



Summary Report of Benefit-Risk Assessment

TALZENNA CAPSULE 0.25MG AND 1MG NEW DRUG APPLICATION

Active Ingredient(s)	Talazoparib tosylate
Product Registrant	Pfizer Private Limited
Product Registration Number	SIN15944P, SIN15945P
Application Route	Abridged evaluation
Date of Approval	22 May 2020

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A INTRODUCTION

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 who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments.

The active ingredient, talazoparib, is a potent inhibitor of poly ADP ribose polymerase 1 (PARP1) and PARP2, which play important roles in deoxyribonucleic acid (DNA) repair. By inhibiting DNA repair, replication, and transcription, talazoparib causes double-strand DNA breaks and cytotoxicity in cancer cells with loss-of-function of either the BRCA1 or BRCA2 tumor suppressor genes.

Talzenna is available as capsules containing talazoparib tosylate equivalent to 0.25 mg and 1 mg. Other ingredients in the capsule are silicified microcrystalline cellulose, hypromellose, titanium dioxide, red iron oxide and/or yellow iron oxide, shellac, propylene glycol, ammonium hydroxide, black iron oxide and potassium hydroxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, talazoparib tosylate, is manufactured at Excella GmbH & Co. KG, Feucht, Germany. The drug product, Talzenna Capsule 0.25mg and 1mg, is manufactured at Excella GmbH & Co. KG, Feucht, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Excella GmbH & Co. KG is adequate to support the approved storage condition and re-test period. The packaging is [REDACTED]. [REDACTED]. The drug substance is approved for storage at or below 25°C with a re-test period of 48 months.

Drug product:

The capsules are manufactured using a standard process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted is adequate to support the approved shelf-life of 36 months when stored at or below 30°C. The in-use period for the drug product packaged in bottles is 45 days after first opening and this is also supported with appropriate data. The container closure system is high-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat induction seal liner containing 30 hard capsules, or polyvinyl chloride/polyvinylidene chloride (PVC/PVdC) blister with an aluminium peel off foil lidding in a carton containing 30 hard capsules.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of talazoparib for the treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer was supported by one pivotal study, EMBRACA. The EMBRACA study was a Phase 3, open-label, randomized study of talazoparib versus protocol-specified physician's choice treatment (PCT) 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. They were also required to have prior treatment with a taxane and/or anthracycline in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated. There was no limit and no specific requirement regarding prior lines of hormonal therapy. Prior platinum was allowed in the neoadjuvant/adjuvant setting provided disease did not recur within 6 months, or in the advanced breast cancer setting in the absence of disease progression on platinum. Patients with first-line locally advanced or metastatic breast cancer with no prior adjuvant chemotherapy could only be enrolled if they would otherwise receive 1 of the 4 PCTs.

Patients were randomized in a 2:1 ratio to receive either talazoparib 1 mg once daily orally or PCT (capecitabine, eribulin, gemcitabine or vinorelbine) at standard doses until radiographic disease progression.

The primary endpoint was progression-free survival (PFS), defined as time from randomization until the date of radiologic progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria as determined by central independent radiology facility (IRF) assessment or death due to any cause, whichever occurred first. Secondary endpoints include objective response rate (ORR) and overall survival (OS). The exploratory endpoint was the duration of response (DOR).

A total of 431 patients were randomized in the study and were included in the intent-to-treat (ITT) population - 287 patients in the talazoparib arm and 144 patients in the PCT arm. The median duration of drug exposure was 6.1 months in the talazoparib arm and 3.9 months in the PCT arm.

The patient demographics and baseline disease characteristics were generally well-balanced between the treatment arms. The majority of patients (98.4%) were female. The overall median age of patients was 46 years (range, 24-88 years), with a lower median age in the talazoparib arm (45 years) than in the PCT arm (50 years). The majority of patients (69.6%) were White; 10.9% were Asian and 3.0% were Black or African American. Across both treatment arms, 241 patients (55.9%) had hormone receptor positive disease, 54.7% in the talazoparib arm and 58.3% in the PCT arm. For patients with hormone receptor-positive disease, 90.4% and 83.3% received at least 1 prior hormonal therapy in any (advanced breast cancer and neoadjuvant/adjuvant) setting in the talazoparib arm and PCT arm, respectively.

Summary of key efficacy results

	Talazoparib	Overall PCT
Primary efficacy endpoint		
PFS by IRF, N	287	144
PFS events, n (%)	186 (64.8%)	83 (57.6%)
Median (95% CI), months	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard ratio (95% CI); 2-sided p-value ^a	0.542 (0.413, 0.711); <0.0001	
Key sensitivity, secondary and exploratory efficacy endpoints		
OS, interim, N	287	144
OS events, n (%)	108 (37.6%)	55 (38.2%)
Median (95% CI), months	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
Hazard ratio (95% CI); 2-sided p-value ^a	0.761 (0.547, 1.060); 0.1053	
Objective response by investigator ^c , N	219	114
ORR (%; 95% CI)	62.6 (55.8, 69.0)	27.2 (19.3, 36.3)
Odds Ratio (95% CI); 2-sided p-value ^b	4.99 (2.93, 8.83); <0.0001	
Objective response by investigator (confirmed CR/PR), N	219	114
ORR (%; 95% CI)	50.2 (43.4, 57.0)	18.4 (11.8, 26.8)
Odds Ratio (95% CI); 2-sided p-value ^b	4.85 (2.69, 9.10); <0.0001	
DOR by investigator, N	137	31
Median (interquartile range), months	5.4 (2.8, 11.2)	3.1 (2.4, 6.7)
PFS by investigator, N	287	144
PFS events, n (%)	217 (75.6%)	102 (70.8%)
Median (95% CI), months	7.0 (5.7, 7.6)	4.4 (2.9, 5.6)
Hazard ratio (95% CI); 2-sided p-value ^a	0.538 (0.420, 0.689); <0.0001	

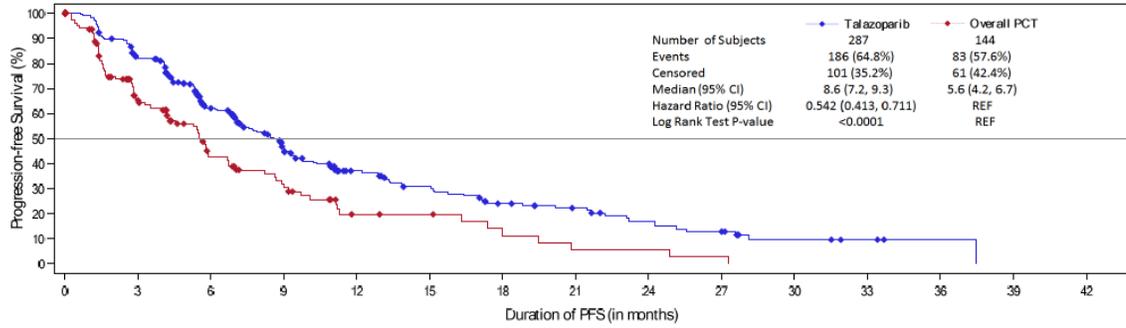
^a Stratified Log-rank test.

^b Based on stratified Cochran-Mantel-Haenszel method.

^c Per RECIST 1.1 confirmation of CR/PR was not required.

The primary analysis of PFS demonstrated a statistically significant improvement for subjects in the talazoparib arm compared to PCT, the hazard ratio (HR) was 0.542, 95% CI: 0.413, 0.711; p<0.0001. The median duration of PFS was 8.6 months in the talazoparib arm compared to 5.6 months in the PCT arm, a 3.0-month improvement. The PFS results were consistent in various sensitivity analyses based on different definitions of progression events and censoring rules, demonstrating robustness of the data.

Kaplan-Meier curves of PFS by IRF (ITT population)

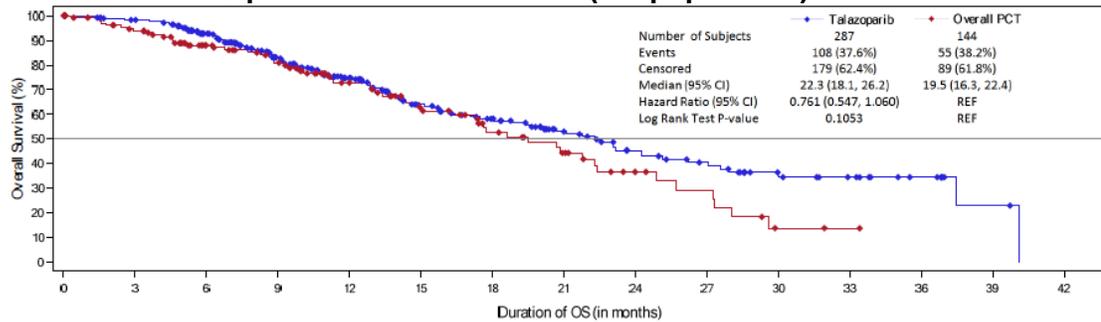


Talazoparib: Evt/Cum.	0/0	50/50	53/103	34/137	17/154	9/163	9/172	2/174	5/179	4/183	2/185	0/185	0/185	1/186	0/186
Patients at Risk	287	229	148	91	55	42	29	23	16	12	5	3	1	0	0
Overall PCT: Evt/Cum.	0/0	41/41	20/61	8/69	7/76	0/76	3/79	2/81	0/81	1/82	1/83	0/83	0/83	0/83	0/83
Patients at Risk	144	68	34	22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

The confirmed ORR based on the investigator assessment was 50.2% for talazoparib and 18.4% for PCT ($p < 0.0001$), with the majority of responses being partial responses in the talazoparib arm (44.7%). The median DOR in the talazoparib arm was 5.4 months compared to 3.1 months in the PCT arm.

At the interim OS analysis, after a median follow-up of 14.2 months (15 September 2017 data cut-off date), there was a trend for longer survival for patients in the talazoparib arm. The median duration of OS was 22.3 months for the talazoparib arm compared to 19.5 months for the PCT arm, the HR was 0.761, 95% CI: 0.547, 1.060; $p = 0.1053$. There was a numerical difference in 2-year survival probability favoring talazoparib compared to PCT (45% versus 37%, respectively). Although a trend for positive OS results had been observed, the observed improvement should be confirmed by the final OS analysis that will be performed after approximately 321 deaths are observed.

Kaplan-Meier curves of OS (ITT population)



Talazoparib: Evt/Cum.	0/0	5/5	15/20	24/44	16/60	17/77	8/85	6/91	7/98	4/102	4/106	0/106	0/106	1/107	1/108
Patients at Risk	287	278	236	179	132	91	74	52	38	30	18	14	8	2	0
Overall PCT: Evt/Cum.	0/0	8/8	7/15	7/22	7/29	7/36	6/42	4/46	3/49	2/51	4/55	0/55	0/55	0/55	0/55
Patients at Risk	144	119	92	78	55	41	28	20	11	8	2	1	0	0	0

Overall, the EMBRACA study met its primary efficacy endpoint and the results adequately supported the efficacy of talazoparib for the treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer who have previously been treated with chemotherapy.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety data of talazoparib comprised a total of 412 patients (286 patients in the talazoparib arm and 126 patients in the PCT arm) enrolled in the EMBRACA study. The median duration of drug exposure was longer in the talazoparib arm (6.1 months) compared to patients in the PCT arm (3.9 months).

Overall Summary of TEAEs (Safety Population)

	Talazoparib (N=286) n (%)	Overall PCT (N=126) n (%)
Any TEAE	282 (98.6)	123 (97.6)
Grade 3 or 4	193 (67.5)	80 (63.5)
Related to study drug ^a	254 (88.8)	112 (88.9)
Associated with death	6 (2.1)	4 (3.2)
Serious	91 (31.8)	37 (29.4)
Serious and related to study drug ^a	26 (9.1)	11 (8.7)
Grade 3 or 4 serious	73 (25.5)	32 (25.4)
Grade 3 or 4 and related to study drug ^a	159 (55.6)	61 (48.4)
Associated with permanent study drug discontinuation	22 (7.7)	12 (9.5)
Associated with dose modification	190 (66.4)	75 (59.5)

N=number of evaluable patients; n=number of patients in the category; PCT=physician's choice treatment; TEAE=treatment-emergent adverse event.

^a Assessed by the investigators as possibly, probably, or definitely related to study drug.

Adverse events (AEs) considered related to study drug were reported with similar incidence in each treatment arm (88.8% in the talazoparib arm vs 88.9% in the PCT arm). The most frequently reported AEs in the talazoparib arm were anemia (52.4%), fatigue (50.3%), nausea (48.6%), headache (32.5%), neutropenia (26.6%), alopecia (25.2%), vomiting (24.8%), diarrhea (22.0%), constipation (22.0%), decreased appetite (21.3%), and back pain (21.0%).

In the talazoparib arm, 4.5% of patients had an AE that was the primary reason for permanent study drug discontinuation, compared to 5.6% of patients in the PCT arm. The AEs that were the primary reason for permanent study drug discontinuation in the talazoparib arm were anemia (0.7%), neutropenia, thrombocytopenia, vomiting, accidental overdose, glioblastoma multiforme, metastases to meninges, cerebral hemorrhage, headache, transient ischemic attack, dyspnea and obstructive airways disorder (0.3% each). AEs of special interest reported for talazoparib and associated with PARP inhibitors include myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and myelosuppression. These AEs of special interest have been adequately described in the warnings and precautions section in the proposed Package Insert.

The utilization of talazoparib dose modifications, including dosing interruptions, with or without dose reductions and/or standard supportive care, appear to have managed hematologic toxicities appropriately, given the low rate of myelosuppression-related AEs associated with permanent study drug discontinuation.

The safety profile of talazoparib was similar to that of other PARP inhibitors used for the treatment of breast cancer. Overall, talazoparib 1 mg daily is well tolerated in patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer and talazoparib-related AEs were manageable through dosing interruption, dose reduction, and/or standard supportive care.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women. BRCA1 and BRCA2 are key components in the repair pathway for DNA double strand breaks, and mutations in these genes account for 20% to 25% of hereditary breast cancers and 5% of all breast cancers. 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.

Talazoparib had been shown to provide treatment benefit in terms of a statistical significant PFS prolongation of 3.0 months for the talazoparib arm compared to the control arm receiving PCT (median PFS by IRF assessment: 8.6 vs. 5.6 months; HR 0.542; 95% CI 0.413, 0.711). The improvement in PFS was considered clinically relevant. The results of the interim OS analysis (median OS: 22.3 vs. 19.5 months; HR 0.761; 95% CI: 0.547, 1.060; $p=0.1053$) suggested a trend for longer survival in the talazoparib arm.

The safety profile of talazoparib was considered acceptable relative to its benefits. Talazoparib was well tolerated in patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer and talazoparib-related AEs were manageable through dosing interruption, dose reduction, and/or standard supportive care. The safety profile of talazoparib was consistent with that of other PARP inhibitors indicated for the treatment of breast cancer.

Overall, the benefit-risk profile of talazoparib in the treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer who have previously been treated with chemotherapy was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Talzenna for the treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer who have previously been treated with chemotherapy was deemed favourable and approval of the product registration was granted on 22 May 2020.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

TALZENNA 0.25 mg hard capsules

TALZENNA 1 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TALZENNA 0.25 mg hard capsules

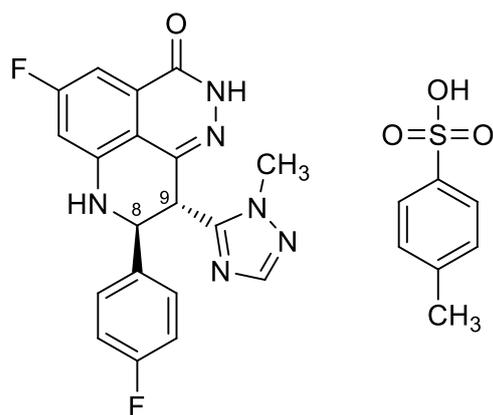
Each capsule contains 0.363 mg talazoparib tosylate equivalent to 0.25 mg talazoparib free base.

TALZENNA 1 mg hard capsules

Each capsule contains 1.453 mg talazoparib tosylate equivalent to 1 mg talazoparib free base.

For the full list of excipients, see Section 6.1.

Structure:



3. PHARMACEUTICAL FORM

Hard capsule.

TALZENNA 0.25 mg hard capsules

Opaque, size #4 hard hypromellose (HPMC) capsule with an ivory cap (printed with “Pfizer” in black) and a white body (printed with “TLZ 0.25” in black).

TALZENNA 1 mg hard capsules

Opaque, size #4 hard hypromellose (HPMC) capsule with a light red cap (printed with “Pfizer” in black) and a white body (printed with “TLZ 1” in black).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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 who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments.

4.2. Posology and method of administration

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

Detection of mutations in hereditary breast cancer-related BRCA1 and BRCA2 genes should be determined by an experienced laboratory using a validated test method (see Section 5.1).

Posology

The recommended dose of TALZENNA is 1 mg capsule taken orally once daily. Patients should be treated until disease progression or unacceptable toxicity occurs.

Missing dose

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

Dose modifications

To manage adverse reactions, consider interruption of treatment or dose reduction based on severity and clinical presentation. Recommended dose reductions are indicated in Table 1.

Table 1. Dose Modification for Toxicities

	Dose Level
Recommended starting dose	1 mg (one 1 mg capsule) once daily
First dose reduction	0.75 mg (three 0.25 mg capsules) once daily
Second dose reduction	0.5 mg (two 0.25 mg capsules) once daily
Third dose reduction	0.25 mg (one 0.25 mg capsule) once daily

Complete blood count should be obtained prior to starting TALZENNA therapy and monitored monthly and as clinically indicated (see Table 2 and Section 4.4).

Table 2. Dose Modification and Management

	Withhold TALZENNA until levels resolve to	Resume TALZENNA
Haemoglobin <8 g/dL	≥9 g/dL	Resume TALZENNA at a reduced dose
Platelet count <50,000/μL	≥75,000/μL	
Neutrophil count <1,000/μL	≥1,500/μL	
Non-haematologic adverse reaction Grade 3 or Grade 4	≤Grade 1	Consider resuming TALZENNA at a reduced dose or discontinue

Concomitant treatment with inhibitors of P-glycoprotein (P-gp)

Strong inhibitors of P-gp may lead to increased talazoparib exposure. Concomitant use of strong P-gp inhibitors during treatment with talazoparib should be avoided. Coadministration 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 the next lower dose. When the strong P-gp inhibitor is discontinued, the TALZENNA dose should be increased (after 3 to 5 half-lives of the P-gp inhibitor) to the dose used prior to the initiation of the strong P-gp inhibitor (see Section 4.5).

Concomitant treatment with inhibitors of Breast Cancer Resistance Protein (BCRP)

The effect of coadministration of BCRP inhibitors with TALZENNA has not been studied. Therefore, concomitant use of strong BCRP inhibitors during treatment with talazoparib should be avoided (see Section 4.5).

Special populations

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment (total bilirubin $\leq 1 \times$ upper limit of normal [ULN] and aspartate aminotransferase (AST) $>ULN$, or total bilirubin >1.0 to $1.5 \times ULN$ and any AST). TALZENNA has not been studied in patients with moderate (total bilirubin >1.5 to $3.0 \times ULN$ and any AST) or severe hepatic impairment (total bilirubin $>3.0 \times ULN$ and any AST) (see Section 5.2).

Renal impairment

No dose adjustment is required for patients with mild renal impairment ($60 \text{ mL/min} \leq$ creatinine clearance [CrCL] $< 90 \text{ mL/min}$). For patients with moderate renal impairment ($30 \text{ mL/min} \leq$ CrCL $< 60 \text{ mL/min}$), the recommended dose of TALZENNA is 0.75 mg once daily. For patients with severe renal impairment ($15 \text{ mL/min} \leq$ CrCL $< 30 \text{ mL/min}$), the recommended dose of TALZENNA is 0.5 mg once daily. TALZENNA has not been studied in patients requiring hemodialysis (see Section 5.2).

Elderly population

No dose adjustment is necessary in elderly (≥ 65 years of age) patients (see Section 5.2).

Pediatric population

The safety and efficacy of TALZENNA in children and adolescents <18 years of age have not been established.

4.3. Contraindications

None.

4.4. Special warnings and precautions for use

Myelosuppression

Myelosuppression consisting of anemia, leukopenia/neutropenia, and/or thrombocytopenia, have been reported in patients treated with talazoparib (see Section

4.8). Do not start talazoparib until patients have recovered from hematological toxicity caused by previous therapy (\leq Grade 1).

Precautions should be taken to routinely monitor hematology parameters and signs and symptoms associated with anemia, leukopenia/neutropenia, and/or thrombocytopenia in patients receiving talazoparib. If such events occur, dose modifications (reduction or interruption) are recommended (see 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.

Myelodysplastic syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML) have been reported in patients who received poly(adenosine diphosphate [ADP] ribose) polymerase (PARP) inhibitors. In the Phase 3 randomized breast cancer study, MDS/AML was reported in no patients who received talazoparib and in 1 out of 126 (0.8%) patients who received chemotherapy. Overall, MDS/AML has been reported in 1 out of 561 (0.2%) solid tumor 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 hematologic toxicity during treatment. If MDS/AML is confirmed, talazoparib should be discontinued.

Embryo-fetal toxicity

Studies in animals have shown embryo-fetal toxicity and talazoparib was clastogenic in *in vitro* and in *in vivo* assays (see Section 5.3). Talazoparib should not be given to pregnant patients or those who plan to become pregnant during treatment. Women of childbearing potential should be advised to avoid becoming pregnant while receiving TALZENNA. TALZENNA may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus (see Section 4.6).

A highly effective method of contraception is required for female patients during treatment with TALZENNA, and for at least 7 months after completing therapy. Since the use of hormonal contraception is not recommended in patients with breast cancer, two non-hormonal and complementary contraception methods should be used. Advise male patients with female partners of reproductive potential and pregnant partners to use effective contraception (even after vasectomy), during treatment with TALZENNA and for at least 4 months after the final dose.

4.5. Interaction with other medicinal products and other forms of interaction

Talazoparib is a substrate for drug transporters P-gp and BCRP and mainly eliminated by renal clearance as unchanged compound.

Agents that may affect talazoparib plasma concentrations

Effect of P-gp inhibitors

Data from a drug-drug interaction study in patients with advanced solid tumors indicated that coadministration of multiple daily doses of a P-gp inhibitor, itraconazole 100 mg twice daily with a single 0.5 mg talazoparib dose increased

talazoparib total exposure (AUC_{inf}) and peak concentration (C_{max}) by approximately 56% and 40%, respectively, relative to a single 0.5 mg talazoparib dose administered alone. Population pharmacokinetic (PK) analysis has shown that concomitant use of strong P-gp inhibitors with TALZENNA increased talazoparib exposure by 44.7%, relative to TALZENNA given alone. If patients must be coadministered a strong P-gp inhibitor, those that result in ≥ 2 -fold increase in the exposure of an *in vivo* probe P-gp substrate, (including but not limited to amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valsopodar, and verapamil), the TALZENNA dose should be reduced to the next lower dose (see Section 4.2).

Population PK analysis has shown that coadministration with relatively weak P-gp inhibitors (including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin) in clinical studies had no significant effect on talazoparib exposure.

Effect of P-gp inducers

Data from a drug-drug interaction study in patients with advanced solid tumors indicated that coadministration of a P-gp inducer (rifampin 600 mg once daily) with a single 1 mg talazoparib dose increased talazoparib C_{max} by 37% with no effect on talazoparib exposure. 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.

Effect of BCRP inhibitors

The effect of BCRP inhibitors on PK of talazoparib has not been studied. Concomitant use of strong BCRP inhibitors (including but not limited to curcumin, cyclosporine, and elacridar [GF120918]) should be avoided (see Section 4.2).

Effect of acid-reducing agents

Population PK analysis indicates that coadministration of acid-reducing agents including proton pump inhibitors (PPI), histamine receptor 2 antagonists (H_2RA), or other acid-reducing agents had no significant impact on the absorption of talazoparib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

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 child bearing potential prior to treatment (see Section 4.4).

A highly effective method of contraception is required for female patients during treatment with TALZENNA, and for at least 7 months after completing therapy. Since the use of hormonal contraception is not recommended in patients with breast cancer, two non-hormonal and complementary contraception methods should be used. Advise male patients with female partners of reproductive potential and pregnant partners to

use effective contraception (even after vasectomy) during treatment with TALZENNA and for at least 4 months after the final dose (see Section 4.4).

Pregnancy

There are no data from the use of TALZENNA in pregnant women. Studies in animals have shown embryo-fetal toxicity (see Section 5.3). TALZENNA may cause fetal harm when administered to a pregnant woman. TALZENNA is not recommended during pregnancy or for women of childbearing potential not using contraception (see Section 4.4).

Breastfeeding

It is unknown whether TALZENNA is excreted in human breast milk. A risk to newborns/infants cannot be excluded and therefore breastfeeding is not recommended during treatment with TALZENNA and for at least 1 month after the final dose.

Fertility

There is no information on fertility in patients. Based on non-clinical findings in testes and ovary, male and female fertility may be compromised by treatment with TALZENNA (see Section 5.3).

4.7 Effects on ability to drive and use machines

No studies have been conducted on the effects of talazoparib on the ability to drive or operate machinery. However, patients experiencing fatigue/asthenia or dizziness while taking talazoparib should exercise caution when driving or operating machinery.

4.8 Undesirable effects

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 tumors, including 286 patients from a randomized Phase 3 study with germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer and 83 patients from a nonrandomized Phase 2 study in patients with germline BRCA-mutated locally advanced or metastatic breast cancer.

The most common ($\geq 25\%$) adverse reactions in patients receiving talazoparib in these clinical studies were fatigue (57.1%), anemia (49.6%), nausea (44.3%), neutropenia (30.2%), thrombocytopenia (29.6%), and headache (26.5%). The most common ($\geq 10\%$) Grade ≥ 3 adverse reactions of talazoparib were anemia (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 anemia (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 summarizes adverse reactions based on pooled dataset listed by system organ class, and frequency category. Frequency categories defined as: very common ($\geq 1/10$) and common ($\geq 1/100$ to $< 1/10$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. 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			
<i>Very common</i>			
Thrombocytopenia ^a	146 (29.6)	63 (12.8)	20 (4.0)
Anemia ^b	245 (49.6)	172 (34.8)	2 (0.4)
Neutropenia ^c	149 (30.2)	77 (15.6)	9 (1.8)
Leukopenia ^d	77 (15.6)	24 (4.9)	1 (0.2)
<i>Common</i>			
Lymphopenia ^e	30 (6.1)	13 (2.6)	0 (0.0)
Metabolism and nutrition disorders			
<i>Very common</i>			
Decreased appetite	100 (20.2)	2 (0.4)	0 (0.0)
Nervous system disorders			
<i>Very common</i>			
Dizziness	69 (14.0)	1 (0.2)	N/A
Headache	131 (26.5)	5 (1.0)	N/A
<i>Common</i>			
Dysgeusia	42 (8.5)	N/A	N/A
Gastrointestinal disorders			
<i>Very common</i>			
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
<i>Common</i>			
Stomatitis	32 (6.5)	0 (0.0)	0 (0.0)
Dyspepsia	41 (8.3)	0 (0.0)	N/A
Skin and subcutaneous tissue disorders			
<i>Very common</i>			
Alopecia ^g	110 (22.3)	N/A	N/A
General disorders and administration site conditions			
<i>Very common</i>			
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 anemia, haematocrit decreased and haemoglobin decreased.

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

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- ^d. Includes preferred terms of leukopenia 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.

Description of selected adverse reactions

Myelosuppression

Myelosuppression-related adverse reactions of anemia, neutropenia, and thrombocytopenia were very commonly reported in patients treated with talazoparib 1 mg/day. Grade 3 and Grade 4 myelosuppression-related events were reported for anemia 34.8% and 0.4%, neutropenia 15.6% and 1.8%, and thrombocytopenia 12.8% and 4.0%. No deaths were reported due to myelosuppression-related adverse reactions. Myelosuppression-related adverse events 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.

4.9 Overdose

There is no specific treatment in the event of talazoparib overdose, and 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action and pharmacodynamics effects

TALZENNA is a potent inhibitor of PARP enzymes, PARP1, and PARP2. PARP enzymes are involved in cellular DNA damage response signaling pathways such as DNA repair, gene transcription, cell cycle regulation, and cell death. PARP inhibitors (PARPi) exert cytotoxic effects on cancer cells by 2 mechanisms, inhibition of PARP catalytic activity and by PARP trapping, whereby PARP protein bound to a PARPi does not readily dissociate from a DNA lesion, thus preventing DNA repair, replication, and transcription and ultimately leading to apoptosis and/or cell death. Treatment of cancer cell lines that are harboring defects in DNA repair genes with talazoparib single agent leads to increased γ H2AX level, which is a marker of double stranded DNA breaks, resulting in decreased cell proliferation and increased apoptosis. The potent cytotoxicity observed with talazoparib against multiple tumor cell lines harboring mutations in the DNA damage response (DDR) pathways, can be attributed to its inhibition of PARP catalytic activity and robust PARP trapping. Talazoparib anti-tumor activity was also observed in the patient-derived xenograft (PDX) BRCA-mutant breast cancer model that was previously treated with a platinum-based regimen. In the PDX model talazoparib decreased tumor growth and increased γ H2AX level and apoptosis in the tumors.

Detection of BRCA mutation

Patients are eligible for TALZENNA treatment if they have a confirmed deleterious or suspected deleterious germline BRCA mutation (i.e., a mutation that disrupts normal gene function; detected using an appropriately validated test).

Clinical efficacy and safety

Randomized Phase 3 study EMBRACA

EMBRACA was an open-label, randomized, parallel, 2-arm multicenter study of TALZENNA versus chemotherapy (capecitabine, eribulin, gemcitabine, vinorelbine) 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.

A total of 431 patients were randomized 2:1 to receive TALZENNA 1 mg capsules once daily or chemotherapy at standard doses until progression or unacceptable toxicity. Of the 431 patients randomized onto EMBRACA, 287 were randomized to the TALZENNA arm and 144 to the chemotherapy arm. Randomization was stratified by prior use of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status (triple-negative breast cancer [TNBC] versus non-TNBC), and history of central nervous system metastasis (yes versus no). The majority of patients 408/431 (95%) were selected using the BRCA_{Analysis} test and BRCA mutation status (breast cancer susceptibility gene 1 [BRCA1] positive or breast cancer susceptibility gene 2 [BRCA2] positive) was similar across both treatment arms.

Patient demographic and baseline characteristics were generally similar between the study treatment arms. The median age of patients treated with TALZENNA was 45 years (range 27 to 84) and 50 years (range 24 to 88) among patients treated with chemotherapy. Of note, 63% versus 47% of patients were <50 years of age in the talazoparib and chemotherapy arms, respectively, 27% versus 47% were 50 to <65 years of age, and 9% versus 7% were ≥65 years of age. Among all randomized patients, 1% versus 2% were males, 66.9% versus 75.0% were White; 10.8% versus 11.1% were Asian, and 4.2% versus 0.7% were Black or African American in the talazoparib and chemotherapy arms, respectively. Almost all patients (97.7%) in both arms had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Approximately 55.9% of patients had hormone receptor-positive (either estrogen receptor [ER]-positive or progesterone receptor [PR]-positive) disease; 44.1% of patients had triple-negative disease and the proportions were balanced across treatment arms. The median time from initial diagnosis of breast cancer to diagnosis of advanced breast cancer was 1.9 years (range 0 to 22) on the talazoparib arm and 2.7 years (range 0 to 24) on the chemotherapy arm. The reported disease-free interval (DFI) was <12 months in 37.6% of patients on the talazoparib arm and in 29.2% of patients on the chemotherapy arms. Among all patients enrolled, the median number of prior cytotoxic regimens for advanced breast cancer was 1 where 38.3% of patients

received no prior regimens for advanced or metastatic disease, 37.4% received 1, 19.7% received 2, and 4.6% received ≥ 3 prior regimens, respectively. Sixteen percent of patients in the talazoparib arm and 20.8% of patients in the chemotherapy arm had received prior platinum treatment. 54.7% of patients had hormone receptor-positive disease in the talazoparib arm, of which 90.4% took a prior hormonal therapy, while 9.6% did not take any prior endocrine therapy. In the chemotherapy arm, 58.3% of patients had hormone receptor-positive disease, of which 83.3% took a prior hormonal therapy, while 16.7% did not take any prior endocrine therapy.

The primary efficacy endpoint was progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by blinded independent central review (BICR). The secondary objectives were objective response rate (ORR), overall survival (OS), safety, and PK. Exploratory objectives included duration of response (DOR), Clinical Benefit Rate at 24 weeks (CBR24), quality of life (QoL) assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30)/EORTC Quality of Life Questionnaire – Breast Cancer Module (QLQ-BR23) and biomarker research.

The study met its primary objective of demonstrating a statistically significant improvement in PFS for TALZENNA compared with chemotherapy (hazard ratio [HR] 0.54; 95% confidence interval [CI]: 0.41, 0.71; p-value <0.0001). A sensitivity analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results. The OS interim analysis was performed at 51% for the total number of planned events. Efficacy data for EMBRACA are summarized in Table 4 and the Kaplan-Meier curves for PFS and OS are shown in Figures 1 and 3. Consistent results were observed across pre-specified patient subgroups (Figure 2).

Table 4. Summary of Efficacy Results – EMBRACA Study

	Talazoparib	Chemotherapy
Progression-Free Survival by BICR	N=287	N=144
Events, number (%)	186 (65%)	83 (58%)
Median (95% CI), months	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard ratio (95% CI)	0.54 (0.41, 0.71)	
2-sided p-value ^a	p<0.0001	
Overall Survival (interim analysis) ^b	N=287	N=144
Events, number (%)	108 (38%)	55 (38%)
Median (95% CI), months	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
Hazard ratio (95% CI)	0.76 (0.55, 1.06)	
2-sided p-value ^a	p=0.1053	
Objective Response by Investigator ^{c,d}	N=219	N=114
ORR (%; 95% CI)	62.6 (55.8, 69.0)	27.2 (19.3, 36.3)
Odds ratio (95% CI)	4.99 (2.9, 8.8)	
2-sided p-value ^e	p<0.0001	
Duration of Response by Investigator ^c	N=137	N=31
Median (IQR), months	5.4 (2.8, 11.2)	3.1 (2.4, 6.7)

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CR=complete response; IQR=interquartile range; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PR=partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SD=stable disease.

a. Stratified Log-rank test.

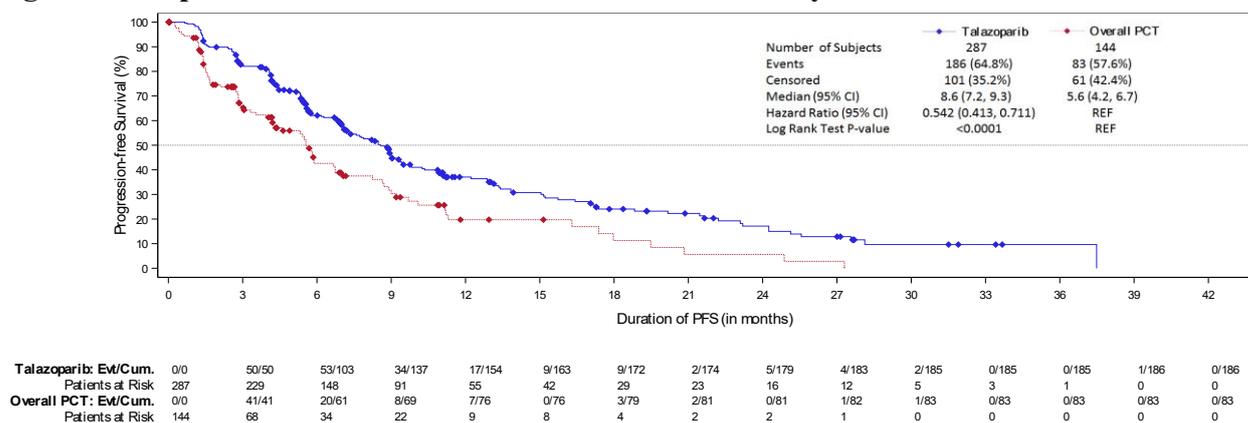
b. 51% of the projected final number of OS events occurred (163 of 321 deaths).

c. Conducted in ITT with measurable disease population who had an objective response. The complete response rate was 5.5% for talazoparib compared to 0% for the chemotherapy arm.

d. Per RECIST 1.1, confirmation of CR/PR was not required.

e. Stratified CMH test.

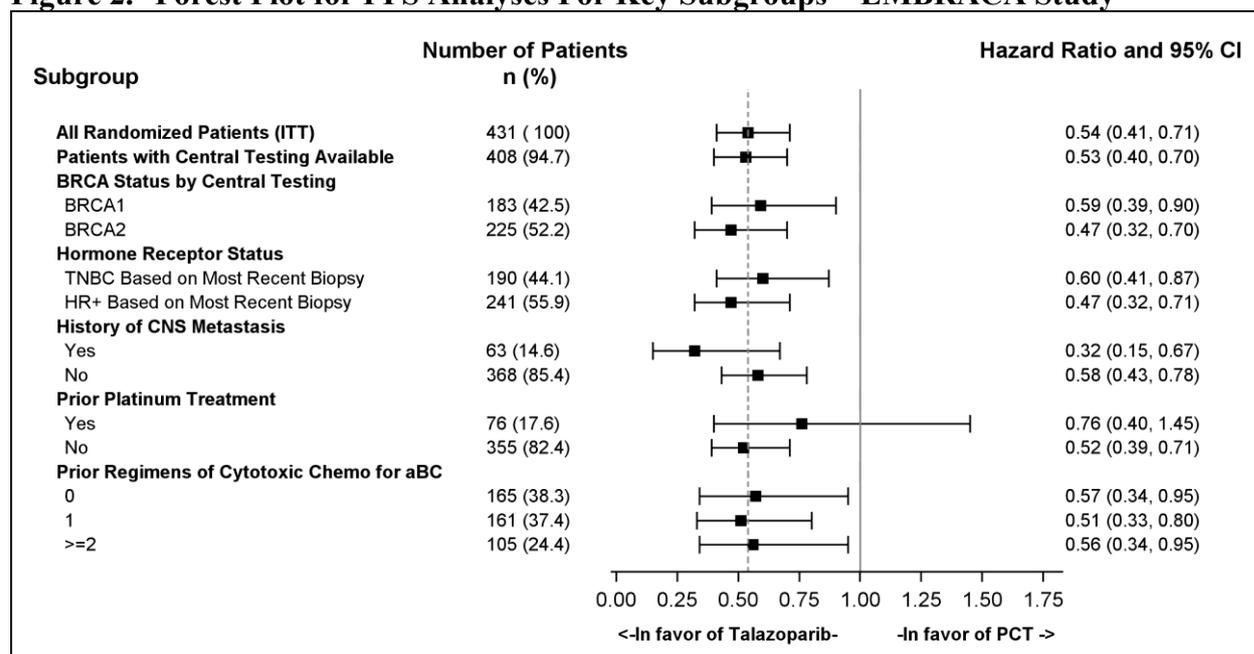
Figure 1. Kaplan-Meier Curves of PFS – EMBRACA Study



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 metastasis) and was relative to overall chemotherapy with <1 favoring talazoparib.

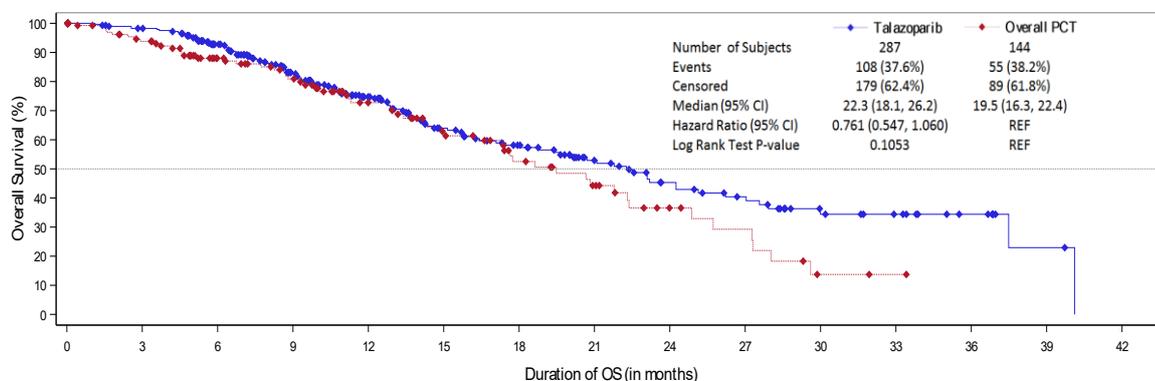
Abbreviations: CI=confidence interval; Cum=cumulative; Evt=event; PFS=progression-free survival; PCT=physician's choice treatment (chemotherapy); REF=reference treatment group.

Figure 2. Forest Plot for PFS Analyses For Key Subgroups – EMBRACA Study



Abbreviations: aBC=advanced breast cancer; BRCA=breast cancer susceptibility gene; CI=confidence interval; CNS=central nervous system; HR+ =hormone receptor-positive; ITT=intent-to-treat; PCT=physician’s choice treatment (chemotherapy); PFS=progression-free survival; TLZ=talazoparib; TNBC=triple-negative breast cancer.

Figure 3. Kaplan-Meier Curves of Overall Survival – EMBRACA Study



Talazoparib: Evt/Cum.	0/0	5/5	15/20	24/44	16/60	17/77	8/85	6/91	7/98	4/102	4/106	0/106	0/106	1/107	1/108
Patients at Risk	287	278	236	179	132	91	74	52	38	30	18	14	8	2	0
Overall PCT: Evt/Cum.	0/0	8/8	7/15	7/22	7/29	7/36	6/42	4/46	3/49	2/51	4/55	0/55	0/55	0/55	0/55
Patients at Risk	144	119	92	78	55	41	28	20	11	8	2	1	0	0	0

Abbreviations: CI=confidence interval; Cum.=cumulative; Evt=event; OS=overall survival; PCT=physician’s choice treatment (chemotherapy); REF=reference treatment group.

Patient-reported symptoms were assessed using the EORTC QLQ-C30 and its EORTC QLQ-BR23. A total of 262 patients in the talazoparib arm and 114 patients in the chemotherapy arm completed the questionnaire at baseline and at least 1 postbaseline visit.

A significantly greater overall improvement from baseline in global health status (GHS)/QoL was observed in the talazoparib arm (3.0 [95% CI: 1.2, 4.8]) compared to the chemotherapy arm (-5.4 [95% CI: -8.8, -2.0]) ($p < 0.0001$). A significantly greater delay in time to clinically meaningful (≥ 10 point decrease from baseline) definitive deterioration in GHS/QoL was observed in the talazoparib arm compared with chemotherapy [(HR: 0.38 [95% CI: 0.26, 0.55]; $p < 0.0001$), median 24.3 months versus 6.3 months].

A significantly greater overall improvement from baseline in breast symptoms was observed in the talazoparib arm (-5.1 [95% CI: -6.7, -3.5]) compared to the chemotherapy arm (-0.1 [95% CI: -2.9, 2.6]) ($p = 0.002$). A significantly greater delay in time to clinically meaningful (≥ 10 point increase from baseline) definitive deterioration in breast symptoms was observed in the talazoparib arm compared with chemotherapy (HR of 0.39 [95% CI: 0.20, 0.78]; $p = 0.005$, median times not reached [NR]).

A significantly greater overall improvement from baseline was observed in the talazoparib arm compared to the chemotherapy arm in role functioning [12.4, 95% CI: (7.1, 17.7) ($p < 0.0001$)] and the following symptoms: fatigue [-12.3, 95% CI: (-17.2, -7.5) ($p < 0.0001$)], pain [-13.3, 95% CI: (-18.5, -8.1) ($p < 0.0001$)] and appetite loss [-11.7, 95% CI: (-17.6, -5.7) ($p = 0.0001$)].

A significantly greater delay in time to clinically meaningful deterioration in the following symptoms was observed in the talazoparib arm compared to the chemotherapy arm for fatigue, [(HR: 0.40 [95% CI: 0.28, 0.56]; $p < 0.0001$), median 17.1 months versus 7.1 months], pain, [(HR: 0.34 [95% CI: 0.23, 0.50]; $p < 0.0001$), median 22.7 months versus 7.5 months], appetite loss, [(HR: 0.32 [95% CI: 0.21, 0.49]; $p < 0.0001$), median NR versus 9.0 months], systemic therapy side effects, [(HR: 0.33 [95% CI: 0.22, 0.51]; $p < 0.0001$), median 24.6 months versus 7.9 months], arm symptoms, [(HR: 0.46 [95% CI: 0.29, 0.73]; $p = 0.0008$), median NR versus 13.2 months]. A significantly greater delay in time to clinically meaningful deterioration was observed in the talazoparib arm compared to the chemotherapy arm for role functioning, [(HR: 0.36 [95% CI: 0.25, 0.52]; $p < 0.0001$), median 20.5 months versus 5.6 months].

5.2. Pharmacokinetic properties

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 area under the plasma concentration-time curve (AUC) and maximum observed plasma concentration (C_{max}) of talazoparib at steady-state was in the range of 126 ng•hr/mL to 208 ng•hr/mL and 11.4 ng/mL to 19.1 ng/mL, respectively. Following repeated daily dosing, talazoparib plasma concentrations reached steady-state within 2 to 3 weeks. The median accumulation ratio of talazoparib following repeated oral administration of 1 mg once daily was in the range of 2.33 to 5.15.

Absorption

Following oral administration of talazoparib, the median time to C_{\max} (T_{\max}) was generally between 1 to 2 hours after dosing. The absolute bioavailability study has not been conducted in humans. However, based on urinary excretion data the absolute bioavailability is at least 54.6% with fraction absorbed of at least 68.7% (see Elimination).

The effect of food

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 C_{\max} of talazoparib was decreased by approximately 46%, the median T_{\max} was delayed from 1 to 4 hours, while the AUC_{inf} was not affected. Based on these results, TALZENNA can be administered with or without food.

Distribution

The population mean apparent volume of distribution (V_{ss}/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 . Renal impairment does not appear to impact talazoparib protein binding as there was no obvious trend in the mean talazoparib fraction of unbound drug (f_u) in human plasma *in vivo* with worsening renal function.

Metabolism

Talazoparib undergoes minimal hepatic metabolism in humans. Following oral administration of a single 1 mg dose of [^{14}C]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 feces. The identified metabolic pathways of talazoparib in humans include: 1) mono-oxidation; 2) dehydrogenation; 3) cysteine conjugation of mono-desfluoro-talazoparib; and 4) glucuronide conjugation.

In vitro, talazoparib was not an inhibitor of cytochrome (CYP)1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 or inducer of CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

In vitro, talazoparib did not inhibit any of the major intestinal, hepatic or renal membrane transporters (P-gp, BCRP, organic anion transporting polypeptide [OATP]1B1, OATP1B3, organic cationic transporter [OCT]1 OCT2, organic anion transporter [OAT]1, OAT3, bile salt export pump [BSEP], multidrug and toxin extrusion [MATE]1 and MATE2-K) at clinically relevant concentrations.

In vitro, talazoparib did not inhibit any of the major uridine-diphosphate glucuronosyltransferase (UGT) isoforms (1A1, 1A4, 1A6, 1A9, 2B7, and 2B15) at clinically relevant concentrations.

Elimination

The mean terminal plasma half-life of talazoparib was 89.8 hours and the population mean apparent oral clearance (CL/F) was 6.45 L/h in cancer patients. In 6 female patients with advanced solid tumors given a single oral dose of [^{14}C]talazoparib, a

mean of 68.7% and 19.7% of the total administered radioactive dose was recovered in urine and feces, respectively. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 54.6% of the administered dose, while unchanged talazoparib recovered in the feces accounted for 13.6%.

Age, sex, race, 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), race (361 White, 41 Asian, 16 Black, 9 Others, and 63 Not reported), and body weight (ranging from 35.7 kg to 162 kg) on the PK of talazoparib. The results have shown that age, sex, race, and body weight had no clinically relevant effect on the PK of talazoparib.

Pediatric population

Pharmacokinetics of talazoparib have not been evaluated in patients <18 years of age.

Elderly population

Of the 494 patients who received TALZENNA, 85 patients were ≥ 65 years of age. No overall differences in safety or effectiveness of TALZENNA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

Renal impairment

Data from a PK trial in advanced cancer patients with varying degrees of renal impairment indicate that talazoparib total exposure (AUC_{0-24}) after multiple talazoparib once-daily doses increased by 12%, 43%, and 163% in patients with mild ($eGFR 60 - 89 \text{ mL/min/1.73 m}^2$), moderate ($eGFR 30 - 59 \text{ mL/min/1.73 m}^2$), and severe ($eGFR 15 - 29 \text{ mL/min/1.73 m}^2$) renal impairment, respectively, relative to patients with normal renal function ($eGFR \geq 90 \text{ mL/min/1.73 m}^2$). Talazoparib C_{max} increased by 11%, 32%, and 89% in patients with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function. Consistent with these findings, a population PK analysis that included 490 patients, where 132 patients had mild renal impairment ($60 \text{ mL/min} \leq CrCL < 90 \text{ mL/min}$), 33 patients had moderate renal impairment ($30 \text{ mL/min} \leq CrCL < 60 \text{ mL/min}$), and 1 patient had severe renal impairment ($CrCL < 30 \text{ mL/min}$), showed that talazoparib CL/F was decreased by 14.4% and 37.1% in patients with mild and moderate renal impairment, corresponding to 17% and 59% increase in AUC, respectively, when compared to patients with normal renal function ($CrCL \geq 90 \text{ mL/min}$). The PK of talazoparib has not been studied in patients requiring hemodialysis.

Hepatic impairment

Based on a population PK analysis that included 490 patients, where 118 patients had mild hepatic impairment (total bilirubin $\leq 1.0 \times ULN$ and $AST > ULN$, or total bilirubin > 1.0 to $1.5 \times ULN$ 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 $3.0 \times ULN$ and any AST) or severe hepatic impairment (total bilirubin $> 3.0 \times ULN$ and any AST).

Cardiac electrophysiology

The effect of talazoparib on cardiac repolarization 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 tumors. Talazoparib did not have a clinically relevant effect on QTc prolongation at the maximum clinically recommended dose of 1 mg once daily.

5.3. Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been conducted with talazoparib.

Genotoxicity

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.

Repeat-dose toxicity

In repeat-dose toxicity studies of up to 13-week duration, talazoparib was clinically tolerated in rats at 0.04 mg/kg/day and in dogs at 0.01 mg/kg/day and the AUC₂₄ exposure margins at the no adverse effect level are 0.2-fold the relevant human exposure. The main findings at subtherapeutic exposures included bone marrow hypocellularity with dose-dependent decrease in hematopoietic cells, depletion of lymphoid tissue in multiple organs and atrophy and/or degenerative changes in testes, epididymis, and seminiferous tubules. 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.

Reproductive toxicology

In an embryo-fetal development study in rats, talazoparib resulted in embryo-fetal death, fetal malformation (depressed eye bulge, small eye, split sternbra, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Talazoparib capsules content

Silicified microcrystalline cellulose (sMCC)

Capsule shell

White body shell

Hypromellose (HPMC)
Titanium dioxide (E171)

Ivory cap

Hypromellose (HPMC)
Yellow iron Oxide (E172)
Titanium dioxide (E171)

Light red cap

Hypromellose (HPMC)
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)

Printing ink

Shellac
Propylene glycol
Ammonium hydroxide
Black iron oxide
Potassium hydroxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Refer to outer carton for expiration date.

6.4. Special precautions for storage

Store at or below 30°C.

6.5. Nature and contents of container

TALZENNA 0.25 mg hard capsules

High-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat induction seal (HIS) liner, containing 30 or 60 or 90 hard capsules.

Polyvinyl chloride/polyvinylidene chloride (PVC/PVdC) blister with an aluminum peel off foil lidding in cartons of 30 × 1, or 60 × 1, or 90 × 1 hard capsules.

TALZENNA 1 mg hard capsules

High-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat induction seal (HIS) liner, containing 30 hard capsules.

Polyvinyl chloride/polyvinylidene chloride (PVC/PVdC) blister with an aluminum foil lidding in cartons of 30 × 1 hard capsules.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York 10017, USA

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Date of Last Revision: April 2020