SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-64091742 niraparib

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Status: Approved

Date: 26 February 2020

Prepared by: Janssen Research & Development, LLC

Protocol No.: 64091742PCR1001
Title of Study: A Safety and Pharmacokinetics Study of Niraparib plus Androgen Receptor-targeted Therapy (Apalutamide or Abiraterone Acetate plus Prednisone) in Men with Metastatic Castration-resistant Prostate Cancer

Study Name: The Bedivere Study

EudraCT Number: 2016-002694-35

NCT No.: NCT02924766

Clinical Registry No.: CR108230

Principal Investigator(s): Fred Saad, MD; CHUM- Centre Hospitalier Universitaire de Montreal, PPD, Canada

Study Centers: United States (4), Canada (2).

Publication (Reference): None

Study Period: 24 October 2016 to 16 July 2019

Phase of Development: 1b

Primary and Secondary Objectives:

Primary	
To determine the safety of niraparib in combination with AR-targeted therapy in men with mCRPC	Part 1 (Dose Selection): RP2D of niraparib in combination with 240 mg apalutamide or 1,000 mg abiraterone acetate plus 10 mg prednisone (5 mg twice daily) Part 2 (Dose Expansion): Incidence and severity of AEs
Secondary	
To evaluate the PK of niraparib and its major metabolite (M1) in combination with AR-targeted therapy	Single-dose and steady-state PK parameters of niraparib and its major metabolite (M1) when dosed in combination with apalutamide or abiraterone acetate plus 10 mg prednisone (5 mg twice daily)
To evaluate the PK of apalutamide and its metabolite (JNJ-56142060; M3) or abiraterone in combination	Steady-state PK parameters of apalutamide and its metabolite (JNJ-56142060; M3) or abiraterone acetate

with niraparib	when dosed in combination with niraparib
AE=adverse event; AR=androgen receptor; mCRPC=metastatic castration-resistant prostate cancer; PK=pharmacokinetics; PSA=prostate-specific antigen; RP2D=recommended Phase 2 dose.	

Methodology: This was a Phase 1b, multicenter, open-label, dose-selection study with dose expansion that enrolled adult subjects with metastatic castration-resistant prostate cancer (mCRPC), with or without DNA-repair anomalies, who received at least 1 line of prior taxane-based chemotherapy and 1 line of androgen receptor (AR)-targeted therapy. The study was comprised of a standard 3+3 dose selection (Part 1), followed by a dose expansion (Part 2) once a recommended Phase 2 dose (RP2D) of niraparib in combination with either 240 mg apalutamide (niraparib+apalutamide) or 1,000 mg abiraterone acetate and 10 mg prednisone (niraparib+AA-P) daily was determined.

The RP2D for niraparib was defined as the clinical dose of 300 mg or the dose that was comparable to or less than the exposure of 300 mg niraparib monotherapy (ie, mean C_{max} 1,398 ng/mL [range: 575 to 2,501 ng/mL] or mean AUC_{tau} 21,380 ng.h/mL [range: 9,159 to 37,324 ng.h/mL]). If a significant drug-drug interaction was observed, then exposure must have remained within therapeutic limits for a dose to be selected. The RP2D must also have had <33% of subjects experienced a dose-limiting toxicity (DLT). The DLT-evaluation period was the first 28 days (Cycle 1). Safety monitoring and decisions regarding dose escalation/de-escalation were made by a safety evaluation team.

Number of Subjects (planned and analyzed):

Planned: As this was a "3+3" study design, a formal sample size determination for Part 1 was not applicable. The planned number of subjects for Part 1 was dependent upon the number of dose escalations needed until the plasma concentration of niraparib was comparable to 300 mg monotherapy or when the MTD was reached, whichever occurred first. The planned number of subjects for Part 2 was based upon estimates of adverse event (AE) incidence rates. It was expected that 30 subjects would be enrolled into Part 2.

Analyzed:

- All subjects who were enrolled in the study were in the Enrolled Population, which was used for subject disposition and antitumor activity analyses.
- All subjects who received at least 1 dose of study drug comprised the Safety Population.
- All subjects who received at least 1 dose of study drug and had sufficient and interpretable PK assessments to calculate PK parameters comprised the PK-evaluable Population.

Diagnosis and Main Criteria for Inclusion: Male subjects >18 years of age (or local age of legal consent) with mCRPC previously treated with at least 1 line of prior taxane-based chemotherapy and at least 1 line of AR-targeted therapy. DNA-repair anomalies were not required for inclusion.

Test Product, Dose and Mode of Administration, Batch No.: Niraparib: 200 or 300 mg administered as 100-mg capsules orally once daily, Batch Nos: B230550, B235620, B244846; Apalutamide: 240 mg administered as 4 x 60-mg tablets orally once daily, Batch Nos: 4373261, 4373598; Abiraterone acetate: 1,000 mg administered as 4 x 250-mg tablets orally once daily, Batch Nos: 4374175, 4376267, 4377148; Prednisone: 10 mg administered as 5-mg tablets orally twice daily, Batch Nos: 4374176, 4374349, 4374396, 4376156

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: Subjects received study treatment until disease progression, unacceptable toxicity, or death.

Criteria for Evaluation:

Safety

The safety parameters evaluated were the incidence, intensity, and type of AEs, vital sign measurements, electrocardiograms, physical examinations, Eastern Cooperative Oncology Group Performance Status, and clinical laboratory measurements.

Pharmacokinetics and Pharmacodynamics

In Part 1, serial PK samples for niraparib and its major metabolite, M1, were collected at various timepoints on Cycle 1 Day 1 and Cycle 2 Day 1 with trough samples collected predose on Cycle 3 Day 1 and on Day 1 of every 3 cycles afterwards. Serial PK samples for apalutamide and its metabolite, M3, or abiraterone were collected at various timepoints on Cycle 1 Day 28 with trough samples collected predose on Cycle 3 Day 1 and on Day 1 of every 3 cycles afterwards.

In Part 2, serial PK samples for niraparib and its major metabolite, M1, were collected at various timepoints on Cycle 2 Day 1with trough samples collected predose on Cycle 3 Day 1 and on Day 1 of every 3 cycles afterwards. Serial trough blood samples for analysis of abiraterone were collected predose at Cycles 2 and 3, and then every 3 cycles thereafter.

Plasma samples were analyzed to determine concentrations of apalutamide using a validated, specific, and sensitive liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor's Department of Bioanalysis. The following PK parameters were derived accordingly: maximum observed plasma analyte concentration (C_{max}), the actual time to reach the maximum observed plasma analyte concentration (t_{max}), plasma analyte concentration versus time curve from dose to 24 hours afterwards (AUC_{24h}), trough plasma concentration prior to dosing or at the end of the dosing interval of any dose other than the first dose (C_{trough}), and metabolite to parent (M/P) ratio AUC_{24hr}.

Statistical Methods:

Safety Analyses

Treatment-emergent AEs (TEAEs) were those reported up to 30 days after the last dose of study drug. Summaries or listings were provided for all TEAEs, including DLTs, and clinical laboratory results. Vital sign and ECG assessments were summarized using descriptive statistics, summaries and listings.

Pharmacokinetic Analyses

The PK parameters calculated for niraparib and its metabolite M1, apalutamide and its metabolite M3, and abiraterone acetate were C_{max}, t_{max}, AUC_{24h}, C_{trough}, and metabolite to parent (M/P) ratio AUC_{24hr}. Summary statistics (number, mean, standard deviation [SD], percent coefficient of variation [%CV], geometric mean, median, minimum, and maximum) were calculated for the plasma concentrations of each analyte at each time point, and for the derived plasma PK parameters. Plasma concentration time graphs of each analyte were prepared as well as graphs of the mean plasma concentration time profiles and overlay graphs with combined individual plasma concentration time profiles.

RESULTS:

STUDY POPULATION:

The number of subjects enrolled and included in the analyses, by treatment group and niraparib dose cohort, is presented in the table below.

Analysis Populations (Study 64091742PCR1001)

	Niraparib+Apalutamide (240 mg)		Niraparib+AA-P (1,000 mg/10 mg)	
	200 mg	300 mg	200 mg	300 mg
Enrolled	3 (100.0%)	3 (100.0%)	19 (100.0%)	8 (100.0%)
Safety Population	3 (100.0%)	3 (100.0%)	19 (100.0%)	8 (100.0%)
PK-evaluable Population				
Cycle 1, Day 1	na	na	4 (21.1%)	7 (87.5%)
Cycle 1, Day 28	3 (100.0%)	2 (66.7%)	na	na
Cycle 2, Day 1	na	na	11 (57.9%)	3 (37.5%)

na=not applicable; PK=pharmacokinetic
Percentages are of the Enrolled Population.

Thirty-three subjects were enrolled and treated; 6 in the niraparib+apalutamide group and 27 in the niraparib+AA-P group. The number of subjects enrolled by treatment group and niraparib dose cohort along with the reasons for discontinuation are presented in the table below.

Treatment Disposition; Safety Analysis Set (Study 64091742PCR1001)

	Niraparib+Apalutamide (240 mg) (N=6)		Niraparib+AA-P (1,000 mg/10 mg) (N=27)	
	200 mg	300 mg	200 mg	300 mg
Analysis Set: Safety	n=3	n=3	n=19	n=8
Discontinued study treatment	3 (100.0%)	3 (100.0%)	19 (100.0%)	8 (100.0%)
Reasons for Discontinuation				
Adverse event	1 (33.3%)	2 (66.7%)	4 (21.1%)	1 (12.5%)
Progressive disease	2 (66.7%)	1 (33.3%)	10 (52.6%)	5 (62.5%)
Physician decision	0	0	2 (10.5%)	0
Withdrawal by subject	0	0	3 (15.8%)	1 (12.5%)
Death	0	0	0	1 (12.5%)

Note: Percentages are calculated with the number of safety subjects in each cohort as the denominator.

SAFETY RESULTS:

Niraparib+Apalutamide:

The overall summary of TEAEs in the niraparib+apalutamide group is presented in the table below. All 6 subjects receiving niraparib+apalutamide experienced at least 1 TEAE.

Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (Study 64091742PCR1001)- Niraparib+Apalutamide

	Niraparib + Apalutamide (240 mg)		
	200 mg	300 mg	All Doses
Analysis set: Safety	n=3	n=3	n=6
Subjects with 1 or more:			
AEs	3 (100.0%)	3 (100.0%)	6 (100.0%)
Related AEs [a]	3 (100.0%)	3 (100.0%)	6 (100.0%)
AEs leading to death [b, c]	0	0	0
Serious AEs	1 (33.3%)	1 (33.3%)	2 (33.3%)
Related serious AEs	1 (33.3%)	1 (33.3%)	2 (33.3%)
AEs leading to discontinuation of study agent [d]	1 (33.3%)	2 (66.7%)	3 (50.0%)
Grade 3 or 4 AEs	2 (66.7%)	3 (100.0%)	5 (83.3%)

Key: AE = adverse event

[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.

[b] AEs leading to death are based on AE outcome of Fatal

[c d] Includes Grade 5 events.

No DLTs were reported in the 200-mg cohort. Two subjects (66.7%) in the 300-mg cohort experienced DLTs. One subject (33.3%) experienced Grade 4 thrombocytopenia. The second subject had Grade 3 fatigue and Grade 3 hypertension (33.3% each).

The median duration of exposure to any study agent was 4.67 months (range: 3.0 to 6.5 months) in the 200-mg cohort and 0.92 (range: 0.9 to 4.0 months) in the 300-mg cohort. All subjects in the niraparib+apalutamide group died due to progressive disease; none of the deaths occurred during treatment.

Serious TEAEs were reported in 1 subject (33%) in the 200-mg cohort (ventricular dyskinesia and ventricular extrasystoles), and in 1 subject (33%) in the 300-mg cohort (thrombocytopenia and fall).

One subject (33%) in the 200-mg cohort discontinued study agents due to ventricular dyskinesia and ventricular extrasystoles, and 2 subjects (67%) in the 300-mg cohort discontinued study agents; 1 due to thrombocytopenia and 1 due to hypertension.

These safety findings along with the PK findings of a significant drug-drug interaction led to the decision not to pursue a RP2D for this combination.

Niraparib+AA-P:

The overall summary of TEAEs in the niraparib+AA-P group is presented in the table below. All 27 subjects receiving niraparib+AA-P experienced at least 1 TEAE. Of the 19 subjects in the 200-mg niraparib+AA-P cohort, 4 subjects were evaluated for DLT, and 15 subjects were in the expansion cohort. All 8 subjects in the 300-mg niraparib+AA-P cohort were evaluated for DLT.

Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (Study 64091742PCR1001)- Niraparib+AA-P

	Niraparib + AAP (1,000 mg/10 mg)		
	200 mg	300 mg	All Doses
Analysis set: Safety	19	8	27
Subjects with 1 or more:			
AEs	19 (100.0%)	8 (100.0%)	27 (100.0%)
Related AEs [a]	19 (100.0%)	6 (75.0%)	25 (92.6%)
AEs leading to death [b, c]	1 (5.3%)	2 (25.0%)	3 (11.1%)
Serious AEs	4 (21.1%)	4 (50.0%)	8 (29.6%)
Related serious AEs	2 (10.5%)	0	2 (7.4%)
AEs leading to discontinuation of study agent [d]	5 (26.3%)	2 (25.0%)	7 (25.9%)
Grade 3 or 4 AEs	12 (63.2%)	7 (87.5%)	19 (70.4%)

Key: AE = adverse event

[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.

[b] AEs leading to death are based on AE outcome of Fatal

[c d] Includes Grade 5 events.

Key: AAP = Abiraterone Acetate + Prednisone.

The median number of cycles started was 4.0 (range: 1.0 to 24.0 cycles) in the 200-mg cohort and 4.5 (range: 1.0 to 12.0 cycles) in the 300-mg cohort. The median duration of exposure was 3.68 months (range: 0.5 to 22.0 months) in the 200-mg cohort and 3.73 months (range: 0.4 to 11.1 months) in the 300-mg cohort.

Niraparib 200 mg was chosen as the RP2D. No DLTs occurred among the 4 subjects evaluated in the niraparib 200 mg+ AA-P combination. One of 8 subjects (13%) in the 300-mg cohort experienced 2 DLTs of fatigue and GGT increased. Two additional subjects in the 300-mg cohort experienced Grade 4 neutropenia at Cycle 2 Day 1. Other safety findings within the 300-mg cohort included 2 subjects (25%) who died due to AEs of general physical health deterioration. Four subjects (50%) in the 300-mg cohort experienced at least 1 SAE: 2 subjects had general physical health deterioration, 1 subject had arthralgia and back pain, and 1 subject had back pain and sepsis. Two subjects (25%) in the 300-mg cohort experienced at least 1 TEAE leading to discontinuation of study agents: 1 subject had fatigue and 1 subject had back pain.

The niraparib 200 mg + AA-P combination was further characterized in an expansion cohort of 15 additional subjects, for a total of 19 subjects in this treatment group. Two subjects (11%) in the 200-mg cohort died during treatment or within 30 days after the last dose of any study drug. One subject (5%) died due to progressive disease, and 1 subject (5%) died due to a TEAE of general physical health deterioration. Four subjects (21%) in the 200-mg cohort had at least 1 SAE: 1 subject had general physical health deterioration, 1 subject had congestive heart failure and myocardial infarction, 1 subject had nausea and vomiting, and 1 subject had dehydration and squamous cell lung cancer. Five subjects (26%) in the 200-mg cohort experienced at least 1 TEAE leading to discontinuation of study agents: 2 subjects had nausea and vomiting, 1 subject had GGT increased, 1 subject had thrombocytopenia, and 1 subject had congestive cardiac failure.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

Niraparib+Apalutamide

Niraparib in combination with apalutamide resulted in decreased niraparib exposures while the apalutamide exposures were comparable relative to monotherapy. For 200 mg niraparib coadministered

with 240 mg of apalutamide, the average C_{max} was 315 ng/mL with an AUC_{24h} of 4,388 ng.hr/mL. After linear scaling from a 200-mg to a 300-mg dose of niraparib for dose-proportional adjustment, the anticipated Cmax and AUC24h values would be 473 ng/mL and 6,582 ng.hr/mL, respectively. These exposures are markedly lower than the historical monotherapy data for niraparib in ovarian cancer patients at 300 mg (Cmax: 1,398 ng/mL and the AUC24h: 21,380 ng.hr/mL). The mean Cmax and AUC24h values were not determined for 300 mg niraparib when coadministered with 240 mg of apalutamide as there were insufficient data for comparison.

Niraparib+AA-P

The mean niraparib C_{max} (985 ng/mL) and AUC_{24h} (17,745 ng/mL) values for 200 mg niraparib+AA-P were within the RP2D target exposure ranges of 575-2,501 ng/mL and 9,159-37,324 ng.h/mL, respectively. Similar C_{trough} values were also observed between the 2 doses, ie, 564 ng/mL and 505 ng/mL for 200 mg and 300 mg of niraparib, respectively. However, as the number of subjects with evaluable PK after Cycle 1 (N_{200mg}: 4, N_{300mg}: 7) and Cycle 2 (N_{200mg}: 11, N_{300mg}: 3) at both doses differed substantially, a conclusion on dose-proportionality of exposures could not be drawn from this study.

STUDY LIMITATIONS:

No conclusion about efficacy can be drawn from this study because the sample size was small and the target population of DRD+ subjects for PARPi therapy was not recruited.

CONCLUSIONS:

- The niraparib+apalutamide combination was discontinued because 2 subjects (66.7%) in the 300 mg niraparib+apalutamide cohort experienced DLTs. Also, drug-drug interaction was observed when niraparib was given in combination with apalutamide, resulting in substantial (66% for C_{max}; 69% for AUC_{24h}) reduction in exposures of niraparib compared to historical monotherapy data.
- The RP2D for niraparib+AA-P was selected as 200 mg. No subjects in the 200-mg cohort experienced a DLT.
  - 300 mg was not selected because 1 subject in the 300 mg cohort experienced 2 DLTs of fatigue and gamma glutamyltransferase increased. Two additional subjects in the 300 mg cohort experienced Grade 4 neutropenia at Cycle 2 Day 1
- In the niraparib 200 mg+AA-P cohort, Grade 3 TEAEs occurring in at least 10% of subjects were thrombocytopenia, hypertension, nausea, vomiting, anemia, and blood phosphorus decreased. One subject experienced a Grade 4 TEAE of thrombocytopenia, and 1 subject had a Grade 5 TEAE of general physical health deterioration.
- The RP2D of niraparib+AA-P was tolerable. The median relative dose intensity for niraparib was 94.6% in the niraparib 200-mg cohort, despite 14 subjects experiencing at least 1 TEAE leading to a dose interruption or reduction. Five subjects in the 200-mg cohort experienced at least 1 TEAE leading to discontinuation of study agents: these were nausea, vomiting, GGT increased, thrombocytopenia, and congestive cardiac failure.
- The steady-state Cmax values at 200 mg or 300 mg niraparib in combination with abiraterone acetate and prednisone were 985 and 1,141, respectively. They were both within the RP2D target exposure range of 575-2,501 ng/mL. The steady-state AUC24h values at 200 mg and 300 mg were 17,745 and 18,536 ng.h/mL, respectively. These values were also within the RP2D exposure range of 9,159-37,324 ng.h/mL.

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