CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc

Investigational Product: Talazoparib

Clinical Study Report Synopsis: Protocol C3441030

Protocol Title: A Phase 1 Study of the Safety, Pharmacokinetics and Anti-Tumor Activity of Talazoparib, Poly (ADP-Ribose) Polymerase (PARP) Inhibitor, in Japanese Patients With Advanced Solid Tumors

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Centers: This study was conducted at 8 sites in Japan. Except for 1 site, all the sites enrolled at least 1 subject. Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: Yoichi Naito, Yasutoshi Kuboki, Masafumi Ikeda et al. Safety, pharmacokinetics, and preliminary efficacy of the PARP inhibitor talazoparib in Japanese patients with advanced solid tumors: Phase 1 study. *Invest New Drugs*. 2021 Jun 23. doi: 10.1007/s10637-021-01120-7

Study Initiation Date: 30 November 2017

Primary Completion Date: 11 January 2021

Data Cut-off Dates: 07 November 2019 (for Dose Escalation Part) and 11 January 2021 (for Expansion Part)

Report Date: 06 August 2021

Previous Report Date: Not Applicable

Phase of Development: Phase 1

Primary and Secondary Study Objectives and Endpoints:

In this document the terms “participant”, “patient” and “subject” are used interchangeably. Study objectives and endpoints are presented in Table S1.

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Table S1. Study Objectives and Endpoints

Types	Objectives	Endpoints
Dose Escalation Part (Solid Tumor)		
Primary		
Safety	• To assess safety and tolerability at increasing dose levels of talazoparib in successive cohorts of subjects with solid tumors in order to select the RP2D/schedule in Japanese subjects.	• First-cycle DLTs.
Secondary		
Safety	• To evaluate the overall safety profile.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE Version 4.03), timing, seriousness, and relationship to talazoparib. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE Version 4.03), and timing. • Vital Signs.
PK	• To characterize the single and steady-state PK of single-agent talazoparib.	Pharmacokinetic parameters of talazoparib: • Single Dose - C_{max}, T_{max}, AUC_{last}, AUC_{tau}, CL/F, V_z/F, $t_{½}$, and AUC_{inf} as data permit. • Multiple Dose (assuming steady-state was achieved) - $C_{ss,max}$, $T_{ss,max}$, $C_{ss,min}$, $AUC_{ss,tau}$, CL/F, R_{ac} ($AUC_{ss,tau}$ /$AUC_{sd,tau}$) and R_{ss} ($AUC_{ss,tau}$ /$AUC_{sd,inf}$) as data permit.
Efficacy	• To assess preliminary evidence of anti-tumor activity of single-agent talazoparib.	• OR, as assessed using the RECIST Version 1.1. • Time-to-event endpoints: eg, DoR and PFS if applicable.
Expansion Part (gBRCAm Breast Cancer)		
Primary		
Efficacy	• To evaluate the anti-tumor activity of single-agent talazoparib in Japanese subjects with gBRCAm HER2-negative locally advanced or metastatic breast cancer.	• Confirmed OR as assessed using RECIST Version 1.1 by investigator assessment.
Secondary		
Efficacy	• To further evaluate anti-tumor activity.	• OR as assessed using RECIST Version 1.1 by BICR. • Disease control defined as subjects with a confirmed CR, confirmed PR and stable disease at 16 and 24 weeks. • Time to event endpoints: TTR, DoR, PFS, and OS.

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Table S1. Study Objectives and Endpoints

Types	Objectives	Endpoints
Safety	• To evaluate the overall safety profile of talazoparib.	• AEs including laboratory abnormalities as characterized by type, frequency, severity (as graded by the NCI CTCAE, Version 4.03), timing, seriousness, and relationship to talazoparib.
PK	• To characterize the PK of single-agent talazoparib.	• Trough concentrations of talazoparib.

Abbreviations: AEs=adverse events; AUC=area under the plasma concentration-time profile; AUC_{inf}=AUC from time 0 to infinity; AUC_{last}=AUC from time 0 to the time of the last quantifiable concentration; $AUC_{ss,tau}$=steady state AUC from time 0 to time tau, the dosing interval, where tau=24 hours (once daily dosing); AUC_{tau}=AUC from time 0 to time tau, the dosing interval, where tau=24 hours (once daily dosing); BICR=blinded independent central review; C_{max}=maximum plasma concentration; CL/F=apparent clearance; CR=complete response; $C_{ss,max}$=steady-state C_{max}; $C_{ss,min}$=steady-state lowest concentration observed during the dosing interval; CTCAE=Common Terminology Criteria for Adverse Events; DLTs=dose limiting toxicities; DoR=duration of response; gBRCAm=germline breast cancer susceptibility gene mutation; HER2=human epidermal growth factor Receptor 2; NCI=National Cancer Institute; OR=objective response; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; PR=partial response; QD=once daily; R_{ac}=accumulation ratio based on AUC (observed); RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; R_{ss}=accumulation ratio based on AUC (predicted); $t_{½}$=terminal half-life; T_{max}=time at which C_{max} occurred; $T_{ss,max}$=steady-state time to C_{max}; TTR=time-to-tumor response; V_z/F=apparent volume of distribution.

METHODS

Study Design: This was a Phase 1 study, consisting of 2 parts; dose escalation part and expansion part.

The **dose escalation part** was an open-label and evaluated safety, preliminary efficacy, and pharmacokinetics (PK) of single-agent talazoparib in sequential cohorts of adult subjects with advanced solid tumors who were resistant to standard therapy or for whom no standard therapy was available. Two dose levels (0.75 mg once daily [QD] and 1.0 mg QD) were evaluated in a modified 3+3 dose escalation scheme; up to 3 subjects were to be enrolled simultaneously in a cohort although sometimes due to logistical or clinical reasons >3 but no more than 9 subjects were enrolled at each dose level. Successive cohorts of subjects received escalating doses of talazoparib on an outpatient basis starting from 0.75 mg QD. Recommended Phase 2 dose (RP2D) was determined based on the incidence of dose limiting toxicity (DLT) cases.

Any of the following adverse events (AEs) occurring in the first cycle of treatment including the PK lead-in period, which were attributable to talazoparib were classified as DLTs:

- Hematologic - Grade 4 neutropenia lasting >7 days; febrile neutropenia for >1 hour; Grade ≥3 neutropenic infection; Grade ≥3 thrombocytopenia associated with Grade ≥2 hemorrhage or requiring transfusion; Grade 4 thrombocytopenia; Grade 3 anemia requiring transfusion; Grade 4 anemia; and if daily dosing interrupted for 7 or

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more total days in the first cycle due to Grade 3 neutropenia or Grade 3 thrombocytopenia.

- Non-hematologic - any Grade ≥3 AE, except, non-clinically significant Grade ≥3 laboratory abnormalities; on-hematologic Grade ≥3 AE deemed not clinically significant; Grade ≥3 nausea, vomiting and diarrhea that responds to medical intervention within 72 hours and Grade ≥3 fatigue that improves to Grade ≤2 within 7 days.

- Liver toxicity - Alanine or aspartate aminotransferase (ALT or AST) >5 × upper limit of normal (ULN) (a lower threshold was to be considered if the ALT/AST abnormalities were accompanied with symptoms and signs of hepatitis) and 2 × increases above the baseline values; ALT/AST ≥3 × ULN concurrent with total bilirubin (TBili) >2 × ULN; and TBili >5 × ULN.

- General toxicity - failure to deliver 75% of doses due to toxicities attributable to talazoparib.

The **expansion part** was an open-label, multicenter, efficacy, safety, and PK study of single-agent talazoparib at RP2D determined in the dose escalation part in adult subjects with locally advanced or metastatic breast cancer, who had deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA) 1 or 2 mutations. The subjects in the expansion part received 1.0 mg QD of talazoparib, which was RP2D identified in the dose escalation part of this study. The expansion part included blinded independent central review (BICR) assessment for the efficacy evaluation.

In all study parts, treatment with talazoparib was to be continued until either disease progression, unacceptable toxicity or withdrawal of consent.

Diagnosis and Main Criteria for Inclusion:

Dose Escalation Part:

Female and/or male subjects aged ≥20 years, who were able to take oral medications and had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, with adequate bone marrow function, renal function and liver function with histological or cytological diagnosis of locally advanced or metastatic solid tumor that was resistant to standard therapy or for which no standard therapy was available were included in the dose escalation part.

Subjects with known symptomatic brain metastases requiring steroids; major surgery, anti-tumor systemic cytotoxic therapies, and radiation therapy within 4 weeks prior to the first dose of study treatment; palliative radiotherapy for the treatment of painful bony lesions within 2 weeks prior to the first dose of study treatment; previous high-dose chemotherapy requiring stem cell rescue; prior irradiation to >25% of the bone marrow were excluded from the dose escalation part.

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Expansion Part:

Females and/or male subjects aged ≥20 years, who were able to take oral medications and had ECOG performance status ≤2, with adequate organ function with histologically or cytologically confirmed carcinoma of the breast (locally advanced breast cancer that was not amenable to curative radiation or surgery and/or metastatic disease), documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation by Myriad Genetics' BRACAnalysis CDx test, with no >3 prior chemotherapy-inclusive regimens for locally advanced or metastatic disease, subjects with prior treatment with a taxane and/or anthracycline in the neo-adjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated, and measurable lesion by the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, were included in the expansion part.

Subjects with first-line locally advanced or metastatic breast cancer without prior neo-adjuvant and adjuvant chemotherapy unless the investigator determined that treatment with a poly adenosine diphosphate-ribose polymerase (PARP) inhibitor such as talazoparib would be in the best interest of the subject; with prior treatment with a PARP inhibitor (not including iniparib); objective disease progression while receiving platinum chemotherapy administered for locally advanced or metastatic disease; cytotoxic chemotherapy, radiation therapy, antihormonal therapy or other targeted anti-cancer therapy within 14 days before starting study treatment; human epidermal growth factor Receptor 2 (HER2) positive breast cancer; active inflammatory breast cancer (classified as T4d by tumor, node, metastasis classification) were excluded from this part.

Study Treatment: Talazoparib capsule was administered orally on a continuous basis QD taken at the same time with or without food. Before serial PK sampling (ie, on Cycle 1 Day -7 and Cycle 1 Day 22), talazoparib was administered with plenty of water on an empty stomach ie, subjects refrained from food and beverages (except for water) for at least 6 hours before and 1 hour after dosing. A cycle was defined as the time from Day 1 dose of one cycle to the next Day 1 dose of the next cycle. If there were no treatment delays, a cycle was 28 days, except for Cycle 1 in the dose escalation part because it contained a 7-day lead-in period, and a single lead-in dose was given on Day -7.

Based on the global Phase 1 study, the maximum tolerated dose (MTD) and RP2D as a single-agent was investigated using the dose escalation scheme starting from 0.025 mg QD up to 1.1 mg QD. The MTD/RP2D was determined as 1.0 mg QD. Based on these results, the starting dose selected for the dose escalation part was 0.75 mg QD, where no DLT was observed and was one level lower than the maximum tolerated dose/RP2D.

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For the expansion part, 1.0 mg QD talazoparib capsules were to be used based on the RP2D identified in the dose escalation part of the study. In subjects with moderate renal impairment (creatinine clearance 30 to 59 mL/min), the starting dose was reduced 1 dose level (0.75 mg QD).

During the study, the 0.25 mg talazoparib capsules were supplied in separate bottles and labeled according to local regulatory requirements. For the expansion part, 1.0 mg talazoparib capsules were supplied as a starting dose; 0.25 mg talazoparib capsules were only be used for subjects who required dose reduction.

The description of the investigational product is provided in Table S2.

Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Talazoparib 0.25 mg bottle 30 count (MDV3800 capsules)	1610237	17-002129	0.25 mg	Capsule
Talazoparib 0.25 mg bottle 30 count (MDV3800 capsules)	1800870	18-000623	0.25 mg	Capsule
Talazoparib 0.25 mg bottle 30 count (MDV3800 capsules)	1912495	19-003204	0.25 mg	Capsule
Talazoparib 1 mg bottle 30 count (MDV3800 capsules)	1800873	18-000626	1 mg	Capsule
Talazoparib 1 mg bottle 30 count (MDV3800 capsules)	1810119	18-002600	1 mg	Capsule
Talazoparib 1 mg bottle 30 count (MDV3800 capsules)	1905903	19-002206	1 mg	Capsule

Efficacy Evaluations:

Tumor Response Assessments: Imaging included chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans. The same imaging technique used to characterize each identified and reported lesion at baseline was employed in the following tumor assessments.

Anti-tumor activity was assessed through radiological tumor assessments conducted at baseline, during treatment, whenever disease progression was suspected (eg, symptomatic deterioration), at the time of withdrawal from treatment (if not done in the previous 6 weeks) and at the time of clinical suspicion of disease progression. Assessment of responses were made using RECIST Version 1.1. In the expansion part, complete response (CR) and partial response (PR) were confirmed by a second image at least 4 weeks from the initial imaging showing response. In addition, BICR was conducted.

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Assessment of Germline BRCA Mutations for Eligibility (Expansion Part Only): Subjects enrolled in the expansion part were required to have deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutations, which were identified by BRAC analysis CDx test.

Pharmacokinetic Evaluations:

The following talazoparib PK parameters were calculated for each subject and each treatment, as applicable, using noncompartmental analysis of concentration-time data. Samples below the lower limit of quantification were set to 0 for analysis. Actual sample collection times were used for the PK analysis. Plasma PK parameters is described in Table S3.

Blood samples (approximately 3 mL) to provide a minimum of approximately 1 mL of plasma for PK analysis were collected into appropriately labeled tubes containing tripotassium ethylenediaminetetraacetic acid.

For the dose escalation part, the blood samples were collected in lead-in phase, at predose and after a single dose of talazoparib at 0.50, 0.75, 1, 2, 3, 4, 6, 8, 10 hour on Cycle 1 Day -7. After that, 24, 48, 72 and 96 hour postdose samples were collected through Cycle 1 Day -6 to Cycle 1 Day -3. Cycle 1 Day 1 predose sample was collected at 168 hour postdose for Cycle 1 Day -7 dose. Predose sample was also collected on Cycle 1 Day 15. Serial PK samples after multiple dose were collected on Cycle 1 Day 22 at predose, 0.50, 0.75, 1, 2, 3, 4, 6, 8, 10 hour. Predose samples were collected on Cycle 1 Day 23 and Day 1 of Cycles 3 and Cycle 4.

For the expansion part, the trough PK samples were collected on Day 1 of Cycle 2 through Cycle 4. In the event of a dose delay on the day of PK sampling (eg due to treatment-related toxicity), the predose PK sample was drawn on the day of dose interruption as an unplanned PK sample.

PK samples were assayed for talazoparib using a validated liquid chromatography with tandem mass spectrometry method in compliance with sponsor's standard operating procedures.

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Table S3. Plasma Pharmacokinetic Parameters of Talazoparib

Parameter	State	Definition	Method of Determination
C_{max}	sd, ss	Maximum plasma concentration	Observed directly from data
T_{max}	sd, ss	Time at which C_{max} occurred	Observed directly from data as time of first occurrence
AUC_{last}	sd	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/log trapezoidal method
AUC_{inf}[a]	sd	Area under the plasma concentration-time profile from time 0 extrapolated to infinity	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasmaconcentration at the last quantifiable time point estimated from the log-linear regression analysis
AUC_{tau}	sd, ss	Area under the plasma concentration-time profile from time 0 to time tau (τ), where τ=24 hours for QD dosing	Linear/log trapezoidal method
$t_{½}$[a]	sd	Terminal half-life	$Log_e(2)/k_{el,}$ where k_{el} was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time profile
CL/F[a]	sd, ss	Apparent clearance	Single dose: $Dose/AUC_{inf}$ Steady-state: $Dose/AUC_{tau}$
V_Z/F[a]	sd	Apparent volume of distribution	Single dose: $Dose/(AUC_{inf} \times k_{el})$ Steady-state: $Dose/(AUC_{tau} \times k_{el})$
C_{min}	ss	Lowest concentration observed during the dosing interval	Observed directly from data
R_{ac}	ss	Accumulation ratio based on AUC (observed)	Steady-state AUC_{tau}/Single dose AUC_{tau}
R_{ss}[a]	ss	Accumulation ratio based on AUC (predicted)	Steady-state AUC_{tau}/Single dose AUC_{inf}
C_{max}(dn)	sd, ss	Dose normalized C_{max}	C_{max}/Dose
AUC_{last}(dn)	sd	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf}(dn)[a]	sd	Dose normalized AUC_{inf}	AUC_{inf}/Dose
AUC_{taut}(dn)	ss	Dose normalized AUC_{tau}	AUC_{tau}/Dose
C_{min}(dn)	ss	Dose normalized C_{min}	C_{min}/Dose

PK parameters for the dose escalation part were calculated using an internally validated software system, electronic noncompartmental analysis (Version 2.2.4); pharmacokinetic concentration data were published using an internally validated software system: open noncompartmental analysis (Version 2.3).
a. If data permit.

Safety Evaluations:

Safety assessments included collection of AEs, serious adverse events (SAEs), vital signs, physical examinations, 12-lead electrocardiogram (ECG), laboratory assessments, including pregnancy tests, possible drug-induced liver injury (DILI) events, and verification of concomitant treatments.

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Statistical Methods:

In general, missing values were not imputed for efficacy and safety endpoints except for impuations according to standard algorithms. Missing or partial date was imputed when date was required for a calculation of duration.

Hypotheses and Decision Rules: There was no formal hypothesis testing planned for this study. In the dose escalation part, the objective was to determine RP2D. The estimated RP2D was the highest tested dose level with DLT rate <33% in at least 6 DLT-evaluable subjects in the per protocol analysis set. In the expansion part, the objective was to estimate objective response rate (ORR). If the lower limit of the 2-sided 90% confidence interval (CI) of confirmed ORR exceeded 18.4%, observed ORR in physician's choice therapy arm in previous Phase 3 study, it was considered that talazoparib shows clinically meaningful anti-tumor activity in Japanese subjects with germline breast cancer susceptibility gene mutation (gBRCAm) locally advanced/metastatic breast cancer.

Primary Estimand: The primary estimand of this study (for both the dose escalation and expansion parts) was a composite estimand (accounting for both treatment adherence and response), defined according to the primary objective and in alignment with the primary endpoint. It included the 4 attributes; population, variable, intercurrent event(s) and population-level summary.

Analysis Sets: analysis sets for this study are provided in Table S4.

All the 9 subjects treated in the dose escalation part, were included in the safety analysis set, full analysis set (FAS), per protocol analysis set (PPAS), PK concentration and PK parameter analysis set.

All the 19 subjects treated in the expansion part were included in the safety analysis set, FAS and PK concentration analysis set.

The safety analysis set was identical to the FAS for the dose escalation and expansion part.

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Table S4. Analysis Sets (Populations for Analysis)

Population	Description
Enrolled	All participants who sign the informed consent document.
FAS	All participants assigned to study treatment and who take at least 1 dose of study treatment.
PPAS	PPAS was evaluable for RP2D and was a subset of the FAS in the dose escalation part only. This set excluded subjects with major treatment deviations in the first cycle.
Safety	All participants assigned to study treatment and who take at least 1 dose of study treatment.
PK parameter	All enrolled participants treated who have sufficient information to estimate at least 1 of the PK parameters of interest in the dose escalation part only.
PK concentration	All enrolled participants who are treated and have at least 1 analyte concentration.

Abbreviations: FAS=full analysis set; PK=pharmacokinetics; PPAS=per protocol analysis set; RP2D=recommended Phase 2 dose.

Analysis of Efficacy Endpoints (Dose Escalation and Expansion Part):

The efficacy analysis was evaluated in the FAS.

Analysis of Primary Efficacy Endpoint (Expansion Part):

Confirmed Objective Response (OR) (Expansion Part): Confirmed OR was evaluated, using composite estimand strategy. The number, percentage and exact 2-sided 90% CI of subjects who experienced confirmed OR as assessed using RECIST Version 1.1 by investigator assessment was presented.

Analysis of Secondary Efficacy Endpoint (Dose Escalation and Expansion Part):

OR (Dose Escalation and Expansion Part): For the dose escalation part, the number and percent of each unconfirmed best overall response and each reason for not evaluable (NE) were presented. The number, percent and its exact 95% CI of the unconfirmed overall response and unconfirmed disease control (DC) was presented, respectively.

For the expansion part, the number and percent of each confirmed and unconfirmed best overall response and each reason for NE based on investigator assessment and BICR assessment were presented, respectively. The number, percent and its exact 90% CI of the confirmed and unconfirmed overall response and confirmed and unconfirmed DC (overall, at 16 weeks and 24 weeks) were presented, respectively.

Time-to-Tumor-Response (TTR) (Expansion Part): TTR based on investigator assessment and BICR assessment were analyzed on the subjects with confirmed CR or PR.

Duration of Response (DoR) (Dose Escalation and Expansion Part): DoR based on investigator assessment and BICR assessment (expansion part only) was analyzed on the subjects with unconfirmed CR or PR (dose escalation part) and confirmed CR or PR (expansion part). The number and percent of event (progressive disease [PD] or death) and

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those censored were presented. The probability of being event-free at 3, 6, 9 and 12 months was be presented with its 95% CI.

Progression Free Survival (PFS) (Expansion Part): PFS based on investigator assessment and BICR assessment (expansion part only) was presented. The number and percent of event (PD or death) and censored were presented. The probability of being event-free at 6, 12 and 18 months was presented with its 95% CI.

Overall Survival (OS) (Expansion Part): The number and percent of event (death) and censored were presented. The probability of being event-free at 12 months was presented with its 90% CI.

Analysis of PK Endpoints (Dose Escalation and Expansion Part):

Plasma PK parameters and concentrations of talazoparib was analyzed on PK parameter and PK concentration analysis set, respectively.

Dose Escalation Part: Plasma PK parameters listed in Table S3 were estimated using noncompartmental analysis. The single dose in lead-in phase and steady-state PK parameters at Cycle 1 Day 22 was summarized descriptively.

Expansion Part: Trough concentrations (C_{trough}) at steady-state was summarized descriptively by cycle and day.

Analysis of Safety Endpoints (Dose Escalation and Expansion Part):

The safety analysis was evaluated in the safety analysis set, except for first-cycle DLTs in the dose escalation part, which was evaluated in PPAS.

Analysis of Primary Safety Endpoint (Dose Escalation Part):

First-Cycle DLTs (Dose Escalation Part): DLTs were evaluated using composite estimand strategy. The number and percentage of subjects who experienced DLTs (hematologic, non-hematologic, liver toxicity and general toxicity) were presented by each dose group and total group.

Analysis of Secondary Safety Endpoint (Dose Escalation and Expansion Part):

All AEs were coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 at the analysis. The toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03.

The focus of AE summaries was on treatment-emergent AEs (TEAEs). AEs were tabulated using descriptive statistics which included incidence of TEAEs by MedDRA preferred term or cluster term, SAEs including deaths, AEs categorized by toxicity Grade ≥3, AEs that led

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to study drug discontinuation, AEs that led to study drug interruption, AEs that led to study drug reduction and AEs by maximum severity and relationship to study drug.

The laboratory toxicities were tabulated using descriptive statistics (number of subjects and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter was the number of subjects evaluable for National Cancer Institute Common Terminology Criteria for AEs grading (ie those subjects for whom a Grades 0, 1, 2, 3 or 4 could be derived).

RESULTS

Subject Disposition and Demography:

Subject Disposition:

A total of 104 subjects were screened including prescreening for BRCA1/2 mutation testing in this study, of which 28 subjects entered the study (9 subjects in the dose escalation part and 19 subjects in the expansion part).

In the dose escalation part, 9 subjects (3 subjects were assigned to talazoparib 0.75 mg QD and 6 subjects were assigned to talazoparib 1.0 mg QD), received at least 1 dose of study treatment. All 9 subjects discontinued during the treatment phase: 8 subjects (88.9%) due to PD and 1 subject due to global deterioration of health status. All 9 subjects entered the follow-up phase (28 to 35 calendar days follow-up after discontinuation of treatment); 8 subjects completed the follow-up phase and 1 subject discontinued due to other reason (subject moved and changed to distant hospital for palliative treatment).

In the expansion part, 3 subjects were screen failure, which does not include prescreening failure. A total of 19 subjects were assigned to talazoparib 1.0 mg QD treatment, but 2 subjects started the treatment at -1 dose level (0.75 mg QD) due to moderate renal impairment (creatinine clearance 30 to 59 mL/min). They all received at least 1 dose of study treatment.

At the time of data cut-off in the expansion part, 11 subjects (57.9%) discontinued during the treatment phase due to PD and 8 subjects were ongoing. Eleven subjects (57.9%) who discontinued during the treatment phase, completed the follow-up phase (28 to 35 calendar days follow-up after discontinuation of treatment); 1 subject discontinued due to death from the long-term follow-up phase.

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Demography:

In the dose escalation part, 4 male and 5 female subjects were enrolled. The mean (±standard deviation [SD]) age of subjects was 61.9 (±12.0) years. The mean (±SD) weight and body mass index (BMI) of subjects in the dose escalation part were 52.6 (±10.4) kg and 21.3 (±3.2) kg/m^2, respectively. All enrolled subjects were Asian (Japanese), not Hispanic or Latino.

In the expansion part, all 19 subjects enrolled were, Asian (Japanese), not Hispanic or Latino females. The mean (±SD) age of subjects was 54.5 (±14.9) years. The mean (±SD) weight and BMI of subjects in the expansion part were 52.6 (±10.7) kg, and 21.2 (±4.0) kg/m^2, respectively.

Efficacy Results:

Primary Efficacy Endpoint Result (Expansion Part):

Best Overall Response, OR Based on Investigator Assessment: The OR (CR or PR) was confirmed by a second image at least 4 weeks from the initial imaging showing response. At the time of data cut-off, in the expansion part; confirmed OR was observed in 11 subjects (57.9% [90% CI: 36.8, 77.0]) per derived investigator assessment and the lower limit of the 2-sided 90% CI exceeded the null proportion of 18.4% (Table S5). Talazoparib 1.0 mg QD showed clinically meaningful anti-tumor activity in Japanese subjects with gBRCAm locally advanced/metastatic breast cancer.

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Table S5. Summary of Best Overall Response (Confirmed), Objective Response and Disease Control Based on Derived Investigator Assessment (RECIST v1.1) - Expansion Part (Full Analysis Set) (Protocol C3441030)

	Talazoparib 1.0 mg (N=19)
Confirmed Best Overall Response, n (%)	
Complete response (CR)	0
Partial response (PR)	11 (57.9)
Stable disease (SD)	7 (36.8)
Non-CR/Non-PD	0
SD+Non-CR/Non-PD	7 (36.8)
Progressive disease (PD)	1 (5.3)
Not evaluable (NE)	0
Objective Response (CR+PR), n (%)	11 (57.9)
90% CI [1]	36.8, 77.0
Disease Control (CR+PR+SD+Non-CR/Non-PD), n (%)	18 (94.7)
90% CI [1]	77.4, 99.7

[1] Clopper-Pearson method used.
PFIZER CONFIDENTIAL SDTM Creation: 22APR2021 (10:58) Source Data: adrsd Table Generation: 06MAY2021 (10:16)
(Cutoff date : 11Jan2021 Snapshot date : 20Apr2021) Output File: ./csr6/C3441030_expansion/adrsd_borc_s001_1_b
Table 14.2.1.2.1.B PF-06944076 is for Pfizer internal use.

Secondary Efficacy Endpoints Results (Dose Escalation and Expansion Part):

Best Overall Response, OR and DC Based on Investigator Assessment (Dose Escalation Part): None of the subjects treated with talazoparib 0.75 mg QD or 1.0 mg QD had unconfirmed OR (CR or PR). As per derived investigator assessment, the DC (CR + PR + stable disease + non-CR/non-PD) was observed in 4 subjects (44.4% [95% CI: 13.7, 78.8]), of which 3 subjects (50.0% [95% CI: 11.8, 88.2]) were in the talazoparib 1.0 mg QD dose group.

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Time to Event Endpoints - PFS and DoR (Dose Escalation Part): In the dose escalation part at the time of data cut-off, for the analysis of PFS; 8 subjects (88.9%) had an event (PD) and 1 subject (11.1%) was censored due to start of new anti-cancer therapy. The median PFS was 3.0 months (95% CI: 1.2, 4.9), and the PFS rate at 6 months was 13.3% (95% CI: 0.7, 44.1). The evaluation of DoR is not applicable, since none of the subjects treated with talazoparib 0.75 mg QD or 1.0 mg QD had OR (unconfirmed).

Best Overall Response, OR and DC Based on BICR Assessment (Expansion Part): In the expansion part at the time of data cut-off, confirmed OR was observed in 10 subjects (52.6% [90% CI: 32.0, 72.6]) per derived BICR assessment. The confirmed DC (CR + PR + stable disease + non-CR/non-PD) was observed in 17 subjects (89.5% [90% CI: 70.4, 98.1]) per derived BICR assessment.

DC at 16 and 24 Weeks (Expansion Part): The confirmed DC (CR + PR + stable disease + non-CR/non-PD) up to Week 16 was observed in 18 subjects (94.7% [90% CI: 77.4, 99.7]) and in 17 subjects (89.5% [90% CI: 70.4, 98.1]), based on derived investigator and BICR assessments, respectively. The DC based on derived investigator and BICR assessments were stable up to Week 24.

Time to Event Endpoints - TTR, DoR, PFS, and OS (Expansion Part): The median TTR observed for talazoparib 1.0 mg QD was 2.63 months (range: 1.2 months to 9.4 months) based on derived investigator assessment.

In the expansion part, at the time of data cut-off, out of the 11 subjects analyzed for DoR; 5 subjects (45.5%) had an event (PD) and 6 subjects (54.5%) were censored as the subjects were ongoing without an event. The median DoR was 6.8 months (95% CI: 2.7, NE), and the DoR rates at 6 and 12 months were 74.1% (95% CI: 28.9, 93.0) and 19.8% (95% CI: 0.9, 56.9), respectively.

As per derived investigator assessment, 12 subjects (63.2%) had an event (PD) and 7 subjects (36.8%) were censored for the analysis of PFS (subjects were ongoing without an event). The median PFS was 7.2 months (95% CI: 4.1, NE), and the PFS rates at 6 and 12 months were 56.8% (95% CI: 31.7, 75.7) and 28.4% (95% CI: 9.3, 51.4), respectively. As per derived BICR assessment, 11 subjects (57.9%) had an event (PD or death) and other 8 subjects (42.1%) were censored for the analysis of PFS (6 subjects were ongoing without an event and 2 subjects started new anti-cancer therapy). The median PFS was 7.2 months (95% CI: 3.9, NE). The PFS rates at 6 and 12 months were 61.1% (95% CI: 35.3, 79.2) and 28.6% (95% CI: 8.3, 53.4), respectively.

In the expansion part, at the time of data cut-off, 2 subjects (10.5%) had an event (death) for the analysis of OS and other 17 subjects (89.5%) were alive and were censored. The median OS was not estimable and OS rate at 12 months was 84.7% (90% CI: 57.5, 95.1).

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Pharmacokinetic Results:

PK Analysis of Talazoparib (Dose Escalation Part):

Pharmacokinetic Parameters of Talazoparib (Dose Escalation Part):

PK parameters are defined in Table S3, and summarized descriptively in Table S6.

Following a single oral dose of talazoparib in Japanese subjects, talazoparib was absorbed rapidly with median time at which maximum plasma concentration (C_{max}) occurred (T_{max}) of 0.983 hour and 0.967 hour for the talazoparib 0.75 mg QD and 1.0 mg QD dose groups, respectively. Overall, exposures as measured by area under the plasma concentration-time profile (AUC) from time 0 to infinity (AUC_{inf}) and C_{max} increased from 0.75 mg QD to 1.0 mg QD talazoparib dose. Mean terminal half-life ($t_{½}$) were 56.60 hours and 50.73 hours for the talazoparib 0.75 mg QD and 1.0 mg QD dose groups, respectively. Geometric mean apparent clearance (CL/F) were 6.968 L/hr and 5.010 L/hr, and geometric mean V_z/F were 551.8 L and 361.1 L, respectively; for talazoparib 0.75 mg QD and 1.0 mg QD dose groups, respectively.

Following multiple oral dosing on Day 22, median T_{max} was around 1 hour for both the talazoparib 0.75 mg QD and 1.0 mg QD dose groups. Similar to lead-in period; AUC from time 0 to time tau, where tau=24 hours for QD dosing (AUC_{tau}), C_{max} and lowest concentration observed during the dosing interval, increased from 0.75 mg QD to 1.0 mg QD talazoparib dose. Based on AUC_{tau} calculation, geometric mean CL/F were 5.898 L/hr and 4.086 L/hr for the talazoparib 0.75 mg QD and 1.0 mg QD dose groups, respectively. Steady-state generally appeared to have been achieved by Day 15 based on similar median C_{trough} (predose).

The geometric mean for the observed accumulation ratio for AUC_{tau} (R_{ac}) were 2.734 and 2.866 for the talazoparib 0.75 mg QD and 1.0 mg QD dose groups, respectively. The predicted accumulation ratio (R_{ss}) compared AUC_{tau} for multiple-dose administration to AUC_{inf} for single-dose administration, and assessed the linearity in PK exposure from single dose to steady-state. Geometric mean R_{ss} were 1.181 and 1.249 for the talazoparib 0.75 mg QD and 1.0 mg QD dose groups, respectively.

Between-subject variability in plasma talazoparib exposure following single-dose (lead-in) and multiple-dose (Day 22) based on geometric percent coefficient of variation, ranged from 14% to 34% for C_{max} and from 6% to 44% for AUC (AUC_{inf}, AUC from time 0 to the time of the last quantifiable concentration, and AUC_{tau}).

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Table S6. Descriptive Summary of Plasma Talazoparib (PF-06944076) Pharmacokinetic Parameter Values - Dose Escalation Part (Pharmacokinetic Parameter Analysis Set) (Protocol C3441030)

Parameter (Units)[a]	Parameter Summary Statistics by PF-06944076 Treatment Group	
	Talazoparib 0.75 mg (N=3)	Talazoparib 1.0 mg (N=6)
Lead-in Single Dose Period (0 to 168 hrs)		
N1, N2	3, 3	6, 4
AUC_{tau} (ng.hr/mL)	46.55 (20)	85.39 (44)
AUC_{last} (ng.hr/mL)	97.48 (17)	159.1 (33)
AUC_{inf} (ng.hr/mL)	107.5 (12)	199.7 (9)
C_{max} (ng/mL)	7.244 (34)	13.78 (26)
T_{max} (hr)	0.983 (0.750-1.92)	0.967 (0.467-1.98)
$t_{1/2}$ (hr)	56.60±17.860	50.73±10.121
CL/F (L/hr)	6.968 (12)	5.010 (9)
V_z/F (L)	551.8 (42)	361.1 (20)
AUC_{inf} (dn) (ng.hr/mL/mg)	143.6 (12)	199.7 (9)
AUC_{last} (dn) (ng.hr/mL/mg)	129.7 (17)	159.1 (33)
C_{max} (dn) (ng/mL/mg)	9.665 (34)	13.78 (26)
Day 22 Steady State Period (0 to 24 hrs)		
N1, N2	3, 3	6, 4
AUC_{tau} (ng.hr/mL)	127.2 (6)	244.7 (21)
C_{max} (ng/mL)	14.44 (26)	32.84 (14)
C_{min} (ng/mL)	2.175 (8)	3.645 (49)
T_{max} (hr)	1.02 (0.967-1.87)	1.03 (0.733-1.92)
CL/F (L/hr)	5.898 (7)	4.086 (21)
R_{ac}	2.734 (24)	2.866 (64)
R_{ss}	1.181 (12)	1.249 (14)
AUC_{tau} (dn) (ng.hr/mL/mg)	169.4 (7)	244.7 (21)
C_{max} (dn) (ng/mL/mg)	19.24 (26)	32.84 (14)
C_{min} (dn) (ng/mL/mg)	2.897 (8)	3.645 (49)

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Table S6. Descriptive Summary of Plasma Talazoparib (PF-06944076) Pharmacokinetic Parameter Values - Dose Escalation Part (Pharmacokinetic Parameter Analysis Set) (Protocol C3441030)

Parameter (Units)[a]	Parameter Summary Statistics by PF-06944076 Treatment Group	
	Talazoparib 0.75 mg (N=3)	Talazoparib 1.0 mg (N=6)

Source: Table 14.4.5.1.A and 14.4.5.2.A
a. Geometric mean (Geometric %CV) for all except: median (range) for T_{max}; Arithmetic mean±SD for $t_{1/2}$.
N = Total number of subjects in the treatment group in the indicated population.
N1 = Number of subjects contributing to the summary statistics.
N2 = Number of subjects where $t_{1/2}$, AUC_{inf}, AUC_{inf}(dn), CL/F, V_z/F (Lead-in Single Dose Period) and R_{ss} (Day 22 Steady State Period) were determined.
NC = Not calculated.
dn=dose normalized to a 1 mg dose.
PFIZER CONFIDENTIAL SDTM Creation: 20MAY2021 (08:21) Source Data: adpp Table Generation: 04JUN2021 (12:01)
(Cutoff date : 07Nov2019 Snapshot date : 31Jan2020) Output
File: ./csr6/C3441030 dose escalation esub PK/adpp s901 sd d22
Table 14.4.5.3.A PF-06944076 is for Pfizer internal use.

PK Analysis of Talazoparib (Expansion Part):

C_{trough} of Talazoparib (Expansion Part):

Median plasma talazoparib C_{trough} for the expansion part is summarized in Table S7. Following multiple oral doses of talazoparib 1.0 mg in Japanese subjects in the expansion part, the geometric mean talazoparib C_{trough} was similar for Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 4 Day 1, for the talazoparib 1.0 mg QD dose group; although there were subjects who had dose reduction due to any cause. This indicated that there was no substantial change in talazoparib C_{trough} with long-term dosing of 1.0 mg QD after steady-state was reached.

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Table S7. Mean Plasma Talazoparib Ctrough on Cycle 2 (Day 1), Cycle 3 (Day 1) and Cycle 4 (Day 1) - Expansion Part (Pharmacokinetic Concentration Analysis Set) (Protocol C3441030)

	Talazoparib 1.0 mg			
Parameter (Unit)	**Cycle 2 Day 1**	**Cycle 3 Day 1**	**Cycle 4 Day 1**	**Mean C_{trough} on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1[b]**
N	12	13	7	17
C_{trough} (pg/mL)[a]	3098 (40)	3423 (41)	2910 (52)	3346 (39)

Source: Table 14.4.4.1.B
N = Number of subjects
a. Geometric mean (Geometric %CV)
b. Geometric mean (Geometric %CV) of within-patients trough values which were calculated using steady-state trough concentrations at each visit for each patient.
For this calculation, the following 2 conditions were used to meet steady state C_{trough} evaluable criteria:
- C_{trough} following at least 7 consecutive days of at 1.0 mg dose of talazoparib once daily prior to the pre-dose PK sampling.
- C_{trough} have the actual sampling time which was within 24 hours +/- 10% after the dose administered the day prior to the PK pre-dose sampling.
PFIZER CONFIDENTIAL SDTM Creation: 31MAY2021 (18:26) Source Data: adpc Table Generation: 04JUN2021 (10:15)
(Cutoff date : 11Jan2021 Snapshot date : 20Apr2021) Output File: ./csr6/C3441030_expansion_PK/adpc_s101_2_b
Table 14.4.4.2.B PF-06944076 is for Pfizer internal use.

Safety Results:

Duration of Treatment and Dose Intensity:

Dose Escalation Part: The median duration of treatment with talazoparib in the dose escalation part was 84.0 days (range: 29 days to 286 days) with 4 subjects (44.4%) who received talazoparib for ≥91 days (1 subject with 0.75 mg QD and 3 subjects with 1.0 mg QD). The median number of cycles started was 3.0 (range: 1 to 9) and 3 subjects (33.3%) had ≥5 cycles in the dose escalation part. A total of 2 subjects (22.2%) had at least 1 dose interruption, of which 1 subject had dose interruption for ≥3 weeks.

The median cumulative talazoparib dose was 83.0 mg (range: 28.00 mg to 154.50 mg) and the median relative talazoparib dose intensity was 100.0% (range: 54.2% to 100.0%), which takes into account the dose reductions due to any cause. Eight subjects had no dose reduction and 1 subject had 2 dose level reductions due to any cause.

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Expansion Part: The median duration of treatment with talazoparib in the expansion part was 196.0 days (range: 80 days to 502 days), with 17 subjects (89.5%) who received talazoparib for ≥91 days. The median number of cycles started was 7.0 (range: 2 to 19) and 16 subjects (84.2%) had ≥5 cycles in the expansion part. A total of 14 subjects (73.7%) had at least 1 dose interruption, of which 9 subjects had dose interruption for ≥3 weeks.

The median cumulative talazoparib dose was 156.50 mg (range: 49.00 mg to 486.00 mg) and the median relative talazoparib dose intensity was 75.0% (range: 53.8% to 100.0%), which takes into account the dose reductions due to any cause. Eight subjects had no dose reduction, 7 subjects (36.8%) had 1 dose level and 4 subjects had 2 dose level reductions due to any cause.

Primary Endpoint Results - First Cycle DLTs (Dose Escalation Part)

A total of 9 subjects were enrolled in the dose escalation part and DLTs were not reported in any subjects receiving talazoparib 0.75 mg QD (3 subjects) or talazoparib 1.0 mg QD (6 subjects). Therefore, the RP2D of single-agent talazoparib was determined to be 1.0 mg QD in Japanese adult subjects with advanced solid tumors.

Treatment-Emergent Adverse Events:

When necessary, TEAEs were manageable by means of dosing interruption, dose reduction, and/or standard supportive medical therapy.

Dose Escalation Part:

All 9 subjects reported at least 1 TEAE of which, 1 subject (11.1%) reported an SAE (brain cancer metastatic). A total of 29 TEAEs were reported, of which 11 TEAEs in 5 subjects (55.6%) were treatment-related. No deaths were reported during the dose escalation part of the study. A total of 3 subjects (33.3%) had Grade ≥3 TEAEs and Grade ≥3 TEAE in 1 subject was considered as related to the study treatment. One subject (11.1%) had a dose reduction and 2 subjects (22.2%) had an interruption of study treatment associated with treatment-related TEAEs. No subject discontinued the study treatment or discontinued from the study due to TEAEs.

Summaries of all-causality and treatment-related TEAEs by MedDRA preferred terms (PTs) with selected cluster terms for the dose escalation part are presented in Table S8 and Table S9, respectively.

For the dose escalation part, the most commonly reported all-causality TEAEs (≥2 subjects) were anemia, ALT increased, neutropenia, rash maculo-papular, stomatitis, and thrombocytopenia. The most commonly reported treatment-related TEAEs (≥2 subjects) were neutropenia, stomatitis, and thrombocytopenia.

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Table S8. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term with Selected Cluster Terms in Decreasing Frequency Order (All Causalities) - Dose Escalation Part (Safety Analysis Set) (Protocol C3441030)

Number of Subjects Evaluable for AEs	Talazoparib 0.75 mg (N=3)	Talazoparib 1.0 mg (N=6)	Total (N=9)
Number (%) of Subjects: by Preferred Term or Cluster Term	n (%)	n (%)	n (%)
ANEMIA	0	2 (33.3)	2 (22.2)
Alanine aminotransferase increased	1 (33.3)	1 (16.7)	2 (22.2)
NEUTROPENIA	1 (33.3)	1 (16.7)	2 (22.2)
Rash maculo-papular	0	2 (33.3)	2 (22.2)
Stomatitis	0	2 (33.3)	2 (22.2)
THROMBOCYTOPENIA	0	2 (33.3)	2 (22.2)
Arthralgia	1 (33.3)	0	1 (11.1)
Aspartate aminotransferase increased	0	1 (16.7)	1 (11.1)
Blood alkaline phosphatase increased	1 (33.3)	0	1 (11.1)
Brain cancer metastatic	1 (33.3)	0	1 (11.1)
Cheilitis	0	1 (16.7)	1 (11.1)
Dental caries	0	1 (16.7)	1 (11.1)
Dysgeusia	1 (33.3)	0	1 (11.1)
Dyshidrotic eczema	0	1 (16.7)	1 (11.1)
Essential hypertension	0	1 (16.7)	1 (11.1)
LEUKOPENIA	0	1 (16.7)	1 (11.1)
Nausea	0	1 (16.7)	1 (11.1)
Oedema peripheral	0	1 (16.7)	1 (11.1)
Otitis media acute	1 (33.3)	0	1 (11.1)
Sinusitis	1 (33.3)	0	1 (11.1)
Sputum increased	0	1 (16.7)	1 (11.1)
Toothache	0	1 (16.7)	1 (11.1)
Tumour pain	1 (33.3)	0	1 (11.1)

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Table S8. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term with Selected Cluster Terms in Decreasing Frequency Order (All Causalities) - Dose Escalation Part (Safety Analysis Set) (Protocol C3441030)

Number of Subjects Evaluable for AEs	Talazoparib 0.75 mg (N=3)	Talazoparib 1.0 mg (N=6)	Total (N=9)
Number (%) of Subjects: by Preferred Term or Cluster Term	**n (%)**	**n (%)**	**n (%)**

Subjects are only counted once per treatment per event.
Includes data up to 30 days after last dose of study drug.
The following preferred terms fall under each cluster term: NEUTROPENIA - Neutropenia or Neutrophil count decreased;
LEUKOPENIA - Leukopenia or White blood cell count decreased; LYMPHOPENIA - Lymphocyte count decreased or Lymphopenia;
THROMBOCYTOPENIA - Platelet count decreased or Thrombocytopenia; ANEMIA - Anaemia or Haematocrit decreased or Haemoglobin decreased.
MedDRA v23.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2021 (15:08) Source Data: adae Table Generation: 12MAY2021 (15:36)
(Cutoff date : 07Nov2019 Snapshot date : 31Jan2020) Output File: ./csr6/C3441030_dose_escalation_esub/adae_s180 Table 14.3.1.2.3.A PF-06944076 is for Pfizer internal use.

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Table S9. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term with Selected Cluster Terms in Decreasing Frequency Order (Treatment Related) - Dose Escalation Part (Safety Analysis Set) (Protocol C3441030)

Number of Subjects Evaluable for AEs	Talazoparib 0.75 mg (N=3)	Talazoparib 1.0 mg (N=6)	Total (N=9)
Number (%) of Subjects: by Preferred Term or Cluster Term	n (%)	n (%)	n (%)
NEUTROPENIA	1 (33.3)	1 (16.7)	2 (22.2)
Stomatitis	0	2 (33.3)	2 (22.2)
THROMBOCYTOPENIA	0	2 (33.3)	2 (22.2)
ANEMIA	0	1 (16.7)	1 (11.1)
Dysgeusia	1 (33.3)	0	1 (11.1)
LEUKOPENIA	0	1 (16.7)	1 (11.1)
Nausea	0	1 (16.7)	1 (11.1)
Rash maculo-papular	0	1 (16.7)	1 (11.1)

Subjects are only counted once per treatment per event.
Includes data up to 30 days after last dose of study drug.
The following preferred terms fall under each cluster term: NEUTROPENIA - Neutropenia or Neutrophil count decreased;
LEUKOPENIA - Leukopenia or White blood cell count decreased; LYMPHOPENIA - Lymphocyte count decreased or Lymphopenia;
THROMBOCYTOPENIA - Platelet count decreased or Thrombocytopenia; ANEMIA - Anaemia or Haematocrit decreased or Haemoglobin decreased.
MedDRA v23.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2021 (15:08) Source Data: adae Table Generation: 12MAY2021 (15:37)
(Cutoff date : 07Nov2019 Snapshot date : 31Jan2020) Output File: ./csr6/C3441030_dose_escalation_esub/adae_s183 Table 14.3.1.3.3.A PF-06944076 is for Pfizer internal use.

Expansion Part:

All 19 subjects reported at least 1 TEAE, of which 1 subject (5.3%) reported an SAE (cholelithiasis). A total of 124 TEAEs were reported, of which 94 TEAEs in 19 subjects were treatment-related.

During the expansion part, 2 deaths which were not considered related to study drug were reported after the safety reporting period; 1 subject died on Day 345 due to disease progression and other subject died on Day 194 for which cause was unknown. A total of 11 subjects (57.9%) had Grade ≥3 TEAEs and Grade ≥3 TEAEs in 10 subjects were considered as related to the study treatment. Nine subjects (47.4%) had a dose reduction and

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8 subjects (42.1%) had an interruption of study treatment associated with treatment-related TEAEs. No subject discontinued the study treatment or discontinued from the study due to TEAEs.

Summaries of all-causality and treatment-related TEAEs by MedDRA PT with selected cluster terms for the expansion part are presented in Table S10 and Table S11, respectively.

For the expansion part, the most commonly reported all-causality TEAEs (≥20% of subjects) were myelosuppression (anemia, neutropenia, leukopenia, thrombocytopenia), stomatitis, alopecia, malaise, gastrointestinal toxicity (nausea, constipation) and headache. The most commonly reported treatment-related TEAEs (≥20% of subjects) were myelosuppression (anemia, neutropenia, leukopenia, thrombocytopenia), stomatitis, alopecia, and malaise.

Table S10. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term with Selected Cluster Terms in Decreasing Frequency Order (All Causalities) - Expansion Part (Safety Analysis Set) (Protocol C3441030)

Number of Subjects Evaluable for AEs	Talazoparib 1.0 mg (N=19)
Number (%) of Subjects: by Preferred Term or Cluster Term	n (%)
ANEMIA	13 (68.4)
NEUTROPENIA	12 (63.2)
LEUKOPENIA	8 (42.1)
Stomatitis	7 (36.8)
Alopecia	6 (31.6)
THROMBOCYTOPENIA	6 (31.6)
Malaise	5 (26.3)
Nausea	5 (26.3)
Constipation	4 (21.1)
Headache	4 (21.1)
Dizziness	3 (15.8)
Fatigue	3 (15.8)
Cheilitis	2 (10.5)
Cough	2 (10.5)
Decreased appetite	2 (10.5)
Diarrhoea	2 (10.5)
Dysgeusia	2 (10.5)
Dyspnoea	2 (10.5)
Nasopharyngitis	2 (10.5)
Oropharyngeal pain	2 (10.5)

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Table S10. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term with Selected Cluster Terms in Decreasing Frequency Order (All Causalities) - Expansion Part (Safety Analysis Set) (Protocol C3441030)

Number of Subjects Evaluable for AEs	Talazoparib 1.0 mg (N=19)
Number (%) of Subjects: by Preferred Term or Cluster Term	**n (%)**
Abdominal pain	1 (5.3)
Abdominal pain upper	1 (5.3)
Alanine aminotransferase increased	1 (5.3)
Arthralgia	1 (5.3)
Ascites	1 (5.3)
Asthenopia	1 (5.3)
Cholelithiasis	1 (5.3)
Conjunctivitis	1 (5.3)
Dermatitis contact	1 (5.3)
Dry eye	1 (5.3)
Dry skin	1 (5.3)
Epigastric discomfort	1 (5.3)
Fall	1 (5.3)
Gastritis	1 (5.3)
Hyperglycaemia	1 (5.3)
LYMPHOPENIA	1 (5.3)
Myalgia	1 (5.3)
Nail pigmentation	1 (5.3)
Pain in extremity	1 (5.3)
Pain of skin	1 (5.3)
Paralysis recurrent laryngeal nerve	1 (5.3)
Pericardial effusion	1 (5.3)
Pruritus	1 (5.3)
Pyrexia	1 (5.3)
Rash	1 (5.3)
Rash maculo-papular	1 (5.3)
Rib fracture	1 (5.3)
Tooth fracture	1 (5.3)
Tooth loss	1 (5.3)
Toothache	1 (5.3)
Urticaria	1 (5.3)
Vomiting	1 (5.3)

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Table S10. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term with Selected Cluster Terms in Decreasing Frequency Order (All Causalities) - Expansion Part (Safety Analysis Set) (Protocol C3441030)

Number of Subjects Evaluable for AEs	Talazoparib 1.0 mg (N=19)
Number (%) of Subjects: by Preferred Term or Cluster Term	**n (%)**

Subjects are only counted once per treatment per event.
Includes data up to 30 days after last dose of study drug.
The following preferred terms fall under each cluster term: NEUTROPENIA - Neutropenia or Neutrophil count decreased;
LEUKOPENIA - Leukopenia or White blood cell count decreased; LYMPHOPENIA - Lymphocyte count decreased or Lymphopenia;
THROMBOCYTOPENIA - Platelet count decreased or Thrombocytopenia; ANEMIA - Anaemia or Haematocrit decreased or Haemoglobin decreased.
MedDRA v23.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22APR2021 (10:58) Source Data: adae Table Generation: 06MAY2021 (10:16)
(Cutoff date : 11Jan2021 Snapshot date : 20Apr2021) Output File: ./csr6/C3441030 expansion/adae s180 b
Table 14.3.1.2.3.B PF-06944076 is for Pfizer internal use.

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Table S11. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term with Selected Cluster Terms in Decreasing Frequency Order (Treatment Related) - Expansion Part (Safety Analysis Set) (Protocol C3441030)

Number of Subjects Evaluable for AEs	Talazoparib 1.0 mg (N=19)
Number (%) of Subjects: by Preferred Term or Cluster Term	**n (%)**
ANEMIA	13 (68.4)
NEUTROPENIA	12 (63.2)
LEUKOPENIA	8 (42.1)
Alopecia	6 (31.6)
Stomatitis	6 (31.6)
THROMBOCYTOPENIA	6 (31.6)
Malaise	5 (26.3)
Constipation	3 (15.8)
Dizziness	3 (15.8)
Headache	3 (15.8)
Nausea	3 (15.8)
Dysgeusia	2 (10.5)
Dyspnoea	2 (10.5)
Fatigue	2 (10.5)
Abdominal pain upper	1 (5.3)
Alanine aminotransferase increased	1 (5.3)
Arthralgia	1 (5.3)
Cheilitis	1 (5.3)
Decreased appetite	1 (5.3)
Dry eye	1 (5.3)
Dry skin	1 (5.3)
Epigastric discomfort	1 (5.3)
Gastritis	1 (5.3)
Hyperglycaemia	1 (5.3)
LYMPHOPENIA	1 (5.3)
Myalgia	1 (5.3)
Nail pigmentation	1 (5.3)
Pain of skin	1 (5.3)
Pericardial effusion	1 (5.3)
Pruritus	1 (5.3)
Rash maculo-papular	1 (5.3)

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Table S11. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term with Selected Cluster Terms in Decreasing Frequency Order (Treatment Related) - Expansion Part (Safety Analysis Set) (Protocol C3441030)

Number of Subjects Evaluable for AEs	Talazoparib 1.0 mg (N=19)
Number (%) of Subjects: by Preferred Term or Cluster Term	**n (%)**
Tooth fracture	1 (5.3)
Urticaria	1 (5.3)
Vomiting	1 (5.3)

Subjects are only counted once per treatment per event.
Includes data up to 30 days after last dose of study drug.
The following preferred terms fall under each cluster term: NEUTROPENIA - Neutropenia or Neutrophil count decreased;
LEUKOPENIA - Leukopenia or White blood cell count decreased; LYMPHOPENIA - Lymphocyte count decreased or Lymphopenia;
THROMBOCYTOPENIA - Platelet count decreased or Thrombocytopenia; ANEMIA - Anaemia or Haematocrit decreased or Haemoglobin decreased.
MedDRA v23.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22APR2021 (10:58) Source Data: adae Table Generation: 06MAY2021 (10:16)
(Cutoff date : 11Jan2021 Snapshot date : 20Apr2021) Output File: ./csr6/C3441030 expansion/adae s183 b
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Grade 3 or Higher Treatment-Emergent Adverse Events:

In the dose escalation part, no Grade 4 or Grade 5 TEAEs reported. Three subjects had all-causality Grade 3 TEAEs (anemia, brain cancer metastatic [1 subject each], and white blood cell [WBC] count decreased and 2 events of neutrophil count decreased [same subject]). Of the 3 subjects with Grade 3 TEAEs; TEAEs in 1 subject were considered treatment-related (WBC count decreased and 2 events of neutrophil count decreased).

In the expansion part, no Grade 4 or Grade 5 TEAEs were reported. A total of 11 subjects had all-causality Grade 3 TEAEs (anemia [9 subjects], neutrophil count decreased [4 subjects], WBC count decreased [2 subjects] and cholelithiasis [1 subject]). Except for the event of cholelithiasis in 1 subject, all Grade 3 TEAEs in remaining 10 subjects were considered treatment-related.

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Serious Adverse Events:

In the dose escalation part, 1 subject treated with talazoparib 0.75 mg QD in the dose escalation part, reported a Grade 3 SAE of brain cancer metastatic, which was considered not related to study treatment.

In the expansion part, 1 subject treated with talazoparib 1.0 mg QD in the expansion part, reported a Grade 3 SAE of cholelithiasis, which was considered not related to study treatment.

Other Significant Adverse Events:

None of the subjects reported TEAEs of acute myeloid leukemia, myelodysplastic syndromes, pneumonitits, venous embolic or thrombotic events; during the dose escalation part or the expansion part.

Laboratory Results:

Hematology:

Dose Escalation Part:

For hemoglobin decreased (anemia), Grade ≥3 value was observed on-treatment for 1 subject (11.1%), whose baseline grade was Grade 0.

For lymphocyte count decreased, Grade ≥3 value was observed on-treatment for 1 subject (11.1%), whose baseline grade was Grade 1.

For neutrophil count decreased, Grade ≥3 value was observed on-treatment for 1 subject (11.1%), whose baseline grade was Grade 0.

For platelet count decreased, none of the subjects had Grade ≥3 values observed on-treatment.

For WBC decreased, Grade ≥3 value was observed on-treatment for 1 subject (11.1%), whose baseline grade was Grade 0.

Expansion Part:

For hemoglobin decreased (anemia), Grade ≥3 values were observed on-treatment for 9 subjects (47.4%). The baseline grades for the 9 subjects with Grade ≥3 on-treatment were, Grade 0 for 7 subjects and Grade 1 for 2 subjects.

For lymphocyte count decreased, Grade ≥3 values were observed on-treatment for 2 subjects (10.5%), the baseline grade for both the subjects was Grade 2.

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For neutrophil count decreased, Grade ≥3 values were observed on-treatment for 4 subjects (21.1%), the baseline grade for all the 4 subjects was Grade 0.

For platelet count decreased, none of the subjects had Grade ≥3 values observed on-treatment.

For WBC decreased, Grade ≥3 values were observed on-treatment for 2 subjects (10.5%), the baseline grade for both the subjects was Grade 0.

Serum Chemistry:

During the dose escalation and expansion part, no on-treatment Grade 3, Grade 4 or Grade 5 values were observed for the chemistry parameters.

Possible DILI:

In the dose escalation part, none of the subjects in the dose escalation part reported any hyperbilirubinemia (total bilirubin >2 × [ULN) or Temple's Corollary (total bilirubin <2 × ULN and ALT >3 × ULN) or possible Hy's Law (total bilirubin >2 × ULN and ALT >3 × ULN) events.

In the expansion part, 1 subject treated with talazoparib 1.0 mg QD reported a Temple's Corollary event. No hyperbilirubinemia or possible Hy's Law events were reported in the expansion part.

Vital Signs:

In the dose escalation part, 1 subject treated with talazoparib 0.75 mg QD reported sitting systolic blood pressure value of <90 mm Hg and 2 subjects treated with talazoparib 1.0 mg QD had sitting systolic blood pressure decreased ≥30 mm Hg from baseline.

In the expansion part, 1 subject reported sitting pulse rate value of >120 bpm and 2 subjects each, reported sitting diastolic blood pressure value of <50 mm Hg and sitting systolic blood pressure value of <90 mm Hg. For 1 subject, the sitting systolic blood pressure decreased ≥30 mm Hg from baseline.

No clinically meaningful differences in vital signs (including diastolic and systolic blood pressure, or pulse rate) were observed during the dose escalation or expansion part.

Electrocardiogram:

In the dose escalation part, 4 subjects each had on-treatment corrected QT interval (QTc) and derived heart rate-corrected QT interval by Bazett's formula (QTcB) intervals between 450 to 480 msec; 1 subject each had on-treatment QRS interval of ≥140 msec; QTc and heart rate-corrected QT interval by Fridericia's formula (QTcF) intervals of ≥500 msec; derived QTcF interval of 480 to 500 msec and derived QTcB interval of ≥500 msec.

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In the expansion part, 1 subject (9.1%) had on-treatment QTc interval of 450 to 480 msec and 2 subjects (18.2%) had on-treatment derived QTcB interval of 450 to 480 msec.

No clinically significant ECG abnormality was reported during both the dose escalation and expansion part.

Conclusions:

Dose Escalation Part:

Efficacy Conclusions:

- These data from the dose escalation part provided preliminary evidence (DC and PFS data) of the anti-tumor effects of talazoparib in subjects with advanced solid tumors with no molecular selection for deoxyribonucleic acid damage response gene mutations.

- Investigator assessed anti-tumor responses (unconfirmed) showed that no subjects at either talazoparib dose level (0.75 mg QD or 1.0 mg QD) achieved a CR or PR (OR), and overall DC (CR+PR+ stable disease + non-CR/non-PD) was seen in 4 subjects.

- Final data showed a best OR of stable disease for 2 subjects, with prostate cancer and gastrointestinal stromal tumor at talazoparib 1.0 mg QD; and a best OR of non-CR/non-PD for 1 subject with prostate cancer at each talazoparib dose level (0.75 mg QD and 1.0 mg QD, each).

PK Conclusions:

- Following a single oral dose of talazoparib in Japanese subjects, talazoparib was absorbed rapidly with median T_{max} of 0.983 hour and 0.967 hour for the talazoparib 0.75 mg QD and 1.0 mg QD dose groups, respectively. Mean terminal $t_{½}$ were 56.60 hours and 50.73 hours for the talazoparib 0.75 mg QD and 1.0 mg QD dose groups, respectively.

- Following multiple oral dosing on Day 22, median T_{max} was around 1 hour for both the talazoparib 0.75 mg QD and 1.0 mg QD dose groups. Steady-state generally appeared to have been achieved by Day 15 based on similar median C_{trough} (predose) concentrations. Geometric mean R_{ac} were 2.734 and 2.866, and geometric mean R_{ss} were 1.181 and 1.249 for the talazoparib 0.75 mg QD and 1.0 mg QD dose groups, respectively.

Safety Conclusions:

- Single-agent talazoparib was generally well tolerated and the RP2D was determined to be 1.0 mg QD in Japanese adult subjects with advanced solid tumors.

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- No DLTs were reported in any subjects receiving talazoparib 0.75 mg QD (n=3) or 1.0 mg QD (n=6).

- The most commonly reported all-causality TEAEs (≥2 subjects) were anemia, ALT increased, neutropenia, rash maculo-papular, stomatitis, and thrombocytopenia.

- No Grade 4 or Grade 5 TEAEs were reported; 3 subjects had Grade 3 TEAEs (anemia, brain metastases [1 subject each], and WBC count decreased and 2 events of neutrophil count decreased [same subject]).

- Two subjects temporarily discontinued treatment due to a TEAE, and 1 subject required a dose reduction due to neutrophil count decreased (for talazoparib 1 mg QD).

Expansion Part:

Efficacy Conclusions:

- Talazoparib 1.0 mg QD showed clinical meaningful anti-tumor activity in Japanese subjects with gBRCAm locally advanced/metastatic breast cancer with confirmed OR rate as assessed using RECIST Version 1.1 by investigator assessment of 57.9% (90% CI: 36.8, 77.0). The lower limit of 2-sided 90% CI exceeded the pre-defined threshold of 18.4%.

- Based on investigator assessment, out of 19 subjects with measurable disease at baseline, no subjects had confirmed CR and 11 subjects (57.9%) had a confirmed PR. Best responses for the remaining subjects were stable disease (7 subjects [36.8%]) and PD (1 subject [5.3%]). The median TTR was 2.63 months (range: 1.2 months to 9.4 months) and median DoR was 6.8 months (95% CI: 2.7, NE). No subjects were not evaluable for OR.

- Based on investigator assessment, high DC rate (94.7% [90% CI: 77.4, 99.7]) was observed.

- Similar OR rate 52.6% (90% CI: 32.0, 72.6) and DC rate 89.5% (90% CI: 70.4, 98.1) were observed by BICR assessment, which also supported the primary analysis based on investigator assessment.

- Median PFS was 7.2 months (95% CI: 4.1, NE) and OS rate at 12 months was 84.7% (90% CI: 57.5, 95.1).

PK Conclusions:

- Following multiple oral dosing of talazoparib 1.0 mg in the expansion part, the geometric mean talazoparib C_{trough} was similar for Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 4 Day 1, for the talazoparib 1.0 mg QD dose group; although there were subjects who had dose

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reduction due to any cause. This indicated that there was no substantial change in talazoparib C_{trough} with long-term dosing of 1.0 mg QD after steady-state was reached.

Safety Conclusions:

- Talazoparib 1.0 mg QD was generally well tolerated with a median relative dose intensity of 75%; and, when necessary, AEs were manageable through dosing interruption, dose reduction, and/or standard supportive medical therapy. No subjects experienced an AE other than disease progression that was associated with permanent discontinuation of talazoparib.

- The most commonly reported TEAEs (≥20% of subjects) were myelosuppression (anemia, neutropenia, leukopenia, thrombocytopenia), stomatitis, alopecia, malaise, gastrointestinal toxicity (nausea, constipation) and headache.

- No Grade 4 or Grade 5 TEAEs were reported; 11 subjects had Grade 3 TEAEs (anemia [9 subjects], neutrophil count decreased [4 subjects], WBC count decreased [2 subjects] and cholelithiasis [1 subject]).

- Two deaths were reported after the safety reporting period; 1 subject died due to disease progression and the cause of the other subject's death was unknown.

- Total of 8 subjects temporarily discontinued treatment due to a TEAE (anemia [6 subjects], neutrophil count decreased [2 subjects], dyspnoea and headache [1 subject each]), and total of 9 subjects required a dose reduction for anemia (8 subjects), neutrophil count decreased (4 subjects) and platelet count decreased (1 subject).

- There were no clinically meaningful changes in vital signs and ECG during the study.

Overall Conclusion

Single-agent talazoparib was generally well tolerated and the RP2D was determined to be 1.0 mg QD in Japanese adult subjects with advanced solid tumors. AEs were manageable through dosing interruption, dose reduction, and/or standard supportive medical therapy. No new safety signals were identified. Talazoparib at a dose of 1.0 mg QD showed clinically meaningful anti-tumor activity in Japanese subjects with gBRCAm locally advanced/metastatic breast cancer in the expansion part. Absorption of talazoparib was rapid after a single oral dose and steady-state appeared to have been achieved by Day 15.