7.34, 32.78) compared with 37.5% (95% CI: 8.52, 75.51) in patients who did not; for patients who received a prior taxane, the ORR was 18.6% (95% CI: 8.39, 33.40) compared with 40.0% (95% CI: 5.27, 85.34) in patients who did not; for patients who received prior eribulin, the ORR was 10.0% (95% CI: 0.25, 44.50) compared with 23.7% (95% CI: 11.44, 40.24) in patients who did not.
- Patients who had a <6-month disease-free interval from the last dose of platinum to disease progression had an ORR of 9.4% (95% CI: 1.98, 25.02), which was lower than among patients whose disease-free interval was ≥ 6 months (46.7% [95% CI: 21.27, 73.41]). A trend was observed of increasing ORRs with increasing disease-free intervals from last dose of platinum to disease progression: 0% ORR with interval <2 months (includes 7 patients who had protocol violations), 6.7% with interval 2 to <4 months, 20.0% with interval 4 to <6 months, and 46.7% with interval ≥ 6 months.
- BRCA status or TNBC status did not have an effect on ORR in Cohort 1.

The following observations were made in the subgroup analyses for Cohort 2:

- A higher proportion of patients with TNBC had an objective response (66.7% [95% CI: 22.28, 95.67] compared with 31.0% [95% CI: 15.28, 50.83] in patients without TNBC).
- Patients in Cohort 2 who received prior treatment with a hormonal/aromatase inhibitor had a lower ORR than those who did not (31.0% [95% CI: 15.28, 50.83] vs. 66.7% [95% CI: 22.28, 95.67)].
- BRCA status did not affect ORR in Cohort 2.

Secondary Efficacy Endpoints

CBR24 by IRF was 27.1% (95% CI: 15.28, 41.85) in Cohort 1 and 45.7% (95% CI: 28.83, 63.35) in Cohort 2. The higher CBR24 in Cohort 2 follows the trend of higher ORR by IRF assessment.

DOR by IRF: Median DOR was 5.8 months (IQR: 3.8, 9.7) in Cohort 1 and 3.8 months (IQR: 2.9, 6.7) in Cohort 2.

PFS by investigator: Median PFS was 4.0 months (95% CI: 2.8, 5.4) in Cohort 1 and 5.6 months (95% CI: 5.5, 7.8) in Cohort 2. For each cohort, the median follow-up time was 13.7 months (based on reverse Kaplan-Meier estimates).

The updated overall survival analysis had a data cut-off date of 07 April 2017, which was later than that of the CSR as the data were immature at the time of the CSR analysis. As of the data cut-off date, 73.5% of patients in Cohort 1 and 62.9% in Cohort 2 had an overall survival event. The median overall survival in Cohort 1 was 12.7 months (95% CI: 9.6, 15.8) and 14.7 months (95% CI: 11.0, 24.4) in Cohort 2.

Selected Exploratory Endpoints

ORR by investigator was 22.9% (95% CI: 12.03, 37.31) in Cohort 1 and 51.4% (95% CI: 33.99, 68.62) in Cohort 2, which was higher than ORR by IRF assessment. The ORR results were demonstrated to be robust through a sensitivity analysis that evaluated the impact of postbaseline antineoplastic therapies. This analysis used response by IRF assessment and included all tumour assessments obtained before initiation of a new antineoplastic therapy. Post-baseline antineoplastic therapies had a negligible effect on ORR by IRF assessment in both cohorts and overall.

The median PFS in Cohort 1 was 4.0 months by investigator and 3.9 months by IRF assessment, and in Cohort 2, PFS was 5.6 months by both investigator and IRF assessment; this suggests agreement between the 2 methods of PFS assessment.

CBR24 by investigator was 37.5% (95% CI: 23.95, 52.65) in Cohort 1 and 65.7% (95% CI: 47.79, 80.87) in Cohort 2. The higher CBR24 in Cohort 2 follows the trend of higher ORR by IRF assessment.

Median DOR by investigator was 4.9 months (IQR: 2.8, 7.1) in Cohort 1 and 4.2 months (IQR: 3.2, 5.6) in Cohort 2.

Median PFS by IRF was 3.9 months (95% CI: 2.6, 5.6) in Cohort 1 and 5.4 months (95% CI: 4.2, 5.6) in Cohort 2.

In the ITT population as of 01 September 2016, 45 of 84 patients (53.6%) of patients had an OS event. More patients in Cohort 1 had events (65.3%) than in Cohort 2 where fewer than half of the patients had an event (37.1%). Data for patients not known to have died as of the data cutoff date were censored at the date the patient was last known to be alive or the data cutoff date, whichever was first.

In Cohort 1, the median duration of OS was 11.8 months (95% CI: 8.8, 15.0) and patients who did not have an OS event had a median follow-up time of 15.6 months. In Cohort 2, the median duration of OS was longer than Cohort 1 at 16.5 months (95% CI: 10.1, not yet reached) and patients who did not have an OS event had a median follow-up time of 17.2 months.

Study PRP-001

This completed first-in-human, single-arm, open-label Phase 1 study evaluated the safety, tolerability, PK, PD, and preliminary efficacy of talazoparib in patients with advanced tumours with DNA-repair pathway deficiencies. The primary objective was to establish the MTD of talazoparib during the dose-escalation (Part 1) phase of the study. Secondary objectives were to evaluate the safety and tolerability of talazoparib and determine the recommended dose for the dose-expansion phase (Part 2). In addition the PK, PD, and preliminary efficacy of talazoparib were investigated. Exploratory objectives included analyzing tumour and DNA-repair pathway markers in blood or tumour tissue and performing pharmacogenomic or pharmacogenetic analysis using blood, surrogate, and/or tumour tissue.

A total of 113 patients were enrolled and 110 were treated; 7 patients still on treatment were rolled into the open-label extension study (Study MDV3800-13) as of 31 January 2017.

Across Parts 1 and 2 of Study PRP-001, 20 patients with breast cancer were enrolled (8 patients in Part 1 and 12 patients in Part 2). Of these 20 patients, 14 patients (all with deleterious gBRCA mutations) received the recommended single-agent talazoparib dose of 1 mg/day and were considered evaluable patients with breast cancer (Evaluable BC Population). These 14 patients comprised the Evaluable BC Population in Study PRP-001.

Efficacy Endpoints

For the Evaluable BC Population (N=14), ORR (confirmed CR or PR) by RECIST 1.1 was 50.0% (1 CR and 6 PR). The ORR was 40.0% for patients with a deleterious gBRCA1 mutation (2 of 5 patients) and 55.6% for patients with a deleterious gBRCA2 mutation (5 of 9 patients). The ORR was 28.6% for patients with TNBC (2 of 7 patients) and 71.4% for patients with non-TNBC (5 of 7 patients). The CBR24 (confirmed CR, PR, or stable disease lasting at least 24 weeks) by RECIST 1.1 was 85.7%.

The median PFS was 8.0 months (95% CI: 6.2, 12.4); and median DOR was 7.4 months (IQR: 4.6, 14.7). The median reduction in breast tumour size was 50.7% (range: -100% to -7%).

Clinical studies in special populations

Table 51: Number of patients aged ≥ 65 years old in clinical studies (integrated safety population – talazoparib 1 mg/day)

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials			
Randomized Study 673-301 TLZ 1 mg/day (N=286)	21 (7.3%)	6 (2.1%)	0 (0.0%)
Non Controlled Trials			
Study 673-201 TLZ 1mg/day (N=83)	13 (15.7%)	1 (1.2%)	0 (0.0%)
Study PRP-001 TLZ 1mg/day (N=77)	18 (23.4%)	3 (3.9%)	1 (1.3%)
MDV3800-14 TLZ 1mg/day (N=37)	12 (32.4%)	2 (5.4%)	4 (10.8%)
Open-Label Ext.[1] MDV3800-13 TLZ 1mg/day	12 (26.1%)	4 (8.7%)	3 (6.5%)

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
(N=46)			
Subtotal Non Controlled Trials (208) [2]	*45 (21.6%)*	*8 (3.8%)*	*5 (2.4%)*
All Trials Total [2] TLZ 1mg/day (N=494)	*66 (13.4%)*	14 (2.8%)	5 (1.0%)

Source: D120 Table 128.1.2, D120 Table 128.1.3, D120 Table 128.1.4

TLZ = talazoparib

[1] Includes all patients who completed studies PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study MDV3800-13 and initiated treatment with talazoparib at 1mg/day in either the originating or extension study.
[2] Patients who started Studies PRP-001 or MDV3800-14 at Talazoparib 1 mg/day and continued in the extension study(MDV3800-13) are counted only once in total number of patients for 'All Trials' and Subtotal Non-Controlled Trials.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

As for most anti-cancer drugs with a defined target hypothesis, the exploratory studies programme was designed to identify a reasonable starting dose from a safety perspective and to show that the compound was sufficiently active in the target population to merit further studies, i.e. in tumours with deleterious BRCA mutations. This was achieved.

The main study supporting this application is study EMBRACA (673-301;C3441009), a Phase III, Open-Label, Randomized, Parallel, 2-Arm, Multi-Centre Study of Talazoparib (BMN 673) Versus Physician's Choice in Germline BRCA Mutation Subjects With Locally Advanced and/or Metastatic Breast Cancer, Who Have Received Prior Chemotherapy Regimens for Metastatic Disease.

The dose regimen for talazoparib in the EMBRACA study was chosen based on preliminary results from the Phase 1 clinical trial (PRP-001; C3441007) involving breast cancer patients, which reported good tolerability of talazoparib up to 1000 µg/day but dose-limiting thrombocytopenia at higher doses (1100 µg/day). This is considered acceptable.

The study accrual lasted approximately 3.5 years (45 months). A total of 196 study centres in 16 countries were involved but only 145 centres were able to recruit 1 or more patients during the 45 months of accrual (mean 3 patients per centre in 45 months).

A total of 995 patients were screened for the study, of which 564 patients failed screening and were not randomized into the study. Most common reasons for screen failure were absence of deleterious or suspected deleterious or pathogenic germline BRCA1 or BRCA2 mutations (64 %) and presence of active CNS metastases that did not meet protocol defined exceptions at screening (11 %).

It is noted that patients with HER2 negative breast cancer and deleterious gBRCA mutations were enrolled without actual proof that the tumour showed homologous repair deficiency (HRD).

Geographic regions were not pre-defined as stratification factor but participating centres were in North America, South America, Europe, Australia and Asia. A total of 190 patients (44.1%) were enrolled in Europe, 156 patients (36.2%) in the USA, and 85 patients (19.7%) in the Rest of World.

The inclusion and exclusion criteria are generally acceptable. According to the initial protocol (v1.0) dated 17th of July 2013 the Applicant enrolled only patients with ECOG performance score 0 or 1 but excluded patients with higher score which does not reflect the general patient population with progressive advanced or metastatic gBRCA mutated breast cancer after several lines of prior treatments. In a scientific advice the CHMP recommended the inclusion of patients with an ECOG performance score 2. After 29 months, or 2/3 of the recruitment time, the protocol was amended to include patients with ECOG PS 2 in order to better reflect the intended target population.

Based on the initial protocol (v1.0), the Applicant excluded patients that had received platinum containing chemotherapy except in case of within adjuvant or neo-adjuvant treatment. The amended protocol v2.0 broadened the inclusion to allow patients that had received platinum containing regimens for advanced or metastatic disease if more than 6 months prior to enrolment. It is noted that the CHMP agreed with the Applicant, in a scientific advice, on the patient population definition, with regard prior treatments, but advised to include platinum cytotoxic treatment as one of the control arm (physician choice treatment), which was not followed. The Applicant argued that at the time of design and initiation of the study this was not considered a regular treatment option for patients with advanced or metastatic breast cancer. Whilst the lack of a platinum containing regimen in the PCT arm is considered a deficiency in the design of the study, the chosen reference arm is nevertheless considered adequate for comparison. The proportions of patients that had received prior platinum in the advanced setting were fairly similar between the two arms (6 % in the talazoparib arm vs. 8 % in the PCT arm).

Several amendments that were made to the patient selection criteria, like i) shorten the time before prior anticancer cytotoxic treatment, radiotherapy or surgery, before study treatment initiation, ii) allowing 1st line patients, iii) softening the requirements regarding prior anthracyclines/taxanes and iv) softening requirements regarding CNS metastases, seem to have been made with the purpose to broaden the patient population and in some way reflect general practice. Overall, the protocol amendment is not considered to have impacted the integrity of the study.

The treatment dose and schedules of the PCT´s options can be considered standard and based on the marketing authorization of each individual agent and in agreement with clinical practice. According to the protocol the treating physicians were allowed to deviate from the dose and / or schedule of the comparator physician choice treatment options if based on investigational centre own guidelines or practice.

According to the study protocol the patient selection aimed at patients eligible for 2nd to 3d line of treatment for advanced or metastatic disease. Within the amendment to the protocol (v2.0) the inclusion criteria were expanded to allow 1st line treatment and up to 3 prior lines of cytotoxic chemotherapy, which would result in more late line patient population and both shorter expected PFS and overall survival. This however did not result in high proportion of patients receiving the study treatment as late line treatment.

Prior treatment with a taxane and/or anthracycline in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated was required (unless contraindicated). Although the majority of the patients (331 [76.8%]) enrolled in the study were treated with both prior anthracycline and taxane, 27 (6.3%) patients received only prior anthracycline therapy, and 61 (14.2%) patients received only prior taxane therapy. In line with the studied population the indication reflects that patients should have been previously treated with an anthracycline and/or a taxane.

Furthermore, sensitivity or resistance to prior hormonal treatment was not an eligibility criterion, however all patients considered for randomization had to be candidates to receive one of the chemotherapy agents available on the PCT arm suggesting that endocrine based therapy was not considered by the investigator as appropriate for these patients. The indication, therefore, reflects that 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.

PFS was chosen as primary endpoint which is acceptable considering cross-over to PARPi is expected in the control arm and expected survival after progression is long (median >1 year).

For PFS, based on a 2:1 randomization allocation ratio (talazoparib: PCT), a total of 288 PFS events were considered necessary to provide 90% power for a 2-sided log-rank test at a 0.05 significance level to detect a hazard ratio [HR] = 0.67. Assuming an exponential distribution of PFS, this should correspond to an increase in median PFS from 4.6 months in control arm to 6.9 months in active arm (from 20 to 30 weeks; a 50% increase in median PFS). The sample size calculations and assumptions are considered adequate.

Secondary endpoints were standard for oncology trials. ORR was not subject to IRF (RECIST 1.1).

As the study case report forms were not designed to collect response on subsequent lines of therapy, the time of the second progressive disease (PFS2) cannot be determined.

Efficacy data and additional analyses

At time of data cut-off, more patients were still ongoing within the allocated treatment, talazoparib vs PCT´s respectively (22.3 vs 4.9%).

The baseline data reflects the patient selection as defined by the inclusion and exclusion criteria in the primary protocol and the intended indication and treatment, locally advanced and/or metastatic germline mutated breast cancer. The majority of patients (98.4%) were female. The overall median age of patients was 46 years (range, 24-88), with a lower median age in the talazoparib arm (45 years) than in the PCT arm (50 years). The majority (182 [63.4%]) of patients in the talazoparib arm were <50 years of age; fewer patients (67 [46.5%]) were aged <50 years in the PCT arm. The majority of patients (69.6%) were White; 10.9% were Asian, 3.0% were Black or African American, 1.4% reported race as Other, and race was not reported for 15.1% of patients. Weight and BMI were similar across both treatment arms. Median baseline weight was 66.0 kg (range, 41.7-157.8) and median BMI was 24.9 kg/m^2 (range 17.2- 56.2). ECOG performance scores were 0, 1, or 2 for 55.0%, 42.7%, and 1.9% of the patients, respectively. The ECOG performance status scores of 1 or 2 were 44.3% and 2.1%, respectively, in the talazoparib arm compared with 39.6% and 1.4%, respectively, in the PCT arm.

Across both treatment arms, 241 patients (55.9%) had HR positive disease (54.7 vs 58.3%). BRCA mutation status was centrally assessed for 94.7% of the patients. For the remaining 23 patients (5.3%) whose samples were not available for central assessment, BRCA status was determined by local assessment. BRCA mutation status (BRCA1-positive or BRCA2-positive) was similar across both treatment arms; BRCA1 46.3 and 43.8% and BRCA2 53.7 and 56.3%. A reversed distribution of germline BRCA1 and 2 in triple negative and HR positive breast cancer was noted. gBRCA 1/2 frequencies vary with geographic area, age, and hormone receptor status. Thus, triple negative breast cancer is more likely occurring in a young woman with gBRCA1.

The median time from initial diagnosis to randomization, and the median time from initial diagnosis to advanced disease, was shorter in the talazoparib arm than in the PCT arm, or respectively 3.9 and 1.9 years for the talazoparib arm and 5.0 and 2.7 years for the PCT arm. The proportion of patients whose breast cancer

progressed to advanced disease ≤ 12 months was higher in the talazoparib arm compared with the PCT arm (37.6% and 29.2%, respectively), suggesting somewhat more aggressive disease characteristics in the talazoparib arm. There was a difference between the treatment arms with regard to measureable disease (ITT population) by independent review facility (IRF), 75.6% vs 65.3%, but the disease burden seems to have been rather similar between treatment arms with visceral disease in 69.7 and 71.5% of patients, in respectively talazoparib and PCT arms, although somewhat more patients in the talazoparib arm had ≥ 3 metastatic sites, or respectively 45.6 vs 41.7%. Patients with bone only metastatic disease were respectively 8.7 and 11.1%. The histology of the primary breast cancer was primarily ductal (87.5%) but somewhat more patients in the talazoparib arm had either lobular or ducto-lobular compared with the PCT arm, or 10.8 vs 4.9%.

Of the 241 patients with HR positive disease, 141 patients (58.5%) had received prior hormonal-based regimen for advanced breast cancer and this was similar between treatment arms. The proportion of patients that had not received any form of anti-hormonal treatment was respectively 9.6 and 16.7% for the talazoparib and PCT treatment arms. Overall, 60.8% of patients had received prior cytotoxic regimens for advanced breast cancer.

The median number of prior cytotoxic regimens for advanced breast cancer was 1 and was similar across both treatment arms. In the talazoparib and PCT arms, 38.7% and 37.5% of patients received no prior regimens for advanced or metastatic disease, 37.3% and 37.5% received 1, 19.9% and 19.4% received 2 and 4.2% and 5.6% received >= 3 prior, respectively. Sixteen percent of patients in the talazoparib arm and 20.8% of patients in the chemotherapy arm had received prior platinum treatment.

At median follow up of 11.2 months, more patients in the talazoparib arm had progressed or died compared with the PCT arm or 64.8 vs 57.6%. The difference seems to be due mainly to more patients with progressive disease at time of the cut-off or 54.7 vs 47.2%, but the number of deaths was similar 10.1 vs 10.4%.

The median duration of PFS was 8.6 months (95% CI: 7.2, 9.3) in the talazoparib arm and 5.6 months (95% CI: 4.2, 6.7) in the PCT arm. Based on stratified cox regression analysis the HR was 0.542 (95% CI: 0.413, 0.711; P < 0.0001) in favour of the talazoparib arm (Unstratified log-rank test with HR 0.587; 95% CI: 0.451, 0.764; P < 0.0001). The estimated 1y PFS rate was higher for the talazoparib arm vs PCT or 37 vs 20%.

Overall, 162 patients (37.6%) were censored from the primary analysis: 101 patients (35.2%) in the talazoparib arm and 61 patients (42.4%) in the PCT arm. The main difference seems to be due to higher number of censored patients due to ''No disease progression or death prior to start of new antineoplastic therapy'' suggesting that more patients in the PCT arm were censored based on change to other anti-neoplastic treatment, possible due to clinical progressive disease, or chemotherapy toxicity and decision to change treatment. One patient (0.3%) in the talazoparib arm and 19 patients (13.2%) in the PCT arm were censored due to no adequate post-baseline tumour assessment. The difference in the proportion of patients censored between arms, 9.8 vs 20.1%, without evident disease progression or death before start new antineoplastic treatment, is not explained.

At median follow up of 11.2 months more patients in the talazoparib arm had progressed or died, according to investigator assessment, compared with the PCT like in the IRF assessment although the difference is somewhat less or 75.6 vs 70.8%. The HR by stratified cox regression analysis was similar or 0.538 (95% CI: 0.420, 0.689; P < 0.0001).

As sensitivity analysis the PFS by investigator was assessed. The median duration of PFS, according to investigator assessment, was 7.0 months (95% CI: 5.7, 7.6) in the talazoparib arm and 4.4 months (95% CI: 2.9, 5.6) in the PCT arm (unstratified log-rank test: HR 0.558 (95% CI: 0.439, 0.710; P < 0.0001)). Interestingly the investigator assessment resulted in higher number of progression events or deaths, 75.6 vs 64.8%, and less PFS improvement, 2.6 vs 3.0 months, compared to IRF assessment but investigator

assessment is generally considered more optimistic and potentially more biased than IRF assessment in open label studies.

Potential evaluation bias between the IRF and investigator assessments with respect to either the progression status of the patient or the timing at which progression occurred were evaluated using 2 measures, the early and late discrepancy rate (EDR and LDR). The differential discordance around each measure is defined as the rate on the experimental arm minus the rate on the control arm. A negative differential discordance for the EDR and/or positive differential discordance for the LDR are suggestive of a bias in the investigator favouring the experimental arm. The overall concordance rate was 77.7% for the talazoparib arm and 80.6% for the PCT arm. The EDR between IRF and investigator was 34.0% for the talazoparib arm and 31.6% for the PCT arm, and the LDR between IRF and investigator was 38.6% for the talazoparib arm and 43.4% for the PCT arm.

Pre-specified subgroup analyses of PFS were conducted to assess the consistency of treatment effects across subgroups defined by the baseline variables listed below. The subgroup analyses used stratified log-rank tests of PFS. The median PFS was estimated using the Kaplan-Meier method and the 95% CI was calculated for each subgroup by treatment. The HR and associated 95% CI were estimated using a stratified Cox regression model and displayed in a forest plot. The sensitivity analyses are considered acceptable and supportive of the primary PFS analysis.

In the subgroup of patients who have received prior platinum, all patients that have ever received platinum compound were included, thus not only for advanced or metastatic disease. The proportion of patients that received carboplatin or cisplatin as prior anti-neoplastic treatment for advanced or metastatic disease was low in both arms, or N = 31 (19 vs 12) or 7.2% for carboplatin and N = 9 (5 vs 4) or 2.1% for cisplatin; total of 40 (9.3%) patients, reflecting the study protocol and the amendment in December 2015.

In conclusion, discrepancy rates comparing IRF with Investigator were on the high side (40%), but early and late discrepancy rates indicated no bias. Censoring rates were therefore higher based on IRF and led, as expected, to prolonged medians to event. Investigator assessment of PFS is from this perspective the preferred metric.

Overall, a rather convincing effect on PFS has been shown (HR 0.54, p<0.0001) which is considered sufficiently large to make it less likely that “missing data” would negatively impact the statistically significant treatment effect. However the magnitude of the effect could be affected. Sensitivity analyses indicating that the positive results are reasonably robust to conservative assumptions with regards to potential bias due to non-administrative censoring were provided.

There were no conspicuous findings with respect to subgroup analyses of PFS, including age (>50,<50 y.) regions, BRCA1/2, hormone receptor status, capsules 4x025 or 1x1 mg).

At the time of the IA for OS at the data cut-off time for the primary PFS analysis 15 September 2017 approximately 38% had died in both treatment arms and 62% were censored. Approximately 58% were alive in the talazoparib arm compared with 45% in the PCT arm, which represents 12.7% difference but patients lost to follow up were less in the talazoparib arm or 4.5 vs 16.7%. OS data are still immature. A positive trend in OS is observed (p=0.1 at about 40% event rates). However, missing data somewhat hampers interpretation. There is, however, no indication of a detrimental effect. The planned final analyses at about 321 deaths (about 74% of ITT population)

Approximately 77% of patients (N=333) had measurable disease and ORR by investigator assessment, without confirmation, was 62.6% in the talazoparib arm compared to 27.2% in the PCT arm, resulting in 35.4% difference in ORR, which was statistically significant with odds ratio of 4.99 (95% CI: 2.93 – 8.83; p < 0.0001).

Of interest is that 5.5% (N=12) of the patients in the talazoparib arm achieved complete response compared to 0 in the PCT arm. In the talazoparib arm only 14.6% had progressive disease as best response. Approximately 2/3 of patients with measurable disease the response assessment was confirmed, resulting in 50.2% ORR (95% CI: 43.41, 57.04) in the talazoparib arm and 18.4% (95% CI: 11.78, 26.77) in the PCT arm, or an 31.8% (95% CI: 22.1, 41.5) difference in proportions (odds ratio of 4.85; 95% CI: 2.69, 9.10; p<0.0001).

Based on subgroup analysis the ORR benefit seem to be more in patients with i) ECOG PS 0 with OR 6.06 vs 3.32 in ECOG PS 1, ii) BRCA1 with OR 7.01 vs 4.15 in BRCA2, iii) TNBC with OR 11.89 vs 2.89 in HR+ status, iv) CNS metastasis with OR 8.95 vs 4.48 when not, v) No prior platinum treatment with OR 5.36 vs 3.16 in the (few) patients that had received prior platinum treatment for breast cancer but this is not specified further based on platinum treatment for primary vs metastatic disease , vi) time from initial diagnosis > 12 months with OR 6.33 vs 4.86 in patients with shorter history of breast cancer and vii) less number of prior treatments with odds ratio 6.86, 5.06 and 2.66 in patients with respectively 0, 1 or ≥ 2 prior treatments.

With respect to ORR, more convincingly superior activity is shown in triple negative tumours (odds ratio 12) than in HR positive tumours (odds ratio 3). It is noticed that about 1/3 of the patients had received no prior cytotoxic therapy for advanced disease.

The median DOR in the talazoparib arm was significantly longer (p = 0.0005) or 5.4 months (interquartile range: 2.8, 11.2 months) vs 3.1 months (interquartile range: 2.4, 6.7 months) in the PCT arm and the responses were durable with 1-year response rate of 23% for patients in the talazoparib arm compared to 0% in the PCT arm.

The definition of time to end of first post-study therapy as the time from randomization to the end date of the first post-study antineoplastic therapy after the first documented disease progression by investigator assessment while on study drug (talazoparib or PCT) is considered acceptable.

Although more patients received post-study treatment in the PCT arm (68 % vs. 62 % in the talazoparib arm) the median time to the end of the first post-study therapy was nearly 2 months longer for the talazoparib arm vs PCT arm or 11.9 months (95% CI: 10.7, 14.1) vs 10.1 months (95% CI: 8.6, 12.4). Post study antineoplastic therapies, including platinum drugs (34.5 vs 33.3%) were similar between treatment groups, except PARP inhibitors, as expected. PARPi were used in 1 vs. 18 % of patients in respectively the talazoparib and PCT arm.

A statistically significant overall change from baseline favouring talazoparib arm compared with PCT arm was observed for the symptoms of fatigue, pain, insomnia, appetite loss, systemic side effects, breast and arm symptoms. Notwithstanding these results, the reliability of the PRO results are hampered by the open label study design, the high proportion of censoring / missing data, the lack of a SAP with type I error control and lack of compliance with HRQoL questionnaires. Therefore, HRQoL data are not considered interpretable.

A biomarker research program in blood and tumour, based on the EMBRACA study, is ongoing. The Applicant has initiated next generation-based DNA sequence analysis of tumour tissue samples collected from patients enrolled in the Phase 3 Study 673-301 (EMBRACA; C3441009). Results from this analysis will include BRCA1/2 tumour mutational status and the tumour mutational status of over 300 other genes. Additional parameters that will be analysed include Somatic Germline Zygosity (derived from a computational method for predicting somatic versus germline origin, zygosity, and subclonality for a subset of variants; Sun et al, 2018), genomic loss of heterozygosity, and tumour mutational burden. The applicant is recommended to submit the biomarker report containing the final results by 31 March 2020.

Supportive efficacy data were provided from a phase II Study 673-201 (C3441008, ABRAZO) and a phase I study PRP-001 (C3441007).

The efficacy of Talzenna in children and adolescents < 18 years of age have not been established. No data are available.

Additional expert consultation

The SAG Oncology was consulted on the following questions.

1. **Can the efficacy of talazoparib, demonstrated by selecting patients through gBRCA mutations in blood samples, be extrapolated to patients with tumours exhibiting only sBRCA mutations?**

   The majority of the SAG agreed that the validity of extrapolating the efficacy associated with PARP inhibitors observed in patients with germline BRCA mutations to patients with tumours with somatic BRCA mutations is only a hypothesis. Clinical data are lacking and extrapolating from the experience in ovarian cancer mainly based on the mechanism of action may not be appropriate in view of potential different tumour biology in terms of tumour microenvironment, immune system involvement, etc., between gBRCA- and sBRCA-associated breast cancers, and also considering that previous exposure to platinum differs in ovarian and breast cancer. Even if the BRCA-mutation is likely to be of great biological importance, the BRCA mutations per se may not be a sufficient “driver” for tumorigenesis in sBRCA-associated breast cancer. Other factors are probably involved, such as the extent of tumour heterogeneity and if somatic BRCA loss is an early or late event, TP53 abnormalities, etc. Thus, the effect of talazoparib in tumours harbouring only a somatic mutation, although an effect is biologically plausible, might be qualitatively or quantitatively different from the effect in gBRCA-associated breast cancer. In conclusion, there is uncertainty about both the treatment effect and a potentially differential side effect profile for sBRCA-associated breast cancer in comparison with gBRCA-associated disease.

   According to a minority of SAG members, however, although acknowledging the challenges expressed above, given that the effect of somatic mutation is in terms of phenotype is similar to what is seen with a germline mutation, it seems counter-intuitive that the response would be different for somatic vs. germline BRCA mutated breast cancer. Safety advantages might also be hypothesized as the drug would act more specifically on cancer cells (albeit not observed in ovarian cancer).

   The SAG agreed that further clinical studies, even just looking at response rate and duration in patients with tumours harbouring somatic mutations, are needed in order to support the hypothesis of sBRCA as a treatment predictive factor in patients with breast cancer. Observational studies (registries) might also be useful to explore this hypothesis. Studies should also investigate the incidence of MDS and AML.

   The SAG further noted that the control group of the pivotal clinical study excluded the use of a platinum-containing regimen, which is considered more efficacious than the physician’s choice monotherapies used in the pivotal trial. Thus, a smaller effect of PARP-inhibition would be expected compared to current standard treatments (although the toxicity profile is likely improved compared to platinum-containing regimen). Furthermore, the compliance in the physician’s choice arm indicated problems. Whether a PARP-inhibitor is more efficacious than platinum-containing regimens in the population of gBRCA-associated metastatic breast cancer has not been established.

Can efficacy be extrapolated from patients with gBRCA mutations to those with tumours displaying germline/somatic mutations in other genes potentially impacting HRD status?

Given the challenges expressed above regarding extrapolation to tumours harbouring somatic mutations and the less clear role for other mutations and other mechanisms causing HRD, further extrapolation is not considered justified.

2. **What methods for establishing the HRD status of breast cancers are appropriate and available?**

Currently, multiple different HRD assays have been explored. No studies of the effect of PARP-inhibitors using HRD as a treatment predictive marker has been presented. Thus, no HRD assay can be considered having clinical validity and utility for predicting PARP inhibitor sensitivity.

3. **What methods for establishing the BRCA1/2 locus-specific loss of heterozygosity (LOH) are appropriate and available? Is there an established relationship between the extent of LOH and the degree HRD in BRCA1/2 germline mutation-associated and sporadic breast tumours?**

There are methods available in a research setting, to test for BRCA1/2 locus-specific loss of heterozygosity; however, the SAG could not confirm to what extent any particular test is well-established. Furthermore, the relationship between LOH and HRD in germline mutation-associated and sporadic breast tumours is unclear, and mechanisms apart from LOH do operate in gBRCA-associated breast cancer as a mechanism for biallelic inactivation of BRCA1 and BRCA2, so the clinical utility of such tests over BRCA testing is not likely to be important in the context of treatment effect with PARP inhibition.

4. **What is the likelihood of non-HRD tumours in patients with gBRCA mutations and HER2-/hormone-receptor positive disease? Does this possibility give rise to further diagnostic considerations?**

There are no data to quantify the rate of “sporadic” cancer in germline mutation carriers, i.e. non-hereditary breast cancers occurring as a consequence of other mechanisms apart from the BRCA mutation in a germline mutation carrier. Such cancers certainly exist, but in general, this is not considered to be of such clinical importance as to warrant further diagnostic considerations.

5. **Could other genotype/phenotype features of breast tumours (e.g. molecular subtype, tumour grade, concomitant mutations, platinum/other chemotherapy sensitivity) indicate HRD, similarly to ovarian cancers?**

The SAG was not aware of any patient, tumour, or treatment characteristics that could be used as a present valid indication of HRD; further clinical data are required.

2.5.4. Conclusions on the clinical efficacy

The results indicate a clinically relevant impact on PFS as well as no detrimental effect on OS. A number of sensitivity analyses indicated that the main outcomes are reasonably robust to assumptions of informative censoring.

Furthermore, the CHMP does not consider extrapolating the efficacy associated with PARP inhibitors observed in patients with germline BRCA mutations to patients with tumours with somatic BRCA mutations acceptable due to residual uncertainties about activity.

2.6. Clinical safety

Patient exposure

The safety database with data cut-off date of 15th of September 2017 encompasses data from 11 sponsor-initiated clinical studies (7 studies completed and 4 ongoing) in which 494 patients received at least 1 dose of talazoparib 1 mg/day thus constituting the "Talazoparib 1 mg/day Population". This population includes the 286 patients from the pivotal Phase III 673-301 study (acronym EMBRACA) pertinent to the applied indication and in which talazopraib 1 mg/day was compared to one of four physician's choice treatments (N=126; PCTs; capecitabine (44 %), eribulin (40 %), gemcitabine (10 %), or vinorelbine (6 %).

Table 52: Extent of Exposure (Integrated Safety Population)

	Randomized Study 673-301		Open-Label Uncontrolled Studies Talazoparib 1 mg/day			Open-Label Extension[a]	Talazoparib 1 mg/day Population[b]
	Talazoparib N=286	PCT N=126	673-201 N=83	PRP-001 N=77	MDV3800-14 N=37	MDV3800-13 N=46	Total N=494
Duration of study drug exposure (months)[c]							
Mean (SD)	8.4 (7.01)	4.5 (3.54)	6.0 (5.13)	7.8 (11.91)	0.6 (0.17)	3.4 (2.27)	7.5 (8.10)
Median	6.1	3.9	4.7	3.5	0.7	2.7	5.4
Minimum, maximum	0.03, 36.9	0.2, 18.1	0.7, 28.3	0.2, 52.7	0.0, 0.8	0.5, 8.6	0.03, 61.1
Duration of study drug exposure (months)[c]							
<1	9 (3.1%)	9 (7.1%)	2 (2.4%)	18 (23.4%)	37 (100.0%)	6 (13.0%)	39 (7.9%)
1 to 3	43 (15.0%)	47 (37.3%)	26 (31.3%)	19 (24.7%)	0 (0.0%)	19 (41.3%)	107 (21.7%)
3 to <6	88 (30.8%)	37 (29.4%)	22 (26.5%)	13 (16.9%)	0 (0.0%)	14 (30.4%)	140 (28.3%)
6 to <12	93 (32.5%)	27 (21.4%)	24 (28.9%)	15 (19.5%)	0 (0.0%)	7 (15.2%)	134 (27.1%)
≥12	53 (18.5%)	6 (4.8%)	9 (10.8%)	12 (15.6%)	0 (0.0%)	0 (0.0%)	74 (15.0%)
Study drug exposure (days)[c]							
Mean (SD)	256.5 (213.43)	137.6 (107.68)	183.7 (156.29)	236.5 (362.49)	19.7 (5.26)	102.1 (69.11)	227.2 (246.41)
Median	186.0	119.5	143.0	106.0	22.0	83.5	165.0
Minimum, maximum	1.0, 1123.0	7.0, 550.0	21.0, 862.0	5.0, 1603.0	1.0, 25.0	16.0, 261.0	1.0, 1859.0
Actual dose intensity (mg/day)[d]							
Mean (SD)	0.9 (1.74)	–	0.8 (0.20)	0.9 (0.17)	1.0 (0.11)	1.0 (0.10)	0.9 (1.33)
Median	0.9	–	0.8	1.0	1.0	1.0	0.9
Minimum, maximum	0.3, 30.0	–	0.3, 1.0	0.1, 1.0	0.3, 1.1	0.5, 1.0	0.1, 30.0
Relative dose intensity (%)[e]							
Mean (SD)	91.7 (173.73)	–	80.1 (19.97)	89.4 (17.25)	97.7 (11.47)	92.2 (15.59)	89.8 (132.65)
Median	87.2	–	81.3	100.0	100.0	100.0	92.8
Minimum, maximum	26.2, 3000.0	–	29.8, 100.0	12.5, 103.6	31.8, 105.0	35.8, 100.0	12.5, 3000.0

Source: Appendix 6 Table 1.2

PCT=physician's choice treatment, SD=standard deviation.

a. Includes all patients who completed treatment in Studies PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study (MDV3800-13), and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study.

b. 35 patients who initiated Studies PRP-001 or MDV3800-14 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once in the total number of patients for the Talazoparib 1 mg/day Population. Excludes the PCT arm of Study 673-301.

c. Defined as (last dose date - first dose date +1) for talazoparib. For patients continuing study drug, the data cutoff date was used as the last dose date of study drug if start date of last dose record before the data cutoff date was available but stop date of this dose record was missing.

d. Defined as the cumulative dose received divided by the duration of treatment in days; only calculated for talazoparib.

e. Defined as actual dose intensity divided by planned dose intensity; only calculated for talazoparib.

Table 53: Dose Modifications Due to Adverse Events (Integrated Safety Population)

	Randomized Study 673-301		Open-Label Uncontrolled Studies Talazoparib 1 mg/day			Open-Label Extension[a]	Talazoparib 1 mg/day Population[b]
	Talazoparib N=286	PCT[h] N=55	673-201 N=83	PRP-001 N=77	MDV3800-14 N=37	MDV3800-13 N=46	Total N=494
Patients with at least 1 dose reduction due to AE	149 (52.1%)	27 (49.1%)	49 (59.0%)	20 (26.0%)	0 (0.0%)	7 (15.2%)	225 (45.5%)
Number of dose reductions due to AE[i]							
1	70 (24.5%)	12 (21.8%)	27 (32.5%)	14 (18.2%)	0 (0.0%)	5 (10.9%)	116 (23.5%)
2	58 (20.3%)	12 (21.8%)	16 (19.3%)	5 (6.5%)	0 (0.0%)	2 (4.3%)	81 (16.4%)
3	20 (7.0%)	3 (5.5%)	6 (7.2%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	27 (5.5%)
>3	1 (0.3%)[j]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Time to first dose reduction due to AE (weeks)[e]							
N	286	55	83	77	37	46	494
Median	19.3	9.3	12.1	NR	NR	NR	23.1
95% CI	(17.1, 30.9)	(6.4, NR)	(9.4, 18.0)	(32.7, NR)	(NR, NR)	(NR, NR)	(18.1, 32.7)
Patients with at least 1 dose interruption due to AE[d]	172 (60.1%)	18 (32.7%)	51 (61.4%)	2 (2.6%)	1 (2.7%)	15 (32.6%)	240 (48.6%)
Number of dose interruptions due to AE							
1	79 (27.6%)	10 (18.2%)	22 (26.5%)	2 (2.6%)	1 (2.7%)	9 (19.6%)	111 (22.5%)
2	42 (14.7%)	5 (9.1%)	20 (24.1%)	0 (0.0%)	0 (0.0%)	4 (8.7%)	67 (13.6%)
3	31 (10.8%)	2 (3.6%)	7 (8.4%)	0 (0.0%)	0 (0.0%)	2 (4.3%)	40 (8.1%)
>3	20 (7.0%)	1 (1.8%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	22 (4.5%)
Duration of each dose interruption due to AE (days)[e]							
Number of dose interruptions due to AE	348	31	92	2	1	23	466
Mean (SD)	10.7 (8.35)	8.5 (6.92)	12.1 (7.09)	4.0 (2.83)	15.0	13.7 (24.39)	11.1 (9.53)
Median	8.0	7.0	12.0	4.0	15.0	8.0	8.0
Minimum, maximum	1.0, 50.0	1.0, 28.0	1.0, 36.0	2.0, 6.0	15.0, 15.0	1.0, 121.0	1.0, 121.0
Total duration of dose interruptions due to AE for each patient (days)[f]							
N	172	18	51	2	1	15	240
Mean (SD)	21.7 (17.58)	14.7 (10.30)	21.7 (14.08)	4.0 (2.83)	15.0	20.9 (31.92)	21.6 (18.00)
Median	18.5	11.0	20.0	4.0	15.0	12.0	18.5
Minimum, maximum	1.0, 96.0	2.0, 38.0	1.0, 62.0	2.0, 6.0	15.0, 15.0	1.0, 131.0	1.0, 131.0
Patients with modified talazoparib dose due to AE[g]							
0.75 mg/day	145 (50.7%)	-	46 (55.4%)	17 (22.1%)	0 (0.0%)	7 (15.2%)	215 (43.5%)
0.50 mg/day	80 (28.0%)	-	23 (27.7%)	8 (10.4%)	0 (0.0%)	2 (4.3%)	113 (22.9%)
0.25 mg/day	22 (7.7%)	-	7 (8.4%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	30 (6.1%)

Source: Appendix 6 Table 1.3

AE=adverse event; CI=confidence interval; NR, not reached; PCT=physician's choice treatment, SD=standard deviation.

a. Includes all patients who completed treatment in Studies PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study (MDV3800-13), and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study.
b. 35 patients who initiated Studies PRP-001 or MDV3800-14 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once in the total number of patients for the Talazoparib 1 mg/day Population. Excludes the PCT arm of Study 673-301.
c. Defined as the time from the first dose date to the date of first occurrence of daily treatment by dose level <1 mg for talazoparib, or by dose level less than maximum of first actual dose or second record of actual dose for capecitabine.
d. Dose interruption is defined as the days in the treatment period at dose 0 mg of study drug.
e. Descriptive statistics were calculated using each dose interruption due to AE for all patients.
f. Descriptive statistics were calculated by adding all days in the treatment period at dose 0 mg of study drug due to AE for each patient.
g. The dose level categories are not mutually exclusive.
h. Only patients who received capecitabine in the PCT arm.
i. Counted as the number of discrete dose reductions per patient regardless of magnitude of reduction in mg/day.
j. Patient in Study 673-301 had >3 dose reductions due to AEs to a dose of 0.1 mg/day.

Adverse events

AEs were coded using the MedDRA version 20.0 and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Treatment-emergent AEs (TEAEs) were defined as any AEs that newly developed or worsened in severity following initiation of study drug. The treatment-emergent period was defined as the period of time from the date and time of the first dose of study drug through 30 days after the last dose (permanent discontinuation of study drug) or the day before initiation of a new antineoplastic therapy, whichever occurred first. All AEs of any grade, regardless of relationship to study drug are presented by decreasing frequency of preferred term.

AEs that changed CTCAE grade were reported as separate events, with the start date of the event at a new grade corresponding to the stop date of the event at the previous grade. Patients with multiple occurrences of events for a given preferred term (PT) were counted once at the worst severity for the PT. If relationship to study drug was missing from the CRF, the AE was counted as related in summary tables. AE listings showed the missing relationship as missing, if applicable.

Table 54: Summary of TEAEs (Integrated Safety Population)

	Randomized Study 673-301		Talazoparib 1 mg/day Population
	Talazoparib (N=286)	PCT (N=126)	Total (N=494)
Any TEAE	282 (98.6%)	123 (97.6%)	484 (98.0%)
Grade 3 or 4	193 (67.5%)	80 (63.5%)	326 (66.0%)
Related to study drug	254 (88.8%)	112 (88.9%)	428 (86.6%)
Associated with death	6 (2.1%)	4 (3.2%)	20 (4.0%)
Associated with death and related to study drug	1 (0.3%)	1 (0.8%)	1 (0.2%)
SAE	91 (31.8%)	37 (29.4%)	156 (31.6%)
SAE related to study drug	26 (9.1%)	11 (8.7%)	42 (8.5%)
Grade 3 or 4 related to study drug	159 (55.6%)	61 (48.4%)	260 (52.6%)
As primary reason for treatment discontinuation[a]	13 (4.5%)	7 (5.6%)	18 (3.6%)
Associated with study drug dose modification[b]	190 (66.4%)	75 (59.5%)	308 (62.3%)

Source: Module 2.7.4 SCS Appendix 6 Table 2.1, Module 2.7.4 SCS Appendix 6 Table 4.3; Study 673-301 CSR Table 14.3.1.4.1

AE=adverse event; CRF=case report form; N=number of patients; PCT=physician's choice treatment; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

a. Derived from the Treatment Discontinuation CRF.
b. Dosing interruptions or dose reductions derived from the AE CRF, Action Taken.

Table 55: TEAEs in ≥20 % of Patients in Either treatment Arm by SOC, PT and maximum Severity (Study 673-301 Safety Population)

SOC Preferred Term	Talazoparib (N=286) n (%)						Overall PCT (N=126) n (%)					
	Grade						Grade					
	Total	1	2	3	4	5	Total	1	2	3	4	5
Patients with ≥1 TEAE	282 (98.6)	-	-	-	-	-	123 (97.6)	-	-	-	-	-
Blood and Lymphatic System Disorders	185 (64.7)	10 (3.5)	27 (9.4)	134 (46.9)	14 (4.9)	0 (0.0)	54 (42.9)	8 (6.3)	9 (7.1)	22 (17.5)	15 (11.9)	0 (0.0)
Anaemia	150 (52.4)	10 (3.5)	29 (10.1)	109 (38.1)	2 (0.7)	0 (0.0)	23 (18.3)	8 (6.3)	9 (7.1)	5 (4.0)	1 (0.8)	0 (0.0)
Neutropenia	76 (26.6)	4 (1.4)	21 (7.3)	43 (15.0)	8 (2.8)	0 (0.0)	37 (29.4)	1 (0.8)	5 (4.0)	17 (13.5)	14 (11.1)	0 (0.0)
Gastrointestinal Disorders	216 (75.5)	123 (43.0)	77 (26.9)	16 (5.6)	0 (0.0)	0 (0.0)	92 (73.0)	35 (27.8)	42 (33.3)	15 (11.9)	0 (0.0)	0 (0.0)
Nausea	139 (48.6)	97 (33.9)	41 (14.3)	1 (0.3)	0 (0.0)	0 (0.0)	59 (46.8)	34 (27.0)	23 (18.3)	2 (1.6)	0 (0.0)	0 (0.0)
Vomiting	71 (24.8)	45 (15.7)	19 (6.6)	7 (2.4)	0 (0.0)	0 (0.0)	29 (23.0)	14 (11.1)	13 (10.3)	2 (1.6)	0 (0.0)	0 (0.0)
Diarrhoea	63 (22.0)	50 (17.5)	11 (3.8)	2 (0.7)	0 (0.0)	0 (0.0)	33 (26.2)	14 (11.1)	12 (9.5)	7 (5.6)	0 (0.0)	0 (0.0)
Constipation	63 (22.0)	44 (15.4)	18 (6.3)	1 (0.3)	0 (0.0)	0 (0.0)	27 (21.4)	16 (12.7)	11 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
General Disorders and Administration Site Conditions[a]	210 (73.4)	111 (38.8)	77 (26.9)	20 (7.0)	0 (0.0)	2 (0.7)	88 (69.8)	48 (38.1)	30 (23.8)	8 (6.3)	0 (0.0)	2 (1.6)
Fatigue	144 (50.3)	84 (29.4)	55 (19.2)	5 (1.7)	0 (0.0)	0 (0.0)	54 (42.9)	33 (26.2)	17 (13.5)	4 (3.2)	0 (0.0)	0 (0.0)
Metabolism and Nutrition Disorders	97 (33.9)	57 (19.9)	23 (8.0)	16 (5.6)	1 (0.3)	0 (0.0)	41 (32.5)	23 (18.3)	11 (8.7)	7 (5.6)	0 (0.0)	0 (0.0)
Decreased appetite	61 (21.3)	44 (15.4)	16 (5.6)	1 (0.3)	0 (0.0)	0 (0.0)	28 (22.2)	19 (15.1)	8 (6.3)	1 (0.8)	0 (0.0)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	158 (55.2)	83 (29.0)	60 (21.0)	14 (4.9)	1 (0.3)	0 (0.0)	63 (50.0)	34 (27.0)	25 (19.8)	4 (3.2)	0 (0.0)	0 (0.0)
Back pain	60 (21.0)	36 (12.6)	17 (5.9)	7 (2.4)	0 (0.0)	0 (0.0)	20 (15.9)	12 (9.5)	6 (4.8)	2 (1.6)	0 (0.0)	0 (0.0)
Nervous System Disorders[b]	156 (54.5)	103 (36.0)	41 (14.3)	10 (3.5)	0 (0.0)	2 (0.7)	70 (55.6)	47 (37.3)	18 (14.3)	3 (2.4)	1 (0.8)	1 (0.8)
Headache	93 (32.5)	66 (23.1)	22 (7.7)	5 (1.7)	0 (0.0)	0 (0.0)	28 (22.2)	20 (15.9)	7 (5.6)	1 (0.8)	0 (0.0)	0 (0.0)

SOC Preferred Term	Talazoparib (N=286) n (%)						Overall PCT (N=126) n (%)					
	Grade						Grade					
	Total	1	2	3	4	5	Total	1	2	3	4	5
Skin and Subcutaneous Tissue Disorders	124 (43.4)	107 (37.4)	15 (5.2)	2 (0.7)	0 (0.0)	0 (0.0)	71 (56.3)	39 (31.0)	25 (19.8)	7 (5.6)	0 (0.0)	0 (0.0)
Alopecia	72 (25.2)	65 (22.7)	7 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	35 (27.8)	25 (19.8)	10 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)
Palmar-plantar erythrodysaesthesia syndrome	4 (1.4)	3 (1.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	28 (22.2)	12 (9.5)	13 (10.3)	3 (2.4)	0 (0.0)	0 (0.0)

Source: Table 14.3.1.2.2
For all percentages, the denominator was the number of patients in each treatment group within the safety population.
Patients with multiple events for a given preferred term, system organ class, or overall were counted once only at the worst severity for the preferred term, system organ class, and overall, respectively.
MedDRA version 20.0
MedDRA=Medical Dictionary for Regulatory Activities; N=number of evaluable patients; n=number of patients in the category; PCT=physician's choice treatment; SOC=system organ class; TEAE=treatment-emergent adverse event.
a. Grade 5 TEAEs were reported as the preferred term of general physical health deterioration in both treatment arms.
b. Grade 5 TEAEs were reported as the preferred terms of cerebral haemorrhage and neurological symptom (1 patient each in the talazoparib arm), and nervous system disorder (1 patient in the PCT arm).

Table 56: TEAEs in Study 673-301 and Talazoparib 1 mg/day Population Occurring in ≥10% of Patients in the Talazoparib 1 mg/day Population (Integrated Safety Population)

Preferred Term	Randomized Study 673-301		Talazoparib 1 mg/day Population
	Talazoparib (N=286)	PCT (N=126)	Total (N=494)
Patients with ≥1 TEAE	282 (98.6%)	123 (97.6%)	484 (98.0%)
Anaemia	150 (52.4%)	23 (18.3%)	243 (49.2%)
Fatigue	144 (50.3%)	54 (42.9%)	235 (47.6%)
Nausea	139 (48.6%)	59 (46.8%)	219 (44.3%)
Headache	93 (32.5%)	28 (22.2%)	131 (26.5%)
Neutropenia	76 (26.6%)	37 (29.4%)	113 (22.9%)
Diarrhoea	63 (22.0%)	33 (26.2%)	112 (22.7%)
Alopecia	72 (25.2%)	35 (27.8%)	110 (22.3%)
Vomiting	71 (24.8%)	29 (23.0%)	110 (22.3%)
Constipation	63 (22.0%)	27 (21.4%)	102 (20.6%)
Decreased appetite	61 (21.3%)	28 (22.2%)	100 (20.2%)
Thrombocytopenia	46 (16.1%)	7 (5.6%)	97 (19.6%)
Back pain	60 (21.0%)	20 (15.9%)	93 (18.8%)
Cough	56 (19.6%)	20 (15.9%)	92 (18.6%)
Dyspnoea	50 (17.5%)	19 (15.1%)	81 (16.4%)
Arthralgia	49 (17.1%)	15 (11.9%)	80 (16.2%)
Dizziness	48 (16.8%)	13 (10.3%)	69 (14.0%)
Abdominal pain	32 (11.2%)	20 (15.9%)	64 (13.0%)
Insomnia	35 (12.2%)	10 (7.9%)	59 (11.9%)
Asthenia	42 (14.7%)	12 (9.5%)	58 (11.7%)
Platelet count decreased	35 (12.2%)	3 (2.4%)	58 (11.7%)
Pain in extremity	40 (14.0%)	14 (11.1%)	56 (11.3%)
Upper respiratory tract infection	37 (12.9%)	13 (10.3%)	55 (11.1%)
Viral upper respiratory tract infection	30 (10.5%)	8 (6.3%)	51 (10.3%)

Source: Module 2.7.4 SCS Appendix 6 Table 2.3
N=number of patients; PCT=physician's choice treatment; TEAE=treatment-emergent adverse event.

Table 57: TEAEs of Grade 3 or 4 Severity in Study 673-301 and Talazoparib 1 mg/day Population Occurring in ≥1% of Patients in the Talazoparib 1 mg/day Population by Preferred Term (Integrated Safety Population)

Preferred Term	Randomized Study 673-301		Talazoparib 1 mg/day Population
	Talazoparib (N=286)	PCT (N=126)	Total (N=494)
Patients with ≥1 Grade 3 or 4 TEAE	193 (67.5%)	80 (63.5%)	326 (66.0%)
Anaemia	111 (38.8%)	6 (4.8%)	172 (34.8%)
Neutropenia	51 (17.8%)	31 (24.6%)	71 (14.4%)
Thrombocytopenia	23 (8.0%)	2 (1.6%)	55 (11.1%)
Platelet count decreased	19 (6.6%)	0 (0.0%)	28 (5.7%)
Neutrophil count decreased	12 (4.2%)	13 (10.3%)	17 (3.4%)
Dyspnoea	7 (2.4%)	3 (2.4%)	15 (3.0%)
Fatigue	5 (1.7%)	4 (3.2%)	13 (2.6%)
Leukopenia	9 (3.1%)	7 (5.6%)	13 (2.6%)
White blood cell count decreased	10 (3.5%)	4 (3.2%)	12 (2.4%)
Pleural effusion	5 (1.7%)	5 (4.0%)	11 (2.2%)
Hyponatraemia	4 (1.4%)	2 (1.6%)	9 (1.8%)
Lymphocyte count decreased	5 (1.7%)	0 (0.0%)	8 (1.6%)
Back pain	7 (2.4%)	2 (1.6%)	7 (1.4%)
Pulmonary embolism	6 (2.1%)	0 (0.0%)	7 (1.4%)
Vomiting	7 (2.4%)	2 (1.6%)	7 (1.4%)
Abdominal pain	2 (0.7%)	2 (1.6%)	6 (1.2%)
Asthenia	5 (1.7%)	2 (1.6%)	6 (1.2%)
Hypokalaemia	3 (1.0%)	2 (1.6%)	6 (1.2%)
Lymphopenia	4 (1.4%)	1 (0.8%)	6 (1.2%)
Pneumonia	3 (1.0%)	2 (1.6%)	6 (1.2%)
Aspartate aminotransferase increased	3 (1.0%)	2 (1.6%)	5 (1.0%)
Headache	5 (1.7%)	1 (0.8%)	5 (1.0%)
Metastases to central nervous system	3 (1.0%)	0 (0.0%)	5 (1.0%)

Source: Module 2.7.4 SCS Appendix 6 Table 3.2
N=number of patients; PCT=physician's choice treatment; TEAE=treatment-emergent adverse event.

Adverse Drug Reactions

In the analysis of adverse drug reactions, cluster terms were used as summarized in the table below.

Table 58: Cluster Terms Used in ADR Analyses

Cluster Term	Preferred Terms Included
ABDOMINAL PAIN	Abdominal pain, Abdominal pain upper, Abdominal discomfort, Abdominal pain lower
ANEMIA	Anaemia, Haematocrit decreased, Haemoglobin decreased
FATIGUE	Fatigue, Asthenia
LEUKOPENIA	Leukopenia, White blood cell count decreased
LYMPHOPENIA	Lymphopenia, Lymphocyte count decreased
NEUTROPENIA	Neutropenia, Neutrophil count decreased
THROMBOCYTOPENIA	Thrombocytopenia, Platelet count decreased

ADR=adverse drug reaction.

ADRs were identified based on whether they were reasonably associated with talazoparib treatment. The applicant evaluated potential association by examining the reporting frequency for all-causality AEs for the talazoparib arm in comparison with the PCT arm in Study 673-301. Further, the applicant also considered the mechanism of action of talazoparib, the available nonclinical toxicology data, and the overall assessment of AEs by the investigators in determining whether AEs were reasonably associated with talazoparib treatment. As the

safety profile of talazoparib was generally similar in patients who received 1 mg/day in Studies 673-301, 673-201, PRP-001, MDV3800-14, and MDV3800-13, the applicant considered the pooling of the respective ADRs to provide the best representation of the safety of talazoparib.

The overall safety profile of Talzenna is based on pooled data from 494 patients who received talazoparib at 1 mg daily in clinical studies for solid tumours, including 286 patients from a randomised Phase 3 study with germline BRCA-mutated (gBRCAm), HER2-negative locally advanced or metastatic breast cancer and 83 patients from a nonrandomised Phase 2 study in patients with germline BRCA-mutated locally advanced or metastatic breast cancer.

The most common (≥ 25%) adverse reactions in patients receiving talazoparib in these clinical studies were fatigue (57.1%), anaemia (49.6%), nausea (44.3%), neutropenia (30.2%), thrombocytopenia (29.6%), and headache (26.5%). The most common (≥ 10%) Grade ≥ 3 adverse reactions of talazoparib were anaemia (35.2%), neutropenia (17.4%), and thrombocytopenia (16.8%).

Dose modifications (dose reductions or dose interruptions) due to any adverse reaction occurred in 62.3% of patients receiving Talzenna. The most common adverse reactions leading to dose modifications were anaemia (33.0%), neutropenia (15.8%), and thrombocytopenia (13.4%).

Permanent discontinuation due to an adverse reaction occurred in 3.6% of patients receiving Talzenna. The median duration of exposure was 5.4 months (range 0.03-61.1).

Table 3 summarises adverse reactions based on pooled dataset listed by system organ class, and frequency category. Frequency categories are defined as: very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 59: Adverse reactions based on pooled dataset from 5 studies (N=494)

System organ class Frequency Preferred term	All grades* n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders			
Very common			
Thrombocytopenia[a]	146 (29.6)	63 (12.8)	20 (4.0)
Anaemia[b]	245 (49.6)	172 (34.8)	2 (0.4)
Neutropenia[c]	149 (30.2)	77 (15.6)	9 (1.8)
Leucopenia[d]	77 (15.6)	24 (4.9)	1 (0.2)
Common			
Lymphopenia[e]	30 (6.1)	13 (2.6)	0 (0.0)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	100 (20.2)	2 (0.4)	0 (0.0)
Nervous system disorders			
Very common			
Dizziness	69 (14.0)	1 (0.2)	N/A
Headache	131 (26.5)	5 (1.0)	N/A
Common			
Dysgeusia	42 (8.5)	0 (0.0)	0 (0.0)
Gastrointestinal disorders			
Very common			
Vomiting	110 (22.3)	7 (1.4)	0 (0.0)
Diarrhoea	112 (22.7)	3 (0.6)	0 (0.0)
Nausea	219 (44.3)	4 (0.8)	N/A
Abdominal pain[f]	105 (21.3)	8 (1.6)	N/A
Common			
Stomatitis	32 (6.5)	0 (0.0)	0 (0.0)
Dyspepsia	41 (8.3)	0 (0.0)	N/A
Skin and subcutaneous tissue disorders			
Very common			
Alopecia[g]	110 (22.3)	N/A	N/A
General disorders and administration site conditions			
Very common			
Fatigue[h]	282 (57.1)	17 (3.4)	1 (0.2)

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

* There were no Grade 5 adverse drug reactions.

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

b. Includes preferred terms of anaemia, haematocrit decreased and haemoglobin decreased.

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

d. Includes preferred terms of leucopenia and white blood cell count decreased.

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

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

g. For talazoparib Grade 1 is 21% and Grade 2 is 2%.

h. Includes preferred terms of fatigue and asthenia.

Adverse Events of Special Interest

The Applicant has adjudicated hepatotoxicity and MDS/AML as adverse events of special interest which were selected following the CIOMS VI guidelines and taking into consideration the known safety data from the PARP inhibitor class of compounds.

Hepatotoxicity

Table 60: Hepatotoxicity-Related TEAEs Assessed by the Modified SMQ of 'Drug-Related Hepatic Disorders – Comprehensive Search', by PT (Integrated Safety Population)

	Randomized Study 673-301		Open-Label Uncontrolled Studies Talazoparib 1 mg/day			Open-Label Extension[a]	Talazoparib 1 mg/day Population[b]
PT	Talazoparib N=286	PCT N=126	673-201 N=83	PRP-001 N=77	MDV3800-14 N=37	MDV3800-13 N=46	Total N=494
Patients with at least 1 TEAE in the SMQ of 'Drug-Related Hepatic Disorders'	26 (9.1%)	25 (19.8%)	13 (15.7%)	10 (13.0%)	0 (0.0%)	4 (8.7%)	53 (10.7%)
Aspartate aminotransferase increased	12 (4.2%)	14 (11.1%)	6 (7.2%)	5 (6.5%)	0 (0.0%)	1 (2.2%)	24 (4.9%)
Alanine aminotransferase increased	8 (2.8%)	14 (11.1%)	4 (4.8%)	3 (3.9%)	0 (0.0%)	1 (2.2%)	16 (3.2%)
Blood alkaline phosphatase increased	8 (2.8%)	3 (2.4%)	3 (3.6%)	4 (5.2%)	0 (0.0%)	0 (0.0%)	15 (3.0%)
Ascites	2 (0.7%)	1 (0.8%)	2 (2.4%)	1 (1.3%)	0 (0.0%)	2 (4.3%)	7 (1.4%)
Hypoalbuminaemia	3 (1.0%)	2 (1.6%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	6 (1.2%)
Blood bilirubin increased	3 (1.0%)	2 (1.6%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	4 (0.8%)
Hepatic pain	2 (0.7%)	1 (0.8%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.8%)
Gamma-glutamyltransferase increased	1 (0.3%)	3 (2.4%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)
Hepatocellular injury	1 (0.3%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Hyperbilirubinaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.6%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Transaminases increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.6%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Bilirubin conjugated increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hepatic enzyme increased	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hepatic steatosis	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hepatitis	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Jaundice	1 (0.3%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Liver disorder	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
International normalised ratio increased	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Liver function test abnormal	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Appendix 6 Table 9.4

PCT=physician's choice treatment; PT=preferred term; SMQ=standardized MedDRA query; TEAE=treatment-emergent adverse event.

a. Includes all patients who completed treatment in Studies PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study (MDV3800-13), and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study.

b. 35 patients who initiated Studies PRP-001 or MDV3800-14 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once in the total number of patients for the Talazoparib 1 mg/day Population. Excludes the PCT arm of Study 673-301.

Hepatotoxicity-related AEs were evaluated using a modified SMQ of 'Drug-Related Hepatic Disorders – Comprehensive Search' which excluded terms within the 'Liver Neoplasms, Benign (Including Cysts and Polyps)' SMQ and 'Liver Neoplasms, Malignant and Unspecified' SMQ. Hepatotoxicity-related TEAEs were reported to a lesser extent in talazoparib exposed patients in the 673-301 study than in the control (9.1 % and 19.8 % respectively). Most commonly reported are increases of ASAT (4.2 %), ALAT (2.8 %) and ALP 2.8 %). One case of liver disorder was associated with death in the talazoparib arm of study 673-301 which was not considered related to study drug by the investigator due to progression of the disease under study.

Myelodysplastic syndrome (MDS) and Acute Myeloid Leukaemia (AML)

MDS and AML have been reported for other PARP inhibitors (<2%) including fatal outcomes (olaparib [Lynparza SmPC], rucaparib [Rubraca SmPC], niraparib [Zejula SmPC]).

MDS

Table 61: Treatment-Emergent Adverse Events of 'Myelodysplastic Syndrome SMQ [Broad]' by PT (Integrated Safety Population)

Preferred Term	-------Randomized Study------- -------673-301------- TLZ 1mg/day (N=286)	PCT (N=126)	-----Open-Label Uncontrolled Studies----- 673-201 TLZ 1mg/day (N=83)	PRP-001 TLZ 1mg/day (N=77)	MDV3800-14 TLZ 1mg/day (N=37)	Open-Label Ext.[1] MDV3800-13 TLZ 1mg/day (N=46)	All Studies Total [2] TLZ 1mg/day (N=494)
Number of patients with at least 1 TEAE of SMQ of 'MDS'	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Pancytopenia	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)

Data cutoff date for 673-301, 673-201 and MDV3800-13 was 15Sep2017. Date of last patient discontinued study for PRP-001 was 30Jan2017, and MDV3800-14 was 22Jun2017.
[1] Includes all patients who completed studies PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study MDV3800-13 and initiated treatment with talazoparib at 1mg/day in either the originating or extension study.
[2] Does not include the PCT arm of 673-301. Patients who started Studies PRP-001 or MDV3800-14 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once in total number of patients for 'All Studies'.
Patients 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 the All Studies column.
AML=acute myeloid leukemia; MDS=myelodysplastic syndrome; SMQ=Standardized MedDRA Query; TEAE=Treatment-Emergent Adverse Event; TLZ=Talazoparib. PCT=Physician's Choice Therapy.
MedDRA Version: 20.0

In the talazoparib arm of study 673-301 two events of pancytopenia were reported (whilst none in the control arm). One of them was considered related to study drug.

AML

Table 62: TEAEs of PTs Selected to Represent Possible Acute Myeloid Leukemia by PT (Integrated Safety Population)

Preferred Term	-------Randomized Study------- -------673-301------- TLZ 1mg/day (N=286)	PCT (N=126)	-----Open-Label Uncontrolled Studies----- 673-201 TLZ 1mg/day (N=83)	PRP-001 TLZ 1mg/day (N=77)	MDV3800-14 TLZ 1mg/day (N=37)	Open-Label Ext.[1] MDV3800-13 TLZ 1mg/day (N=46)	All Studies Total [2] TLZ 1mg/day (N=494)
Number of patients with at least 1 TEAE of 'AML'	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acute Promyelocytic Leukaemia	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Data cutoff date for 673-301, 673-201 and MDV3800-13 was 15Sep2017. Date of last patient discontinued study for PRP-001 was 30Jan2017, and MDV3800-14 was 22Jun2017.
[1] Includes all patients who completed studies PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study MDV3800-13 and initiated treatment with talazoparib at 1mg/day in either the originating or extension study.
[2] Does not include the PCT arm of 673-301. Patients who started Studies PRP-001 or MDV3800-14 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once in total number of patients for 'All Studies'.
Patients 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 the All Studies column.
TEAE=Treatment-Emergent Adverse Event. TLZ=Talazoparib. PCT=Physician's Choice Therapy.
MedDRA Version: 20.0

PFIZER CONFIDENTIAL Source: yerubu /Volumes/data/usrfiles/programming/mdv3800/iss/tlfscs/prod/programs/tlf/t_aept.sas 08FEB18:13:49 Output File: t_09_03_aept_aml.rtf

No reports of cases identified as AML were reported in the `Talazoparib 1 mg/day Population´.

Other Significant AEs by Organ System or Syndrome

Myelosuppression

Table 63: TEAEs of Myelosuppression by PT in the 673-301 study (safety population)

Preferred Term	Talazoparib (N=286) n (%)	Overall PCT (N=126) n (%)
Patients with ≥1 TEAE of 'cytopenia' (SMQ)	195 (68.2)	63 (50.0)
Anaemia	150 (52.4)	23 (18.3)
Neutropenia	76 (26.6)	37 (29.4)
Thrombocytopenia	46 (16.1)	7 (5.6)
Platelet count decreased	35 (12.2)	3 (2.4)
Neutrophil count decreased	28 (9.8)	18 (14.3)
White blood cell count decreased	27 (9.4)	5 (4.0)
Leukopenia	23 (8.0)	12 (9.5)
Lymphocyte count decreased	12 (4.2)	2 (1.6)
Lymphopenia	12 (4.2)	2 (1.6)
Haematocrit decreased	5 (1.7)	1 (0.8)
Red blood cell count decreased	4 (1.4)	1 (0.8)
Haemoglobin decreased	3 (1.0)	0 (0.0)
Pancytopenia	2 (0.7)	0 (0.0)
Febrile neutropenia	1 (0.3)	1 (0.8)
Monocyte count decreased	0 (0.0)	1 (0.8)

Source: Table 14.3.2.5.2
For all percentages, the denominator was the number of patients in each treatment group within the safety population.
Patients with multiple events for a preferred term were counted once only for each preferred term.
Events ere sorted by decreasing frequency of preferred term in the talazoparib arm.
MedDRA Version: 20.0
MedDRA=Medical Dictionary for Regulatory Activities; N=number of evaluable patients; n=number of patients in the category; PCT=physician's choice treatment; SMQ=standardized MedDRA query; TEAE=treatment-emergent adverse event.

Whilst most chemotherapy are expected to have a (more or less) negative impact on the bone marrow, it is noted that in the 673-301 study anaemia of all grades appeared at a higher incidence with talazoparib as compared to the control arm (52.4 % and 18.3 % respectively) as did thrombocytopenia (26.9 % and 7.1 % in the respective arms [frequencies based on the composite of PTs for selected cluster terms]). Neutropenia was slightly less common in the talazoparib arm (34.6 %) as compared to the control arm (42.9 %). There was one case of febrile neutropenia reported in each treatment arm but no cases of neutropenic sepsis.

Myelosuppression-related AEs associated with permanent discontinuations of talazoparib in study 673-301 were anaemia (0.7%), neutropenia (0.3%), and thrombocytopenia (0.3%). Corresponding proportions in regard to dose modifications were anaemia (38.1%), neutropenia (19.2%), thrombocytopenia (10.5%), decreased platelet count (6.6%), decreased neutrophil count (4.5%), decreased white blood cell count (4.2%), and febrile neutropenia (0.3%).

A total of 25 patients (8.7 %) in the talazoparib arm required growth factor support (G-CSF, mainly filgrastim) compared to 22 patients (17.5 %) in the control arm. In the talazoparib arm, about 3 % required a platelet transfusion and 38 % RBC transfusions with a median number of two RBC transfusions per patient. In the PCT arm no patients required any platelet transfusions whilst 5.6 % required a RBC transfusion with a median of one per patient.

In total about 10 % received EPO in the talazoparib group as compared to 1.6 % in the PCT group (2 patients in the eribulin treatment group).

The incidence of TEAEs of anaemia (all grades and Grade 3/4) peak at about 3-4 months after start of study drug and thereafter subsides. In terms of incidence of TEAEs for anaemia after dose reductions (all grades and Grade

3/4) it is clear that dose reductions are indicated up to and during the first 2 months. The same pattern is evident also in relation to thrombocytopenia and neutropenia.

Pneumonitis

One case of pneumonitis (0.2%) occurred in the 673-201 study. The event was a Grade 1 pneumonitis and considered treatment related. Concurrently, the patient had a dosing interruption of talazoparib due to Grade 3 pneumonia, which was not considered related to study drug by the investigator. Study drug was resumed after resolution of pneumonia, and the AE of pneumonitis resolved by Day 85.

Second Primary Malignancies

Based on non-clinical studies, talazoparib is considered clastogenic indicating the potential for genotoxicity in humans. In the `Talazoparib 1 mg/day Population´, seven AEs of second primary malignancies were reported for six patients (squamous cell carcinoma of skin [2 patients], and basal cell carcinoma, glioblastoma multiforme, intraductal proliferative breast lesion, neoplasm skin, and ovarian neoplasm [1 patient each]. Of these events, three were reported in three patients in the talazoparib arm of Study 673-301.

Serious adverse event/deaths/other significant events

Serious adverse events (SAE)

Table 64: SAEs in Study 673-301 and Talazoparib 1 mg/day Population Occurring in ≥1% of patients in the Talazoparib 1 mg/day Population by Preferred Term (Integrated Safety Population)

Preferred Term	Randomized Study 673-301		Talazoparib 1 mg/day Population
	Talazoparib (N=286)	PCT (N=126)	Total (N=494)
Patients with ≥1 serious TEAE	91 (31.8%)	37 (29.4%)	156 (31.6%)
Anaemia	17 (5.9%)	0 (0.0%)	24 (4.9%)
Dyspnoea	4 (1.4%)	0 (0.0%)	11 (2.2%)
Pleural effusion	4 (1.4%)	7 (5.6%)	11 (2.2%)
Platelet count decreased	4 (1.4%)	0 (0.0%)	7 (1.4%)
Pneumonia	3 (1.0%)	2 (1.6%)	7 (1.4%)
Pyrexia	7 (2.4%)	2 (1.6%)	7 (1.4%)
Thrombocytopenia	2 (0.7%)	0 (0.0%)	6 (1.2%)
Vomiting	5 (1.7%)	2 (1.6%)	6 (1.2%)
Abdominal pain	3 (1.0%)	2 (1.6%)	5 (1.0%)
Back pain	5 (1.7%)	1 (0.8%)	5 (1.0%)
Metastases to central nervous system	3 (1.0%)	0 (0.0%)	5 (1.0%)

Source: Module 2.7.4 SCS Appendix 6 Table 7.2
N=number of patients; PCT=physician's choice treatment; TEAE=treatment-emergent adverse event.

Similar overall proportions in terms of SAE reports are recognised between the two treatment-arms (31.8 % and 29.4 %, talazoparib and PCT respectively). For the talazoparib treated patients in the pivotal study, anaemia is the most common cause for SAE (5.9 %) with pyrexia second (2.4 %).

Deaths

Table 65: Summary of Deaths (Study 673-301 Safety Population)

Death Summary	Talazoparib (N=286) n (%)	Overall PCT (N=126) n (%)
Total number of deaths	108 (37.8)	53 (42.1)
Cause of death[a]		
Disease progression	96 (88.9)	51 (96.2)
Other	12 (11.1)	2 (3.8)
Attempted suicide with medicine[b]	1 (0.9)	0 (0.0)
Cardiac and respiratory arrest	1 (0.9)	0 (0.0)
Cardiac decompensation on pulmonary infection	1 (0.9)	0 (0.0)
Cardiopulmonary failure	1 (0.9)	0 (0.0)
Cardiorespiratory arrest due to a pulmonary infection	1 (0.9)	0 (0.0)
Cerebral hemorrhage	1 (0.9)	0 (0.0)
Cerebral ischemia	1 (0.9)	0 (0.0)
Circulatory-respiratory failure	1 (0.9)	0 (0.0)
Death occurred due to sepsis	0 (0.0)	1 (1.9)
Suspected VOD of the liver[c]	1 (0.9)	0 (0.0)
Unknown	0 (0.0)	1 (1.9)
Unknown cause of death	1 (0.9)	0 (0.0)
Unknown per obituary	1 (0.9)	0 (0.0)
Worsening neurological symptoms	1 (0.9)	0 (0.0)
Deaths within 30 days after the first dose of study drug	0 (0.0)	1 (1.9)
Cause of death		
Other	0 (0.0)	1 (1.9)
Death occurred due to sepsis	0 (0.0)	1 (1.9)
Deaths within 30 days after the last dose of study drug	10 (9.3)	5 (9.4)
Cause of death		
Disease progression	7 (6.5)	4 (7.5)
Other	3 (2.8)	1 (1.9)
Cerebral hemorrhage	1 (0.9)	0 (0.0)
Death occurred due to sepsis	0 (0.0)	1 (1.9)
Suspected VOD of the liver[c]	1 (0.9)	0 (0.0)
Worsening neurological symptoms	1 (0.9)	0 (0.0)

Source: Table 14.3.2.1.3

For all percentages, the denominator was the number of patients in each treatment group within the safety population.

eCRF=electronic case report form; N=number of evaluable patients; n=number of patients in the category; PCT=physician's choice treatment; TBL=total bilirubin; VOD=veno-occlusive liver disease.

a. From the Cause of Death eCRF

b. The patient had discontinued talazoparib 57 days prior to death.

c. Standard VOD diagnostic criteria (such as hepatomegaly and right upper quadrant pain) were not observed; the presenting laboratory data included only elevated liver transaminases (not TBL).

A total of 37.8 % died in the talazoparib arm in the 673-301 study as compared to 42.1 % in the control arm, the majority due to disease progression. The proportion of deaths occurring within 30 days after last dose of study drug was similar between treatment arms (9.3 % and 9.4 % respectively) with the majority due to progressive disease (6.5 % and 7.5 % respectively).

Laboratory findings

Haematology

In the 673-301 study, the haematology laboratory abnormalities that increased ≥2 toxicity grades from baseline were low neutrophils (50.3 %), low leukocytes (47.2 %), low haemoglobin (44.4 %), low platelets (24.8 %), and low lymphocytes (25.9 %). In terms of severity, the overall majority of reports were of Grade 1 or 2 but for decreased haemoglobin it amounted to 38.8 % Grade 3 or 4 reports with 14.7 % for platelets and 21.0 % for neutrophils.

Chemistry

The proportion of ≥ 2 toxicity grade increases from base-line regarding chemistry laboratory abnormalities was fairly low. In talazoparib treated patients in the 673-301 study the proportions were: ALT 2.1 %, AST 1.7 %, ALP 2.4 %, TBL 2.1 % and creatinine 0.3 %. THe overall the majority of events in talazoparib treated patients in the pivotal study were of Grade 1 or 2 with a further low proportion of Grade 3/ 4 events (ALT 1.0 %, AST 1.7 %, ALP 2.1, TBL 1.4 % and creatinine none).

Liver Test Abnormalities

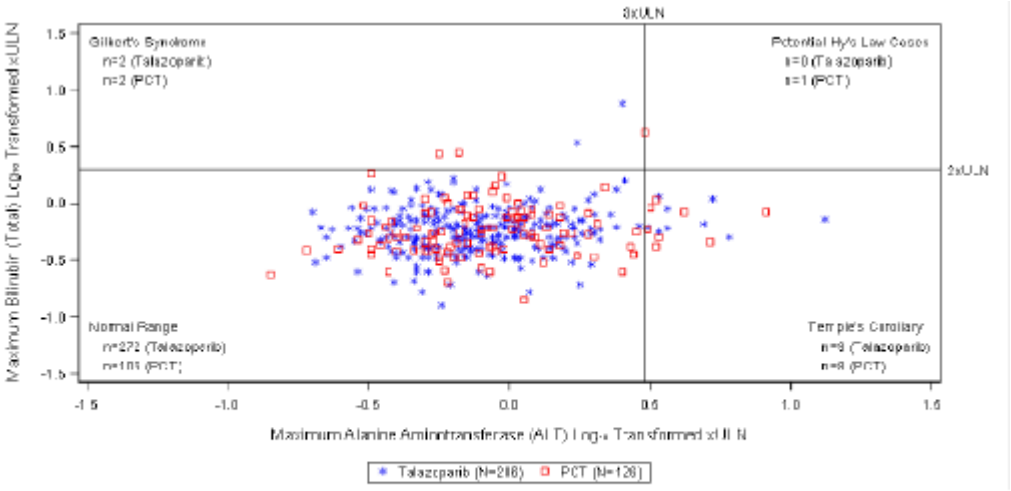
Table 66: Summary of Liver Laboratory Tests (Integrated Safety Population)

	Randomized Study 673-301		Open-Label Uncontrolled Studies Talazoparib 1 mg/day			Open-Label Extension[a]	Talazoparib 1 mg/day Population[b]
Selected Liver Laboratory Test	Talazoparib N=286	PCT N=126	673-201 N=83	PRP-001 N=77	MDV3800-14 N=37	MDV3800-13 N=46	Total N=494
Baseline							
No. patients with baseline result[c]	286 (100.0%)	126 (100.0%)	83 (100.0%)	77 (100.0%)	37 (100.0%)	46 (100.0%)	494 (100.0%)
ALT or AST ≥3 × ULN	9 (3.1%)	5 (4.0%)	4 (4.8%)	1 (1.3%)	0 (0.0%)	2 (4.3%)	14 (2.8%)
TBL >2 × ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Postbaseline							
No. patients with postbaseline result[d]	283 (99.0%)	118 (93.7%)	83 (100.0%)	76 (98.7%)	36 (97.3%)	44 (95.7%)	488 (98.8%)
ALT or AST ≥3 × ULN	17 (5.9%)	13 (10.3%)	13 (15.7%)	7 (9.1%)	1 (2.7%)	2 (4.3%)	39 (7.9%)
ALT or AST >5 × ULN	6 (2.1%)	5 (4.0%)	4 (4.8%)	3 (3.9%)	0 (0.0%)	0 (0.0%)	13 (2.6%)
ALT or AST >10 × ULN	3 (1.0%)	0 (0.0%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
ALT or AST >20 × ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TBL >2 × ULN	5 (1.7%)	3 (2.4%)	1 (1.2%)	6 (7.8%)	0 (0.0%)	1 (2.2%)	13 (2.6%)
ALT or AST ≥3 × ULN and TBL >2 × ULN (any visit date)	5 (1.7%)	1 (0.8%)	1 (1.2%)	4 (5.2%)	0 (0.0%)	0 (0.0%)	10 (2.0%)
ALT or AST ≥3 × ULN and TBL >2 × ULN (concurrent or within 14 days)	5 (1.7%)	1 (0.8%)	1 (1.2%)	4 (5.2%)	0 (0.0%)	0 (0.0%)	10 (2.0%)
ALT or AST ≥3 × ULN and TBL >2 × ULN and ALP <2 × ULN (any visit date)	4 (1.4%)	0 (0.0%)	1 (1.2%)	3 (3.9%)	0 (0.0%)	0 (0.0%)	8 (1.6%)
ALT or AST ≥3 × ULN and TBL >2 × ULN and ALP <2 × ULN (concurrent or within 14 days)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.9%)	0 (0.0%)	0 (0.0%)	3 (0.6%)

Source: Appendix 6 Table 10.7

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; No.=number; PCT=physician's choice treatment; TBL=total bilirubin; TEAE=treatment-emergent adverse event; ULN=upper limit of normal.

a. Includes all patients who completed treatment in Studies PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study (MDV3800-13), and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study.
b. 35 patients who initiated Studies PRP-001 or MDV3800-14 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once in the total number of patients for the Talazoparib 1 mg/day Population. Excludes the PCT arm of Study 673-301.
c. Patients with baseline result of any parameter of ALT, AST, TBL, or ALP.
d. Patients with postbaseline result of any parameter of ALT, AST, TBL, or ALP.



Source: Figure 14.3.4.7.2
ALT=alanine aminotransferase; eDISH=evaluation of Drug-Induced Serious Hepatotoxicity; n=number of patients in the category; PCT=physician's choice treatment; ULN=upper limit of normal.

Figure 13: Maximum TBL vs Maximum ALT (Talazoparib 1 mg/day Population)

Based on the liver test findings, no patients met the criteria for Hy's law.

Electrocardiograms

Local investigators assessed the clinical relevance of locally obtained ECG findings in most studies. Limited ECG assessments were obtained in Studies 673-301 and 673-201. In the Phase I, FIH, dose escalation study PRP-001 study, the effect of talazoparib on cardiac repolarization was investigated. There were no clear indications that talazoparib negatively affects cardiac repolarization (see non clinical and pharmacology sections).

Safety in special populations

Gender

Safety data were analysed for males (10.3%) and females (89.7%) in the Talazoparib 1 mg/day population (N=494). Of AEs reported for ≥10% of patients in the Talazoparib 1 mg/day Population, AEs reported at a ≥10% higher incidence in females compared with males were anemia, nausea, headache, neutropenia, diarrhea, alopecia, vomiting, back pain, and pain in extremity. In males compared with females, no events were reported at a ≥10% higher incidence.

Age

Safety data by age was dichotomised according to patients <65 years and ≥ 65 years. In the 673-301 study only 27 patients were 65 or older in the talazoparib arm and eight in the control arm.

MedDRA Terms	Age <65 N=409	Age 65-74 N=66	Age 75-84 N=14	Age 85+ N=5
Total AEs (%)	403 (98.5)	63 (95.5)	14 (100)	4 (80)
Serious AEs – Total (%)	126 (30.8)	22 (33.3)	7 (50)	1 (20)
- Fatal (%)	15 (3.7)	3 (4.5)	2 (14.3)	0
- Hospitalization/prolong existing hospitalization	116 (28.4)	18 (27.3)	7 (50)	1 (20)
- Life-threatening	8 (2.0)	2 (3.0)	0	0
- Disability/incapacity	1 (0.2)	1 (1.5)	0	0
- Other (medically significant)	13 (3.2)	5 (7.6)	1 (7.1)	0
AE leading to drop-out	15 (3.7)	2 (3.0)	0	1 (20)
Psychiatric disorders	101 (24.7)	11 (16.7)	2 (14.3)	1 (20)
Nervous system disorders	205 (50.1)	30 (45.5)	8 (57.1)	0
Accidents and injuries	46 (11.2)	13 (19.7)	1 (7.1)	0
Cardiac disorders	32 (7.8)	5 (7.6)	0	0
Vascular disorders	67 (16.4)	9 (13.6)	0	0
Cerebrovascular disorders	2 (0.5)	2 (3.0)	0	0
Infections and infestations	194 (47.4)	24 (36.4)	6 (42.9)	1 (20)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	74 (18.1)	14 (21.2)	3 (21.4)	0
<other AE appearing more frequently in older patients>	N/A	N/A	N/A	N/A

Race

Because of the imbalances of race among patients in Study 673-301 (69.4% White, 10.7% Asian, 2.9% Black or African American, and 1.5% other), coupled with the high proportion of patients whose race was unknown (15.5%), the impact of race on the safety of talazoparib treatment could not be adequately assessed in either Study 673-301 or the Talazoparib 1 mg/day Population.

Body mass Index (BMI)

Safety data by BMI were analysed for the following three groups of patients in the Talazoparib 1 mg/day Population based on BMI: ≤18 kg/m2 (N=10; 2.0%), >18-30 kg/m2 (N=383; 77.7%), and >30 kg/m2 (N=100; 20.3%). In the Talazoparib 1 mg/day Population, AEs reported for ≥20% of patients with BMI >18-30 kg/m2 were anemia, fatigue, nausea, headache, neutropenia, diarrhea, alopecia, vomiting, constipation, decreased appetite, and thrombocytopenia. AEs reported for ≥20% of patients with BMI >30 kg/m2 were similar, but constipation and thrombocytopenia were reported for <20% of patients and cough and dyspnea were also reported for ≥20% of patients. As only 2.0% of patients in the Talazoparib 1 mg/day Population had a BMI ≤18 kg/m2, no comparison with this BMI group was possible.

Renal impairment

Mild renal impairment was defined as a creatinine clearance of 60-89 mL/min (N=157 [32 % of the Talazoparib 1 mg/day population]), moderate renal impairment 30-59 mL/min (N=36 [7 %]) and severe impairment ≤29 mL/min (N=1).

In the Talazoparib 1 mg/day Population, 60.7% of patients had normal renal function at study baseline, 31.8% had mild renal impairment, 7.3% had moderate renal impairment, and 0.2% (1 patient) had severe renal impairment. AEs reported for ⩾20% of patients in the normal renal function group were anemia, fatigue, nausea, headache, neutropenia, diarrhea, vomiting, and constipation. AEs reported for ⩾20% of patients in the mild renal impairment group were similar but additionally included decreased appetite, while headache, vomiting, and constipation were reported for <20% of patients. AEs reported for ⩾20% of patients in the moderate renal impairment group were also similar to those reported for ⩾20% of patients with normal renal function, but with the addition of thrombocytopenia and decreased platelet count, while headache and diarrhea were reported for <20% of patients. Only 1 patient in the Talazoparib 1 mg/day Population had severe renal impairment so comparisons with this group were not possible.

Hepatic impairment

Hepatic impairment was defined as TBL or AST > ULN at baseline. Patients in the `Talazoparib 1 mg/day´ population had baseline TBL up to 1.5× ULN (up to 3× ULN for patients with Gilbert's syndrome) and ALT or AST up to 2.5× ULN (or up to 5× ULN if due to liver metastases). Of this population (N=494), 127 patients (25.7 %) had hepatic impairment at study baseline. AEs reported for ⩾20% of patients in the normal hepatic function group were anemia, fatigue, nausea, headache, neutropenia, diarrhea, alopecia, vomiting, constipation, and decreased appetite. AEs reported for ⩾20% of patients in the hepatic impairment group were similar, but alopecia and decreased appetite were reported for <20% of patients, and thrombocytopenia was also reported for ⩾20% of patients.

Thrombocytopenia was the only AE reported at a ⩾10% higher incidence in patients with hepatic impairment than patients with normal hepatic function in the talazoparib arm of Study 673-301 (27.8% in the hepatic impairment group vs 12.1% in normal hepatic function group). No AEs were reported at a ⩾10% higher incidence in the Talazoparib 1 mg/day Population; the biggest difference between hepatic function groups was for thrombocytopenia (26.8% in the hepatic impairment group vs 17.2% in the normal hepatic function group), which was also reported at a higher incidence in patients with hepatic impairment in the PCT arm of Study 673-301 (11.1% vs 3.3%).

Discontinuation due to adverse events

Table 67: TEAEs That Were the Primary Reason for Permanent Study Drug Discontinuation, by Descending Frequency of PT (Integrated Safety Population)

PT	Randomized Study 673-301		Open-Label Uncontrolled Studies Talazoparib 1 mg/day			Open-Label Extension[a]	Talazoparib 1 mg/day Population[b]
	Talazoparib N=286	PCT N=126	673-201 N=83	PRP-001 N=77	MDV3800-14 N=37	MDV3800-13 N=46	Total N=494
Patients with at least 1 TEAE as primary reason for treatment discontinuation	13 (4.5%)	7 (5.6%)	3 (3.6%)	0 (0.0%)	0 (0.0%)	2 (4.3%)	18 (3.6%)
Anaemia	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	3 (0.6%)
Accidental overdose	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Aspartate aminotransferase increased	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Breast cancer metastatic	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Cerebral haemorrhage	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Dyspnoea	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Glioblastoma multiforme	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Headache	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Metastases to meninges	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Muscular weakness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	1 (0.2%)
Neutropenia	1 (0.3%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Obstructive airways disorder	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Thrombocytopenia	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Transient ischaemic attack	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Vomiting	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

Source: Appendix 6 Table 5.2

PCT=physician's choice treatment; PT=preferred term; TEAE=treatment-emergent adverse event.

a. Includes all patients who completed treatment in Studies PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, subsequently enrolled in the open-label extension study (MDV3800-13), and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study.

b. 35 patients who initiated Studies PRP-001 or MDV3800-14 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) are counted only once in the total number of patients for the Talazoparib 1 mg/day Population. Excludes the PCT arm of Study 673-301.

The proportion of permanent discontinuations of talazoparib due to TEAEs is overall reassuringly low (4.5 % in study 673-301 and 3.6 % in the overall `Talazoparib 1 mg/day´ population). In the 673-301 study, anaemia was the reason for discontinuation of talazoparib in two patients. Otherwise there were isolated miscellaneous reasons for permanent discontinuation.

Safety update

Updated safety data were submitted for the 1 mg dataset (494 patients in the initial submission and 502 patients in the updated data set; all 8 additional patients were in the open-label extension Study MDV3800-13 [Study C3441010]). The overall data cutoff date for the updated safety review was 31 January 2018. Earlier data cutoff dates were used for studies with no active patients as of the safety update data cutoff date (Talazoparib NDA 90-Day Safety Update Report).

Table 68: Clinical study data cut-off dates for the safety update

Study No.	Study Phase / Descriptor	Initial Submission Data Cutoff Date[a]	Safety Update Data Cutoff Date[a]	Included in the Integrated Safety Population
673-301 (EMBRACA, C3441009)	Phase 3 open-label, randomized to talazoparib or PCT (capecitabine, eribulin, gemcitabine, vinorelbine)	15 September 2017	31 January 2018	Yes
673-201 (ABRAZO, C3441008)	Phase 2 open-label, 2-stage, 2-cohort	15 September 2017	31 January 2018	Yes
PRP-001 (C3441007)	Phase 1 open-label in advanced solid tumors	30 January 2017[b]	30 January 2017[b]	Yes[c]
MDV3800-14 (C3441005)	Cardiac study	22 June 2017	22 June 2017	Yes
MDV3800-13 (C3441010)	Open-label extension	15 September 2017	31 January 2018	Yes[d]
MDV3800-01 (C3441001)	Renal study	15 September 2017[e]	31 January 2018[e]	No
MDV3800-02 (C3441002)	Hepatic study	15 September 2017[e]	31 January 2018[e]	No
MDV3800-03 (C3441003)	ADME study	21 June 2017[e]	21 June 2017[e]	No
MDV3800-04 (C3441004)	DDI study	15 September 2017[e]	31 January 2018[e]	No
PRP-002 (C3441022)	Phase 1 open-label in advanced hematological malignancies	22 May 2014[e]	22 May 2014[e]	No
673-103 (C3441023)	Food effect study in healthy volunteers	23 April 2013	23 April 2013	No

ADME=absorption, distribution, metabolism, and excretion; CSR=clinical study report; DDI=drug-drug interaction; NA=not applicable; No.=number; PCT=physician's choice treatment; SCS=Summary of Clinical Safety.

a. Either the submission cutoff date or the final date of data collection for the final CSR.
b. Last patient discontinued the study 30 January 2017.
c. Patients treated at 1 mg/day only were included in the Integrated Safety Population.
d. Patients who initiated treatment with talazoparib 1 mg/day in either the originating or extension study were included in the Integrated Safety Population.
e. Data cutoff for patient narratives only.

Adverse Events

The most frequently reported AEs (≥ 25%) in patients treated with talazoparib 1 mg/day were anemia, fatigue, nausea, and headache, as in the initial submission. In the Talazoparib 1 mg/day Population, for myelosuppression-related AEs, Grade 3 anemia was reported for 34.9% of patients (0.5% increase from initial submission), Grade 3 neutropenia for 12.7% of patients (0.1% decrease), and Grade 3 thrombocytopenia for 8.8% of patients (0.1% decrease); Grade 4 occurrences of these myelosuppression-related AEs were reported in 0.6% of patients for anemia, 2.0% of patients for neutropenia, and 2.4% of patients for thrombocytopenia (0.2%, 0.4%, and 0.2% increases from initial submission, respectively).

Myelosuppression-related AEs were manageable through dosing interruption, dose reduction, and/or supportive care. Permanent discontinuation of talazoparib treatment associated with an AE was reported for 4.0% of patients in the Talazoparib 1 mg/day Population (increase 0.4%), including permanent discontinuations due to anemia in 0.6% of patients (% unchanged).

Deaths

In the Talazoparib 1 mg/day Population, the percentage of patients who died (including deaths that occurred both ≤ 30 days after and deaths >30 days after the last dose of study drug) increased by approximately 8% (42 patients) from the initial submission to the safety update data cutoff date (36.4% of patients [180/494] in the initial submission and 44.2% of patients [222/502] in this safety update). Deaths attributed to progressive

disease increased from 31.6% of patients (156/494) in the initial submission to 38.6% of patients (194/502) in this safety update.

Since the initial submission, 2 new deaths (one patient with Grade 5 ovarian cancer and one patient with Grade 5 failure to thrive) occurred within 30 days after the last dose of study drug (24 patients [4.9%] in the initial submission and 26 patients [5.2%] in this Safety update).

AEs of Special Interest

Hepatotoxicity

Overall, the frequency and severity of hepatotoxicity-related AEs were similar to those reported in the initial submission. In summary, based on the liver test findings and other patient data, no patients met the criteria for Hy's law.

MDS

There were no additional reports of MDS AEs since the initial submission. Two patients with AEs coded with the PT of pancytopenia were reported in the Talazoparib 1 mg/day Population, which on medical review, were considered not consistent with MDS.

AML

In patients in the Talazoparib 1 mg/day Population, no AEs that possibly represented AML were reported in the initial submission or up to the clinical database snapshot date for this safety update.

In patients who received talazoparib at doses other than 1 mg/day, an AE of Grade 4 leukemia was reported in 1 patient in the initial submission. The event was consistent with a diagnosis of AML, and a diagnosis of AML evolving from MDS was subsequently established. No additional AEs that possibly represented AML were reported since the initial submission in patients who received talazoparib at doses other than 1 mg/day. There was 1 patient in the PCT arm with a reported AE of Grade 4 AML.

Subsequent to the clinical database snapshot for this safety update, an AE of AML was reported for a patient from Study 673-301 in the Talazoparib 1 mg/day Population. This patient received prior systemic anticancer treatment that included 6 cycles of neoadjuvant cyclophosphamide, docetaxel, doxorubicin, and 6 cycles of carboplatin and paclitaxel albumin for her advanced disease. The patient also received prior radiation therapy.

The Investigator considered there was a reasonable possibility that Acute myeloid leukaemia was related to the study drug, but unrelated to concomitant drugs and clinical trial procedure. The Sponsor considered that the patient's prior systemic anticancer treatment that included 6 cycles of neoadjuvant cyclophosphamide, docetaxel, doxorubicin, and 6 cycles of carboplatin and paclitaxel albumin for her advanced disease and prior radiation therapy provide an alternative etiology for Acute myeloid leukaemia.

Myelosuppression-Related AEs

Myelosuppression-related AEs were defined by the modified SMQ of 'Haematopoietic Cytopenias' (SMQ modifications) as in the initial submission. The incidence of myelosuppression-related AEs was similar to those reported in the initial submission.

Pneumonitis

In the initial submission, Grade 1 non serious pneumonitis was reported in 1 patient in Study 673-201; no additional AEs of pneumonitis have been reported in patients at any dose since the initial submission.

Second Primary Malignancies

In the Talazoparib 1 mg/day Population, second primary malignancies were reported in 6 patients in the initial submission; no new cases were reported since the initial submission.

Post marketing experience

Talazoparib received first regulatory approval on 16 October 2018 in the United States (US) and is not currently marketed in any other countries/territories. Very limited post-marketing data is available.

2.6.1. Discussion on clinical safety

The safety database with data cut-off date 15th of September 2017 consists of data from 494 patients that received at least 1 dose of talazoparib 1 mg/day including the 286 patients from the 673-301 study (acronym EMBRACA) where talazoparib 1 mg/day was compared to one out of four physician's choices. As the control arm consisted of these four alternatives representing conventional chemotherapy, any comparisons of its composite safety profile to that of talazoparib in this open label study is not considered of any clinical relevance.

Overall, there were no clinically relevant differences identified between the findings in the 673-301 study compared to the composite talazoparib 1 mg/day population.

The 673-301 study (EMBRACA)

The mean and median duration of exposure in the 673-301 study was 8.4 months and 6.1 months respectively in the talazoparib arm as compared to 4.5 months and 3.9 months for the control arm. A total of 32.5 % and 18.5 % received talazoparib between 6 and 12 months and ≥ 12 months respectively. There was no difference between mean and median for the talazoparib actual dose intensity (0.9 mg/day) and the mean and median for relative dose intensity (%) was 91.7 % and 87.2 % respectively. From the dose intensity perspective, talazoparib appears reasonably tolerable.

The actual dose intensity of capecitabine, approximately 2000mg/m^2/day, can be considered adequate in case of palliative treatment, reflecting the most accepted starting dose of 1000mg/m^2 BID, although the protocol prescribed 1250mg/m^2 BID. Among patients who received capecitabine (n=55), 81.8% received a starting dose of between 1000 to 1250 mg/m^2 BID for 14 days out of a 21-day cycle.

Similar proportions of patients receiving either talazoparib or capecitabine, or approximately 50% of patients, needed dose reductions due to AE´s but the median time to first dose reduction was twice longer for the talazoparib patients (19.3 vs 9.3 weeks). Dose interruptions were significantly more common for the talazoparib arm compared to the capecitabine arm, which may reflect the continuous treatment regimen.

The difference in study drug exposure between talazoparib and PCT was approximately 4 months for the mean value (8.4 vs 4.5) but 2 months for the median value (6.1 vs 3.9) which is explained by more patients remaining on treatment with talazoparib beyond 14 months as compared with the PCT arm.

A high proportion of TEAEs leading to talazoparib dose modifications (defined as any dose reduction or dosing interruption) was reported in the 673-301 study (66.4 %). Over 50 % of the talazoparib treated patients had at least one dose reduction due to AEs whereof about 25 % had one and 20 % had two dose reductions whilst a few were in need of 3 or more (~7 %).

A high proportion of dose modifications (defined as any dose reduction or dosing interruption) due to TEAEs was reported in talazoparib exposed patients (66.4 %) with 52.1 % in need of (at least one) dose reduction (the

median time to first AE associated dose reduction is close to 5 months i.e. occurs rather late) and 60.1 % requiring dose interruptions (mean and median time was 10.7 and 8.0 days respectively). In about half of the patients the talazoparib dose was reduced to 0.75 mg/day (1st step in the dose reduction algorithm in Section 4.2 of the SmPC) whilst 28% were reduced to 0.50 mg/day and a limited number of patients (7.7 %) had a dose reduction to 0.25 mg/day due to AEs. Notably, the high rates of dose modifications did not translate into a corresponding magnitude of AE associated treatment discontinuations which are considered reassuringly low (4.5 %) and indicative of a manageable toxicity with appropriate risk minimisation measures.

Report rates were high in the talazoparib arm for any TEAE (98.6 %), Grade 3 or 4 (67.5 %) and a fairly high for SAE reports (31.8 %). The reliability in regard to the adjudication of drug-relatedness is likely to be hampered by the fact that this is an open label study. It is recognised that the findings in the 673-301 study were in line with the observations in the overall "Talazoparib 1 mg/day" population.

Almost all patients reported at least one TEAE, similar between treatment arms. For talazoparib treated patients, anaemia was the most common reported TEAE (52.4 %) followed by fatigue (50.3 %) and nausea (48.6 %). For the control arm nausea was the most common reported TEAE (46.8 %) followed by fatigue (42.9 %) and neutropenia (29.4 %) which may be as expected with conventional chemotherapy. The majority of hematologic AEs in both treatment arms were Grade 3 or 4 (46.9% and 4.9%, respectively, in the talazoparib arm and 17.5% and 11.9%, respectively, in the PCT arm). Non-hematologic AEs were generally Grade 1 or 2. In terms of GI disorders, the rates of TEAEs between talazoparib treated patients and patients in the control arm were fairly similar: nausea (48.6 % in both arms), diarrhoea (22.0 % and 26.2 % respectively), vomiting (24.8 % vs. 23.0 %) and constipation (22.0 % vs. 21.4 %).

The Applicant evaluated the potential association with talazoparib by examining the reporting frequency for all-causality AEs for the talazoparib arm in comparison with the PCT arm in addition to consider the mechanism of action of talazoparib, available nonclinical toxicology data and the overall assessment of AEs by the investigators in determining whether AEs were reasonably associated with talazoparib treatment. The approach for the adjudication of ADRs appears overall reasonable.

The predominant ADRs for talazoparib are related to bone marrow toxicity and anaemia of all grades appeared at a higher incidence with talazoparib as compared to the control arm consisting of conventional chemotherapy (52.4 % and 18.3 % respectively) as did thrombocytopenia (26.9 % and 7.1 % respectively). Neutropenia was slightly less common in the talazoparib arm (34.6 %) as compared to the control arm (42.9 %). Dose modifications due to myelosuppression included anaemia 38.1%, neutropenia 19.2%, thrombocytopenia 10.5%, decreased platelet count 6.6%, decreased neutrophil count 4.5%, decreased white blood cell count 4.2%, and febrile neutropenia 0.3%. Corresponding proportions for permanent discontinuations of talazoparib are however low (anaemia 0.7%, neutropenia 0.3%, and thrombocytopenia 0.3%). In terms of neutropenia only one case of febrile neutropenia was reported but no cases of neutropenic sepsis. In terms of administered support, about 9 % in the talazoparib arm required growth factors (G-CSF, mainly filgrastim) and 38 % RBC transfusions (median number of two RBC transfusions per patient) and about 3 % required a platelet transfusion. In the PCT arm 22 patients (17.5 %) received growth factor support whilst 5.6 % required a RBC transfusion (median of one per patient) but none any platelet transfusions.

Myelosuppression-related adverse reactions of anaemia, neutropenia, and thrombocytopenia were very commonly reported in patients treated with talazoparib 1 mg/day.

Other common TEAEs reported for talazoparib were fatigue (50.3 %) and nausea (48.6 %). For the control arm nausea was the most common reported TEAE (46.8 %) followed by fatigue (42.9 %) and neutropenia (29.4 %) which is as expected with conventional chemotherapy.

In terms of GI disorders, the rates of TEAEs between talazoparib treated patients and patients in the control arm were fairly similar: nausea (48.6 % in both arms), diarrhoea (22.0 % and 26.2 % respectively), vomiting (24.8 % vs. 23.0 %) and constipation (22.0 % vs. 21.4 %).

Most frequently reported Grade 3 or 4 events for talazoparib pertain to its exertion on the bone marrow. Grade 3 and Grade 4 myelosuppression related events were reported for anaemia 34.8% and 0.4%, neutropenia 15.6% and 1.8%, and thrombocytopenia 12.8% and 4.0%. Neutropenia was more frequently reported for the control arm (24.6 %). Notably Grade 3 or 4 infections were infrequent in both arms (4.2% in the talazoparib arm vs 6.3% in the PCT arm).

No deaths were reported due to myelosuppression related adverse events. Myelosuppression related adverse drug reactions associated with dose modifications were reported for up to approximately 30% of patients in the talazoparib 1 mg/day population and those associated with permanent study drug discontinuation were reported for less than 1% of patients.

The SmPC adequately reflects that myelosuppression consisting of anaemia, leucopenia/neutropenia, and/or thrombocytopenia, have been reported in patients treated with talazoparib (see SmPC sections 4.4 and 4.8). Talazoparib should not be started until patients have recovered from haematological toxicity caused by previous therapy (≤ Grade 1). Precautions should be taken to routinely monitor haematology parameters and signs and symptoms associated with anaemia, leucopenia/neutropenia, and/or thrombocytopenia in patients receiving talazoparib. If such events occur, dose modifications (reduction or interruption) are recommended (see SmPC section 4.2). Supportive care with or without blood and/or platelet transfusions and/or administration of colony stimulating factors may be used as appropriate.

It is noted that pulmonary embolism was reported in 6 patients (2.1 %) in the talazoparib arm as compared to none in the control arm however further data revealed 9 patients (3.1%) in the talazoparib arm that were reported for a VTE compared with 8 patients (6.3%) in the PCT arm in the 673-301 study. A search of VTE in the 1 mg/day talazoparib Population (N=494) has furthermore been conducted that showed an overall frequency of VTEs of 2.8%. Hence available data is not suggestive of an increased risk of VTEs by talazoparib.

Similar overall proportions in terms of SAE reports were reported between the two treatment-arms (31.8 % and 29.4 %, talazoparib and PCT respectively). For the talazoparib treated patients, anaemia is the most common cause for SAE (5.9 %) with pyrexia second (2.4 %).

Hepatotoxicity-related TEAEs occurred to a lesser extent in the talazoparib exposed patients in the 673-301 study than in the control (9.1 % and 19.8 % respectively). Most commonly reported are increases of ASAT (4.2 %), ALAT (2.8 %) and ALP 2.8 %).

One case of pneumonitis (0.2%) occurred in the 673-201 study. The event was a Grade 1 pneumonitis and considered treatment related. However this was not considered to warrant inclusion in the SmPC.

A total of 37.8 % died in the talazoparib arm in the 673-301 study as compared to 42.1 % in the control arm, the vast majority due to disease progression. The proportion of deaths occurring within 30 days after last dose of study drug was similar between treatment arms (9.3 % and 9.4 % respectively) with the majority due to progressive disease (6.5 % and 7.5 % respectively). The proportion of AE associated deaths occurring during this period of study time does not evoke any immediate concern (3 patients; 2.8 % in the talazoparib arm).

It is recognised that the studies programme included also patients with non-BRCA disease status, however due to the very limited number of these patients enrolled no conclusions can be drawn with regards to safety between gBRCA vs. non-BRCA.

Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in patients who received poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, including talazoparib. Overall, MDS/AML has been reported in 2 out of 584 (0.3%) solid tumour patients treated with talazoparib in clinical studies. Potential contributing factors for the development of MDS/AML include previous platinum-containing chemotherapy, other DNA damaging agents or radiotherapy. Complete blood counts should be obtained at baseline and monitored monthly for signs of haematologic toxicity during treatment. If MDS/AML is confirmed, talazoparib should be discontinued (see SmPC section 4.4).

The risk of MDS/AML is addressed in section 4.4 of the Talzenna SmPC and included in the Safety Specification for talazoparib as an important potential risk.

For the important potential risks myelodysplastic syndrome/acute myeloid leukaemia and second primary malignancies (other than MDS/AML) a causal relationship with talazoparib has not been established. Cases reported in the continuing development talazoparib program and in post-marketing surveillance will be continually reviewed and patient monitoring guidance is provided to healthcare professionals in the SmPC to increase awareness of HCPs on this important potential risk, as applicable.

A safety update has been submitted providing an additional 4.5 months of data (from 15 September 2017 to 31 January 2018). The limited availability of post-marketing data is recognised (first regulatory approval on 16 October 2018 in the US and the product is not currently marketed in any other countries/territories). It is agreed however, that overall the data from this update are in line with the observations made in the initial submission.

There were no new cases reported in terms of second primary malignancies, pneumonitis and MDS. In terms of AML, no AEs that possibly represented AML were reported in the initial submission or up to the clinical database snapshot date for this safety update in the Talazoparib 1 mg/day Population. However, subsequent to this snapshot date, an AE of AML was reported for one patient from Study 673-301 in the Talazoparib 1 mg/day Population. The Investigator considered there was a reasonable possibility whilst the Applicant considered that the patient's prior systemic anticancer treatment provided an alternative etiology for AML. As mentioned further above, MDS/AML is classified as important potential risks in the RMP which is supported.

A comparison in regard to TEAEs between patients with normal renal function and mild renal impairment did not reveal any clinical relevant differences. The proportion of patients with moderate renal impairment and certainly in severe renal impairment is too limited to draw any firm conclusion. However, a population PK analysis showed that talazoparib CL/F decreased by 37 % in patients with moderate renal impairment corresponding to a 59% increase in exposure (AUC) compared to patients with normal renal function. Exposure-safety analysis indicated that higher talazoparib exposure was associated with a higher risk for Grade 3 or higher anaemia and thrombocytopenia, and had a trend for association with Grade 3 or higher neutropenia. Given talazoparib higher exposure in patients with moderate renal impairment which was associated with increased incidence of haematological AEs, a reduced starting dose of 0.75 mg once daily is recommended for this subpopulation (see discussion on clinical pharmacology and SmPC section 4.2). The use in Severe Renal Impairment is included under missing information in the list of safety concerns. A study of talazoparib in patients with renal impairment (Study MDV3800-01) is ongoing to further elucidate the effect of varying degrees of renal impairment on the PK and safety of talazoparib in patients with solid tumours (see RMP, category 3 study).

No clinically relevant difference was observed except possibly thrombocytopenia that was more commonly reported in patients with hepatic impairment (26.8 %) as compared to patients with normal hepatic function (17.2 %). TEAE reports of anaemia and thrombocytopenia were similar between the populations (~49 % and 23 % respectively). A study of talazoparib in patients with hepatic impairment (Study MDV3800-02) is ongoing to

further elucidate the effect of hepatic impairment on the safety of talazoparib. The applicant is recommended to submit the results of study MDV3800-02 as soon as available.

Thrombocytopenia was reported at a ⩾10% higher incidence in patients with hepatic impairment than patients with normal hepatic function in the talazoparib arm of Study 673-301 (27.8% in the hepatic impairment group vs 12.1% in normal hepatic function group). As talazoparib undergoes only minimal hepatic metabolism and further based on the PK/PD profile of talazoparib, this is not considered to be of any major clinical relevance.

Safety data were analysed for males (10.3%) and females (89.7%) in the Talazoparib 1 mg/day population (N=494). Due to the overall limited number of male patients (only seven male patients were enrolled in the 673-301 study) no firm conclusion can be drawn as regards the safety profile of talazoparib according to gender.

Safety data by age was dichotomised according to patients <65 years and ≥ 65 years. In the 673-301 study only 27 patients were 65 or older in the talazoparib arm and eight in the control arm. This discrepancy is as can be expected in a study population with BRCA mutated breast cancers as these patients tend to develop their tumours at an younger age compared to breast cancer in general (especially associated with BRCA 1 mutated cancers). Based on the presented data it is recognised that increased age appears not to be specifically associated with increased risk of talazoparib associated AEs. Given however the low number of patients no firm conclusion can be drawn.

There were very few patients enrolled in the age cohorts of 75-84 (N= 14) and ≥85 to draw any firm conclusion. No differences of any major clinical relevance between the < 65 and 65-74 age groups were observed.

Because of the imbalances of race among patients in Study 673-301 (69.4% White, 10.7% Asian, 2.9% Black or African American, and 1.5% other), coupled with the high proportion of patients whose race was unknown (15.5%), the impact of race on the safety of talazoparib treatment could not be adequately assessed in either Study 673-301 or the Talazoparib 1 mg/day Population. Based on the population PK analysis, talazoparib exposure was 19.2% lower in Asian patients compared with non-Asian patients. The effect of race on talazoparib exposure was not considered clinically relevant. Based on the population PK analysis talazoparib exposure was 19.2% lower in the Asian (10.7% of patients in the 673-301 study) compared with non-Asian patients (see SmPC section 5.2).

Safety data by BMI were analysed for the following three groups of patients in the Talazoparib 1 mg/day Population based on BMI: ≤18 kg/m2 (N=10; 2.0%), >18-30 kg/m2 (N=383; 77.7%), and >30 kg/m2 (N=100; 20.3%). The proportion of patients in the BMI ≤18 kg/m2 (N=10; 2.0%) wasis too limited to draw any conclusions. Although overall no clinically relevant differences were observed between the BMI >18-30 kg/m2 (77.7%) and the BMI >30 kg/m2 (20.3%) cohorts aside from anaemia (45.7 % and 56.0 % respectively) and fatigue (45.4 % and 56.0 % respectively), some AEs were more common in patients with BMI of > 30 kg/m2 compared to lower BMI.

Reproductive and developmental toxicity is based in findings from animal studies and has been included as an important potential risk in the RMP (see discussion on non-clinical aspects). Talazoparib may cause foetal harm when administered to a pregnant woman based on non-clinical findings. Based on non-clinical findings in testes (partially reversible) and ovary (reversible), Talzenna may impair fertility in males of reproductive potential (see section 5.3). There are no available clinical data on talazoparib use in pregnant women or any information on fertility in patients to confirm a drug-associated risk. Talzenna is not recommended during pregnancy or for women of childbearing potential not using contraception (see SmPC section 4.4). The SmPC contains adequate instructions to avoid pregnancy and utilise contraception in male and female patients.

Women of childbearing potential should not become pregnant while receiving Talzenna and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment (see SmPC section 4.4).

Women of childbearing potential must use two highly effective and complementary forms of contraception prior to starting treatment with talazoparib, during treatment, and for 7 months after stopping treatment with talazoparib. Since the use of hormonal contraception is not recommended in patients with breast cancer, two non-hormonal and complementary contraception methods should be used (see SmPC sections 4.4 and 4.6). Regular pregnancy tests could be considered during treatment. Male patients with female partners of reproductive potential or pregnant partners should be advised to use effective contraception (even after vasectomy), during treatment with Talzenna and for at least 4 months after the final dose.

Regarding breastfeeding, it is unknown whether talazoparib is excreted in human breast milk. A risk to breast fed children cannot be excluded and therefore breast-feeding is not recommended during treatment with Talzenna and for at least 1 month after the final dose (see SmPC section 4.6).

Hypersensitivity to the active substance or to any of the excipients listed in the SmPC section 6.1 is a contraindication.

Talzenna may have a minor influence on the ability to drive and use machines. Fatigue/asthenia or dizziness may occur following administration of talazoparib.

There is limited experience of overdose with talazoparib. No adverse reactions were reported in one patient who accidentally self-administered thirty 1 mg capsules of talazoparib on Day 1 and was immediately treated with gastric decontamination. Symptoms of overdose are not established. In the event of overdose, treatment with talazoparib should be stopped, and physicians should consider gastric decontamination, follow general supportive measures and treat symptomatically (see SmPC section 4.9).

The safety of Talzenna in children and adolescents < 18 years of age has not been established. No data are available (see SmPC section 4.2).
From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics. Adequate recommendations in terms of dose adjustments have been reflected in section 4.2 of the SmPC to manage adverse drug reactions. Interruption of treatment or dose reduction based on severity and clinical presentation should be considered (see SmPC section 4.2, Table 1 and Table 2). Complete blood count should also be obtained prior to starting Talzenna therapy and monitored monthly and as clinically indicated (see SmPC section 4.2 Table 2 and SmPC section 4.4).

Additional expert consultations

See clinical efficacy section.

2.6.2. Conclusions on the clinical safety

The safety profile of talazoparib (mainly characterised by myelosuppression) appears to be manageable with appropriate risk minimization measures as evidenced by the low treatment discontinuation rate.

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

To address the use in patients with severe renal impairment, the applicant should provide the results of study MDV3800-01 (C3441001) evaluating the PK and safety profile of talazoparib multiple daily oral doses of 0.5 mg in patients with varying degrees of renal impairment as compared to patients with normal renal function (see

Category 3 study in the RMP).

2.7. Risk Management Plan

Safety concerns

Table 69: Summary of the Safety Concerns

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

Pharmacovigilance plan

Table 68. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
MDV3800-01 (C3441001) *ongoing*	To evaluate the PK and safety profile of talazoparib multiple daily oral doses of 0.5 mg in patients with varying degrees of renal impairment as compared to patients with normal renal function.	Use in severe renal impairment.	Final CSR Submission	*31 December 2019*

Risk minimisation measures

Table 69: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Myelodysplastic syndrome/Acute myeloid leukaemia (MDS/AML)	Routine risk minimisation measures: SmPC Section 4.4, where advise is given to discontinue talazoparib if MDS/AML is confirmed Package leaflet (PL) section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
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 utilised to collect further data on this safety concern. Additional pharmacovigilance activities: None
Missing Information		
Use in severe renal impairment	Routine risk minimisation measures: SmPC Section 4.2, 5.2 where advice is given to reduce the talazoparib dose from 1 mg once daily to 0.75 mg once daily in patients with	Additional pharmacovigilance activities: Study in patients with renal impairment.

	moderate renal impairment. Use of talazoparib in patients with severe renal impairment should be at prescribing physician's discretion based on the risk/benefit assessment with caution.	

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 16 October 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of talazoparib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers talazoparib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Talzenna (talazoparib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety

information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication is for Talzenna as monotherapy for the treatment of adult patients with breast cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer.

About 5% of breast cancers arise in women carrying deleterious heterozygous germline mutations in the cancer susceptibility genes BRCA1 and BRCA2. Whilst women in the general European population have a 12% lifetime risk of developing breast cancer, about 55% to 65% of women who inherit a BRCA1 mutation and approximately 45% of women who inherit a BRCA2 mutation will develop breast cancer by the age of 70. gBRCA mutations are found in 10% of male breast cancer patients with the majority with mutations in BRCA2. gBRCA2 mutations are associated with a lifetime risk of breast cancer between 5% to 10% in men.

Heterozygous germline BRCA mutations, however, are insufficient to compromise DNA repair, with loss of heterozygosity required for homologous repair deficiency to be manifested in BRCA-mutant breast cancer, along with presumed high sensitivity to PARPi (or platinum compounds).

BRCA1 is associated with younger age, HR negative status and basal phenotype, whilst the opposite is true for BRCA2. This means that middle aged HR positive breast cancer in BRCA1 carriers may not be related to the gBRCA carrier state.

3.1.2. Available therapies and unmet medical need

Treatment of patients with advanced or metastatic breast cancer is palliative and the aim of the treatment is to reduce symptoms and prolong life with preservation of quality of life. Treatment of advanced or metastatic breast cancer can include surgery, radiotherapy, interventional radiology and systemic palliative treatment with number of different anti-neoplastic agents including anti-hormonal drugs, biologicals, targeted treatments and cytotoxic agents. The use of systemic treatments is generally sequential, mainly monotherapy, based on patient characteristics, patient previous medical history, previous treatments, disease biology, and disease burden.

For patients with progressive germline BRCA mutated, HER2 negative, locally advanced or metastatic breast cancer and indication for new anti-neoplastic treatment, after exhaustion of anti-hormonal agents and anti-CDK4/6 agents if indicated, treatment with PARP inhibitors or next line palliative chemotherapy, including capecitabine, eribulin and platinum containing cytotoxic agents, can be considered as next treatment option.

First-line therapy of gBRCA associated breast cancer still follows similar clinical guidelines as for non-BRCA tumours. Platinum compounds and recently the PARPi olaparib (NEJM 2017) are increasingly used as second or later lines of therapy.

Regardless the available treatment options the disease condition remains incurable with limited life expectancy and near continuous need for palliative systemic treatment with the side effects that generally follow cytotoxic treatments, including fatigue and general health deterioration, and intermittently progressive disease with

increasing disease related symptoms. There is an unmet medical need for patients with advanced or metastatic incurable gBRCA HER2 negative breast cancer.

3.1.3. Main clinical studies

The EMBRACA study is an open-label, randomised, parallel, 2-arm multicentre Phase 3 study of talazoparib versus chemotherapy (capecitabine [44%], eribulin [40%], gemcitabine [10%], vinorelbine [7%]) in patients with germline BRCA mutated HER2 negative locally advanced or metastatic breast cancer who received no more than 3 prior cytotoxic chemotherapy regimens for their metastatic or locally advanced disease. Patients were required to have received treatment with an anthracycline and/or a taxane (unless contraindicated) in the neoadjuvant, adjuvant and/or metastatic setting. Patients with prior platinum therapy for advanced disease were required to have no evidence of disease progression during platinum therapy. No prior treatment with a PARP inhibitor was permitted.

The primary efficacy endpoint was progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, as assessed by blinded independent central review (BICR).

3.2. Favourable effects

The study demonstrated a statistically significant improvement in PFS based on IRF for talazoparib compared with chemotherapy at event rates of 65% (talazoparib) and 58% (control) with a median PFS of 8.6 months (95% CI 7.2, 9.3) vs 5.6 months (95%CI 4.2, 6.7) (HR 0.54 (95% CI 0.4; 0.7, p<0.0001).

The investigator assessment at event rates of 76% (tazoparib) and 71% (control) reported a HR of 0.54 (95% CI 0.4; 0.7, p<0.0001) and median PFS of 7.0 and 4.4 months respectively.

ORR (investigator, confirmation not required) was 63% in the talazoparib arm vs. 27% in the control arm (Odds ratio 4.99 (2.9, 8.8), p< 0.0001).

Median duration of response by investigator was 5.4 (interquartile range 2.8; 11.2) months in the talazoparib arm vs 3.1 (interquartile range 2.4; 6.7) months in the chemotherapy arm.

The overall survival conducted at 38% event rates reported a HR of 0.76, p=0.11, with median OS of 22 months vs. 19.5 months respectively. Survival rates at 2-year were 45% and 37%, respectively.

3.3. Uncertainties and limitations about favourable effects

Imbalances in withdrawal rates at baseline and prior to endpoints constitute the main uncertainties, both with respect to PFS and OS. During the review, the applicant provided a number of sensitivity analyses indicating that the metrics are reasonably robust to assumptions of informative censoring. As the extent of bias that might be introduced cannot be precisely defined there is a residual uncertainty in the effect estimates due to the amount of missing data; however, the uncertainty and extent of potential bias, given the sensitivity analyses provided, is not large enough to questions the beneficial effect of talazoparib.

The duration of response is in relation to the high response rate shorter than expected, i.e. resistance develops fast. Factors determining secondary resistance is one of the objectives of exploratory trials, not yet reported. Due to the lack of a direct comparison with platinum chemotherapy, the relative efficacy of PARPi compared to platinum chemotherapy has not been defined. Further, efficacy has not been evaluated in platinum refractory patients. Thus there is a general uncertainty on the appropriate positioning of talazoparib in a treatment context where platinum based chemotherapy is an option. The applicant is recommended to investigate predictive

biomarkers that could impact the efficacy of Talzenna in different lines of therapy in patients with BRCA1- and BRCA2-mutated tumours and breast tumours of particular histological and molecular subtypes. The investigation of efficacy in platinum-resistant tumours and comparative efficacy to platinum agents is recommended.

3.4. Unfavourable effects

The safety is based on data from 494 patients that have received at least one dose of talazoparib 1 mg daily including the 286 patients from the 673-301 study. The safety observations in this study compares well with the findings in the overall `Talazoparib 1 mg/day´ population. The mean and median duration of talazoparib exposure was 8.4 months and 6.1 months respectively. A rather limited 18.5 % have received talazoparib for ≥ 12 months at time of data cut-off date. A high proportion of dose modifications (defined as any dose reduction or dosing interruption) due to TEAEs was reported in talazoparib exposed patients (66.4 %) with 52.1 % in need of (at least one) dose reduction (median time to first AE associated dose reduction is close to 5 months i.e. occurs rather late) and 60.1 % requiring dose interruptions (mean and median time was 10.7 and 8.0 days respectively). Notably, the high rates of dose modifications did not translate into a corresponding magnitude of AE associated treatment discontinuations which are considered reassuringly low (4.5 %) and indicative of a manageable toxicity with appropriate risk minimisation measures.

The predominant ADRs for talazoparib are related to bone marrow toxicity. Anaemia of all grades appeared at a higher incidence with talazoparib as compared to the control arm (52.4 % and 18.3 % respectively) as did thrombocytopenia (26.9 % and 7.1 % respectively). Neutropenia was slightly less common in the talazoparib arm (34.6 %) as compared to the control arm (42.9 %) however only one case of febrile neutropenia was reported in each arm and no cases of neutropenic sepsis. Aside from frequent dose modifications in order to manage the bone marrow toxicity, supportive measures were required. About 9 % required growth factors (G-CSF) and 38 % RBC transfusions (median number of two RBC transfusions per patient) and about 3 % required a platelet transfusion. In the PCT arm 22 patients (17.5 %) received growth factor support whilst 5.6 % required a RBC transfusion (median of one per patient) but none any platelet transfusions.

Other common TEAEs reported for talazoparib were fatigue (50.3 %) and nausea (48.6 %). For the control arm nausea was the most common reported TEAE (46.8 %) followed by fatigue (42.9 %) and neutropenia (29.4 %) which is as expected with conventional chemotherapy. In terms of GI disorders, the rates of TEAEs between talazoparib treated patients and patients in the control arm were fairly similar: nausea (48.6 % in both arms), diarrhoea (22.0 % and 26.2 % respectively), vomiting (24.8 % vs. 23.0 %) and constipation (22.0 % vs. 21.4 %).

Most frequently reported Grade 3 or 4 events for talazoparib in the 673-301 study were anaemia (38.8 %), neutropenia (17.8 %) and thrombocytopenia (8.0 %). Notably Grade 3 or 4 infections were infrequent in both arms (4.2% in the talazoparib arm vs 6.3% in the PCT arm).

Hepatotoxicity-related TEAEs were reported in a lesser extent in talazoparib exposed patients in the 673-301 study than in the control (9.1 % and 19.8 % respectively). Most commonly reported are increases of ASAT (4.2 %), ALAT (2.8 %) and ALP (2.8 %).

A total of 37.8 % died in the talazoparib arm in the 673-301 study as compared to 42.1 % in the control arm, the vast majority due to disease progression. The proportion of deaths occurring within 30 days after last dose of study drug was similar between treatment arms (9.3 % and 9.4 % respectively) with the majority due to progressive disease (6.5 % and 7.5 % respectively). A total of 3 patients (2.8 %) died due to AEs in the talazoparib arm.

MDS/AML has been reported in 2 out of 584 (0.3%) solid tumour patients treated with talazoparib in clinical studies. Potential contributing factors for the development of MDS/AML include previous platinum-containing chemotherapy, other DNA damaging agents or radiotherapy. The risk of MDS/AML is addressed in section 4.4 of the Talzenna SmPC. In the "Talazoparib 1 mg/day Population", seven AEs of second primary malignancies were reported for six patients. Myelodysplastic syndrome/acute myeloid leukaemia and second primary malignancies (other than MDS/AML) are classified as important potential risk in the RMP.

3.5. Uncertainties and limitations about unfavourable effects

The precise risk of second primary malignancies is not well characterised. Cases reported in the continuing development talazoparib program and in post-marketing surveillance will be continually reviewed (RMP) and patient monitoring guidance is provided to healthcare professionals in the SmPC.

3.6. Effects Table

Table 70: Effects Table for Talzenna indicated for the treatment of adult patients with germline BRCA mutated HER2 negative locally advanced or metastatic breast cancer (data cut-off: 15 Sept 2017)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS by IRF Event rate In follow-up Median PFS	Time from randomization until the date of radiologic	 % % month	 65 21 8.6	 58 5 5.6	IRF Censoring IRF. vs investigator	**Study 673-301 (EMBRACA)**
HR (95%CI) p-value	progressive disease per modified RECIST 1.1 as determined by central IRF assessment, or death due to any cause		HR 0.54 (0.4: 0.7) P<0.0001			
PFS by inv. Event rate median	Time from randomisation to	% month	76 7.0	71 4.4	Investigator "better" median estimates	
HR (95%CI) p-value	progression or death		HR 0.54 (0.4; 0.7) P<0.0001			
OS Event rate Lost to follow up Median	Time from randomisation until death due to any cause	% % month	38 4.5 22.3	38 17 19.5	HR non-constant	

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
HR (95%CI) p-value			HR 0.76 P=0.11			
Response rate Measurable disease ORR CR DOR		 N (%) % % month	 291 (76%) 63 5.5 5.4	 114 (79%) 27 0 3.1	Investigator assessment Confirmed response not required	
Unfavourable Effects						
Any TEAE - Grade 3 or 4		%	98.6 67.5	97.6 63.5	Potential uncertainties relate to the open label design	
≥ 1 SAE - Anaemia - Pyrexia - Vomiting - Back pain - Platelet count ↘		%	31.8 5.9 2.4 1.7 1.7 1.4	29.4 0 1.6 1.6 0.8 0		
Anaemia - Any - Grade 3 or 4		%	 52.4 38.8	 18.3 4.8		
Fatigue - Any - Grade 3 or 4		%	 50.3 1.7	 42.9 3.2		
Nausea - Any - Grade 3 or 4		%	 48.6 -	 46.8 -		
Neutropenia - Any - Grade 3 or 4		%	 26.6 17.8	 29.4 24.6		
Diarrhoea - Any - Grade 3 or 4		%	 22.0 -	 26.2 -		
Thrombocytopenia - Any - Grade 3 or 4		%	 16.1 8.0	 5.6 1.6		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The prolongation of PFS compared with chemotherapy is modest, but the positive study result established talazoparib as an effective treatment within the scope of the indication. Withdrawal, excluding administrative censoring, prior to event is imbalanced with a clearly higher rate in the control group. OS data indicate no detrimental effect. Furthermore, sensitivity analyses indicate that the PFS and OS outcomes are reasonably robust to assumptions of informative censoring.

It is apparent that exposure to talazoparib requires to rather a high extent dose modifications, but the rate of treatment discontinuations is reassuringly low meaning that toxicity (mainly bone marrow toxicity and in particular anaemia) can be reasonably well managed with appropriate risk minimisation measures such as dose reductions, interruptions and standard supportive care.

3.7.2. Balance of benefits and risks

In light of the poor prognosis of BRCA1/2 mutated HER2 negative locally advanced or metastatic breast cancer, the efficacy results of the EMBRACA study are considered clinically relevant and outweigh the risks associated with the treatment which can be managed with risk minimisation measures (see SmPC and RMP).

3.7.3. Additional considerations on the benefit-risk balance

Substantial clinical benefit including OS benefit has been shown for anthracyclines and taxanes that are current standard of care. It is considered that anthracycline and/or a taxane should be specified prior regimens in the indication unless patients were not suitable for these treatments. The indication also reflects that HR+ breast cancer patients should have been treated with a prior endocrine-based therapy or be considered unsuitable for endocrine-based therapy in line with the studied population.

Further to a SAG oncology consultation, the CHMP considered that it was not possible to extrapolate results also to patients with sBRCA mutations and therefore the indication is limited to patients with gBRCA mutations, according to inclusion criteria. While the proportion of men in the study program is very low, it is still considered possible to extrapolate results to men, based on the common biological and pharmacological rationale.

3.8. Conclusions

The overall Benefit/Risk balance of Talzenna is positive for the following indication: Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2 mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments (see SmPC section 5.1). Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Talzenna is favourable in the following indication:

Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and 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 also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that talazoparib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.