Study Report Synopsis

Study ID: 213362

Official Title of Study: An Open-Label, Randomized-Sequence, Multicenter, Single-Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Formulation Compared to Niraparib Capsule Formulation in Patients With Advanced Solid Tumors

NCT ID: NCT03329001

Date of Document (Extension phase): 10-Oct-2023

Date of Document (Stage 3): 8-June-2022

Date of Document (Stage 2): 18-May-2020

Date of Document (Stage 1): 07-Feb-2020

SYNOPSIS

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: Niraparib

Name of active substance: Niraparib tosylate monohydrate

Study Number: 213362

Title: An Open-Label, Randomized-Sequence, Multicenter, Single-Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Formulation Compared to Niraparib Capsule Formulation in Patients with Advanced Solid Tumors (Extension Phase)

Investigator(s): multi-center study

Study center(s): A total of 16 sites in the US enrolled participants to the Extension Phase of this study.

Publication(s): None at the time of this report.

Study Period: 20 December 2017 to 15 June 2023

Phase of Development: 1

Objectives: As results for the separate Stages of the study were previously reported, only the objectives relevant for the Extension Phase of this study are presented.

Extension Phase:

- To evaluate the safety of continuously dosed niraparib in participants with advanced solid tumors.

Methodology: Study 213362 was a multicenter, open-label study in participants with advanced solid tumors. This was a 3-stage, randomized-sequence, single-crossover study to assess the relative bioavailability and bioequivalence of niraparib tablet formulation relative to the capsule formulation (Stages 1 and 2, respectively) and to assess the effect of a high-fat meal on the pharmacokinetics (PK) of the niraparib tablet formulation (Stage 3).

When participants completed the PK Phase of the study (at least 7 days following the second dose of niraparib), the Sponsor worked with the Investigators to determine if the participants would benefit from continued access to niraparib therapy. Eligibility to participate in the Extension Phase was at the discretion of the Investigators and the Sponsor, following the review of the study's Extension Phase's respective inclusion criteria and completion of the required screening assessments. Continued treatment in the study was based on documented evidence of clinical benefit determined by local standard of care for disease assessment frequency.

Participants had up to 28 days (21 days for Stage 3 only; up to 28 days may have been acceptable following discussion between the Sponsor and Investigator) after completion of the PK Phase to complete the screening assessments and the Screening Visit.

At the Cycle 1/Day 1 Visit, participants underwent safety assessments and received study drug supply for the duration of 1 cycle (300 mg or 200 mg tablets of niraparib for QD dosing or 3×100 mg or 2×100 mg tablets/capsules of niraparib for QD dosing). The participants remained on the same formulation (tablet versus capsule) throughout the Extension Phase. Participants returned on the first day of every treatment cycle (28 ± 7 days) to receive study drug and for safety assessments.

Visits continued approximately every 4 weeks until treatment discontinuation. In line with the niraparib prescribing information, dose interruptions (no longer than 28 days) were allowed based on adverse events (AEs). In addition, dose reductions to 200 mg QD, and to 100 mg QD, were allowed based on AEs. Any dose reductions differing from the study protocol defined dosing had to be discussed with the Medical Monitor. Participants could continue in the Extension Phase until the participant met 1 of the withdrawal criteria.

Number of participants: Overall, 190 participants received at least 1 dose of niraparib in the Extension Phase.

Diagnosis and main criteria for inclusion: Participants had to meet inclusion criteria for the prior study Stage they enrolled on, including a histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumours that had failed to respond to standard therapy, had progressed despite standard therapy, or for which no standard therapy existed, and who may have benefited from treatment with a poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor as assessed by the Investigator. Participants enrolled in the Extension Phase of the study had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, had adequate organ function, and both male and female participants must have adhered to contraception requirements.

Treatment administration: The starting dose of niraparib in the Extension Phase was based on the participant's baseline actual body weight or platelet count collected at Screening for Extension Phase:

- Participants with a baseline actual body weight of ≥77 kg and screening platelet count of ≥150 000/μL took 1×300 mg strength tablet or 3×100 mg tablets/capsules QD.
- Participants with a baseline actual body weight of <77 kg or screening platelet count of <150 000/μL took 1×200 mg strength tablet or 2×100 mg tablets/capsules QD. For participants with initial starting dose of 200 mg QD, escalation to 300 mg QD was permitted after 2 cycles of therapy if no treatment interruption or discontinuation was required during the first 2 cycles of Extension Phase therapy and after approval from the Sponsor.

Batch numbers:

- 100 mg capsule: 1801021, M10642, 1808201, M10928, 2101011, M10654, FP259101-E19012, FP259101-E19003

- 100 mg tablet: KH17/0075, M10740, M11265, CT-C21002
- 200 mg tablet: KH17/0076, M10795
- 300 mg tablet: KH17/0077, M10723

Criteria for evaluation: The safety parameters evaluated during the conduct of the study included treatment emergent adverse events (TEAEs), discontinuations due to AEs, physical examinations, vital signs, clinical laboratory results and the use of concomitant medications.

Statistical methods: No sample size calculations were defined for the Extension Phase of the study.

The following participant populations were defined for the Extension Phase:

- Safety Population in the Extension Phase: All participants who receive any amount of niraparib in the open-label Extension Phase of the study.

All AEs were classified by system organ class (SOC) and preferred term (PT) using the most up to date version of MedDRA (v26.0) and were collected and recorded in the electronic case report form for each participant from the time of randomization and/or treatment assignment until 30 days after the last dose of study drug.

The severity of toxicities was graded according to the common technical criteria for adverse events (CTCAE) (v4.03). Within the same Medical Dictionary for Regulatory Activities (MedDRA) PT, only the most severe AE for each participant was counted in tabulations by severity. Within a MedDRA SOC, participants with more than 1 MedDRA PT were counted only once for the most severe AE reported. The Investigator provided a causality assessment (related or not related) regarding the relationship of the event with the study drug and/or study procedure for all AEs. Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), and secondary cancers (new malignancies [other than MDS or AML]) were considered adverse events of special interest (AESIs) for niraparib during the Extension Phase.

AEs were classified into the following time periods for the analysis of the Extension Phase:

- Extension Screening Period:
  - For participants in the Extension Phase, AEs that began after the end of the PK Phase until the date of the first dose in the Extension Phase.
- Open-Label Extension Phase:
  - Any AEs that started on or after the first dose in the Extension Phase.
- Any AEs with onset during the PK Phase/Extension Screening Period and ongoing/resolved during the Extension Phase were listed separately.

Results Summary

Disposition and Demographics:

Overall, 190 participants received at least 1 dose of niraparib in the Extension Phase, of which, 124 received tablet and 66 received capsule. Overall, 58.9% of participants entered the Extension Phase on the 300 mg starting dose.

Overall, the median age of participants who entered the Extension Phase (at the time of the PK Phase Screening Visit) was 64.5 years. The majority of participants were female, White, and not Hispanic or Latino. The median body mass index for participants entering the Extension Phase was 27.8 kg/m^2. Most participants had an ECOG performance status of 0 or 1 at study entry.

All participants who receive any amount of niraparib in the Extension Phase were included in the Safety Population in the Extension Phase (N=190).

Safety Results:

TEAEs were reported for most participants (97.4%) during the Extension Phase. The most frequently reported TEAEs were nausea (47 participants [37.9%] tablet cohort; 28 participants [42.4%] capsule cohort), vomiting (39 participants [31.5%] tablet cohort; 19 participants [28.8%] capsule cohort), fatigue (34 participants [27.4%] tablet cohort; 22 participants [33.3%] capsule cohort), and anemia (35 participants [28.2%] tablet cohort; 21 participants [31.8%] capsule cohort).

Overall, 148 participants (77.9%) had treatment-related TEAEs, 95 participants (76.6%) in the tablet cohort and 53 (80.3%) in the capsule cohort. Forty participants (32.3%) in the tablet cohort had a serious TEAE and 20 participants (30.3%) in the capsule cohort reported serious TEAEs. There were 5 (4%) related serious TEAEs in the tablet cohort, and 5 (7.6%) in the capsule cohort reported. TEAEs with CTCAE toxicity Grade ≥3 were reported for 79 participants (63.7%) in the tablet cohort, and 44 participants (66.7%) in the capsule cohort; 39 participants (31.5%) in the tablet cohort, and 26 participants (39.4%) in the capsule cohort, reported related TEAEs with CTCAE toxicity Grade ≥3.

AESIs were reported for 4 participants: AML for 1 participant (0.8%) in the tablet cohort, basal cell carcinoma for 1 participant (1.5%) in the capsule cohort, external ear neoplasm malignant for 1 participant (1.5%) in the capsule cohort, and squamous cell carcinoma of skin for 1 participant (1.5%) in the capsule cohort. All 4 events were considered unrelated to study treatment by the Investigator.

TEAEs leading to death were reported for 3 participants overall (1.6%), 2 (1.6%) in the tablet cohort (death and sepsis), and 1 (1.5%) in the capsule cohort (upper gastrointestinal hemorrhage). These were the 3 reported deaths due to any cause during the Extension Phase. None of the events were considered related to study treatment in the opinion of the Investigator.

Overall, the most common TEAEs leading to treatment dose reduction were thrombocytopenia (8 participants [6.5%] tablet cohort; 4 participants [6.1%] capsule cohort), platelet count decreased (9 participants [7.3%] tablet cohort; 3 participants [4.5%] capsule cohort), and anemia

(6 participants [4.8%] tablet cohort; 5 participants [7.6%] capsule cohort). TEAEs leading to treatment discontinuation were reported for 17 participants (8.9%) including 8 participants (6.5%) in the tablet and 9 participants (13.6%) in the capsule cohorts. The most common TEAEs leading to treatment discontinuation were anemia, thrombocytopenia and fatigue (1 participant each in the tablet [0.8%) and capsule [1.5%] cohorts).

Conclusions: The Extension Phase results in participants with advanced solid tumors showed a similar safety profile of niraparib to that observed in other clinical trials. There were no new safety signals observed. When comparing the incidence and type of TEAEs reported during the Extension Phase, the safety profile of participants receiving niraparib tablet was generally comparable to that of participants receiving niraparib capsule.

Document Date: 10 October 2023

Synopsis

Name of company: TESARO, Inc. (a GlaxoSmithKline company)

Name of finished product: Niraparib **Name of active substance:** Niraparib tosylate monohydrate

Study Number: 213362 (3000-01-004)

Title: An Open-Label, Randomized-Sequence, Multicenter, Single-Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Formulation Compared to Niraparib Capsule Formulation in Patients with Advanced Solid Tumors.

Investigator(s): Multi-center study

Study Center(s): A total of 7 sites in the US randomized patients to Stage 3 of this study.

Publication(s): No publications on Stage 3 data were available at the time of this report.

Study Period: 21-APR-2021 to 30-DEC-2021

Phase of Development: 1

Objectives and Endpoints (Criteria for Evaluation):

Note: Stage 1 and Stage 2 of the study are complete and were reported previously in separate clinical study reports (CSRs). The Extension Phase is ongoing and will be reported separately in the final CSR. The focus of this CSR is the objectives pertaining to the Stage 3 Pharmacokinetic Phase of the study.

Primary:

- Stage 1: To obtain preliminary assessment of the relative bioavailability (BA) of 300 mg niraparib administered as a tablet versus capsule formulation and to estimate the intra-subject variability of niraparib pharmacokinetics (PK).
- Stage 2: To evaluate if the tablet formulation (1×300 mg) of niraparib is bioequivalent (BE) to the capsule formulation (3×100 mg).
- Stage 3: To assess the effect of a high-fat meal on niraparib PK following a single 300 mg dose of the tablet formulation.

Secondary:

- Stage 1, Stage 2, and Stage 3: To evaluate the safety of single dose niraparib when administered as a tablet or capsule formulation in patients with advanced solid tumors.
- Extension Phase: To evaluate the safety of continuously dosed niraparib in patients with advanced solid tumors.

Methodology:

This was a multicenter, open-label, 3-stage, randomized-sequence, single-crossover study to assess the relative BA and BE of niraparib tablet formulation relative to the capsule formulation in patients with advanced solid tumors. Stage 3 of the protocol was a single cohort, randomized-sequence, 2 period, single dose, crossover study to assess effect of food on the PK of the niraparib tablet formulation. The methods, analyses, and results presented in this CSR are from the Stage 3 PK Phase of the study.

Stage 3 of the study consisted of a Screening Period (Day -21 to Day 1) and a PK Phase (PK Period 1 and PK Period 2; details given below). When patients completed the PK Phase of the study, they had the option to enter an Extension Phase of the study, provided the required screening assessments were performed and they were deemed eligible. Patients who did not participate in the Extension Phase of the study had an End of Treatment (EOT) visit followed by a Safety Follow-up Visit.

Following informed consent, all patients underwent screening procedures within 21 days prior to the first dose of study drug to determine eligibility for study entry. Screening procedures included medical, surgical, cancer, and medication history; complete physical examination, including vital signs, height, and weight; Eastern Cooperative Oncology Group (ECOG) performance status; clinical laboratory assessments (complete blood count (CBC), chemistry, and urinalysis); pregnancy test for women of childbearing potential (WOCBP); baseline tumor assessment; and electrocardiogram (ECG).

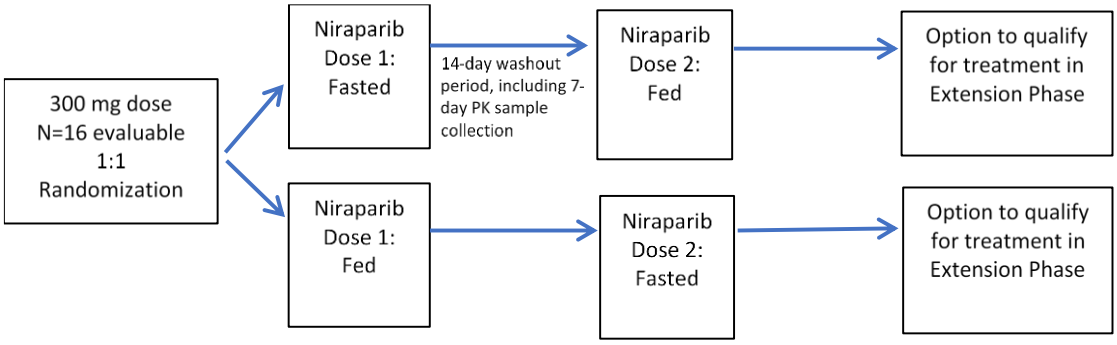
In Period 1, patients received a single 300 mg niraparib tablet either following a 10-hour fast or directly following consumption of a high-fat meal, followed by a 7-day PK sampling and an additional 7-day (+4 days) washout period. In Period 2, patients were crossed-over to receive a single 300 mg niraparib tablet in a fasted state or following a high-fat meal, followed by a 7-day PK sampling period. All patients fasted for a minimum of 4 hours post-dose in both periods. Patients who received the tablet in the fasted state in the first treatment period received the tablet following a high-fat meal in the second treatment period and vice versa.

Patients were administered niraparib on Day 1 in PK Period 1 and returned to the clinic on days 2, 3, 4, 5, 6, and 8 for PK sample collection. On Day 15, patients were administered niraparib in PK Period 2 and returned to the clinic on days 16, 17, 18, 19, 20, and 22 for PK sample collection. Blood was collected for PK assessments at the following time points relative to niraparib dosing: pre-dose (30 minutes prior to dosing) and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, and 168 hours post-dose.

Patients who participated in the Extension Phase proceeded into screening for the Extension Phase directly after completing the PK period. Patients who did not participate in the Extension Phase of the study had an EOT Visit followed by a Safety Follow-up Visit. The EOT Visit occurred within 7 days of the decision to discontinue study treatment for any reason. If the first dose of a new anticancer therapy occurred within 14 days of the decision to discontinue study treatment, all assessments required for the Safety Follow-up Visit occurred at the EOT Visit, and this visit was considered the Safety Follow-up Visit. If the first dose of the new anticancer therapy occurred >14 days of the decision to discontinue study, the Safety Follow-up Visit occurred 30+7 days after

the last dose of the study drug or at the start of any new anticancer therapy, whichever occurred first.

Study design: Single-Crossover study (Stage 3)



Abbreviation: PK=pharmacokinetics.
Notes: Stage 1 and Stage 2 of the study are complete and were reported previously in separate clinical study reports. The Extension Phase is ongoing; the results of the Extension Phase will be reported separately.

Number of Patients:

Approximately 20 patients were planned to be enrolled in Stage 3.

A total of 35 unique patients were screened, and 28 patients were randomized and received study drug.

Diagnosis and Main Criteria for Inclusion:

Patients had histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that failed to respond to standard therapy, had progressed despite standard therapy, or for which no standard therapy exists, and who may have benefited from treatment with a poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor as assessed by the Investigator.

Patients enrolled in Stage 3 of the study were at least 18 years of age, had an Eastern Cooperative Oncology Group performance status of 0 to 2, had adequate organ function, and had recovered to baseline or Grade 1 toxicity from prior cancer therapy. Both male and female patients must have adhered to contraception requirements. Additionally, the patients should have been able to eat a high-fat meal and able to fast for a minimum of 10 hours before niraparib dosing and for 4 hours after niraparib dosing.

Treatment Administration:

Niraparib ([3S]-3-[4-phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, and highly selective PARP1 and PARP2 inhibitor. The study drug was supplied as 300 mg niraparib tablets.

Patients received a single oral dose of niraparib 300 mg tablet following a 10-hour fast or directly following consumption of a high-fat meal, followed by a 14-day (±4 days)

Washout/PK period, followed by another dose of niraparib 300 mg tablet in a fasted state, or following a high-fat meal (crossed-over).

Batch number: M10723.

Criteria for Evaluation:

Pharmacokinetics:

The PK parameters that were estimated for Stage 3 included maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{0-t}), area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), apparent systemic clearance (CL/F), first time to reach maximum observed plasma concentration (t_{max}), terminal elimination half-life ($t_{1/2}$), apparent volume of distribution (Vz/F), and apparent terminal rate constant (λ_z). An absence of a food effect was established if the 90% confidence interval (CI) for the ratio of the population geometric least-squares (LS) means between fed and fasted states, was contained in the equivalence limits of 0.8000 – 1.2500 (80% to 125%) for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}.

Safety:

Safety parameters evaluated during the conduct of the study included treatment-emergent adverse events (TEAEs), discontinuations due to adverse events (AEs), physical examinations, vital signs, clinical laboratory results, and use of concomitant medications.

Statistical Methods:

Sample Size Justification:

Assuming the true ratio of means was 1 (one) and the intra-subject coefficient of variation (CV) was 20% for AUC_{0-t} and $AUC_{0-\infty,}$ with 16 evaluable patients, there was approximately 83% probability that the 90% CI of the ratio of geometric LS means would be within 0.800 and 1.250 (80% - 125%). Based on the results of a food effect (FE) study conducted using the capsule formulation, an effect of a high-fat meal on C_{max} was possible. The sample size of 16 patients was deemed adequate to characterize this effect. AUC_{0-t} and $AUC_{0-\infty}$ are the primary parameters for analysis.

The primary analysis was based on the FE Evaluable population as it was the most conservative approach, which maximized the benefits of the crossover design, where each patient served as their own control. Results for the PK Evaluable Population were also summarized and reported for this study.

To account for non-evaluable patients, approximately 20 total patients were targeted for enrollment. The non-evaluability rate arising during the study conduct was continuously monitored by the Sponsor, and the total number of enrolled patients were adjusted accordingly with the aim to target the resulting sample size of 16 evaluable patients.

Analysis Populations:

The following patient populations were defined for the Stage 3 PK analyses:

- **PK Population**: All patients who received at least 1 (one) dose of niraparib and had at least one measurable niraparib concentration.
- **PK Evaluable Population**: All patients who completed at least 1 PK period and had sufficient concentration data to accurately estimate at least 1 (one) PK parameter, without significant niraparib pre-dose concentration (pre-dose concentration >5% of C_{max}) in at least one period, and without events or protocol deviations deemed to affect PK. Patients with significant niraparib pre-dose concentration were excluded from the analysis of that period, but were included in the analysis of the other period, as appropriate and as data were available.
- **FE Evaluable population**: All patients who completed both PK Periods and had sufficient PK sample collection to accurately estimate PK parameters in both periods, without significant niraparib pre-dose concentration (>5% of C_{max}) in both PK Periods, and without events of protocol deviations deemed to affect PK. Patients who had a significant niraparib pre-dose concentration (>5% of C_{max}) in either period were excluded from the FE Evaluable population.

The following patient populations were defined for the Stage 3 safety analyses:

- **Safety Population in the Stage 3 PK Phase**: All patients who received any amount of niraparib during the Stage 3 PK Phase of the study.

Pharmacokinetics:

Individual patient niraparib concentration-time data were graphically presented on linear and semi-logarithmic scales. Individual patient PK parameter values were derived by noncompartmental methods using Phoenix WinNonlin Version 8.0. Actual elapsed time was used in parameter estimation. Plasma concentrations and PK parameters (with parameter-level exclusions) were summarized using descriptive statistics for each active treatment using the PK Evaluable Population and the FE Evaluable Population.

The statistical analyses followed the principles recommended in the FDA guidelines for FE studies.

Primary PK variables included C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. All other parameters were secondary variables.

To assess the relative BA between niraparib dosed in fed versus fasting states, the values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were evaluated using the following statistical analyses:

A linear mixed-effects model with fixed effects for sequence, period, and treatment and a random effect for patient nested within sequence. This analysis was based on the FE Evaluable population. LS means and 95% CI for LS means for the 2 treatment states, LS treatment state differences, and 90% CI for the treatment state differences on log-scale were obtained. The results were transformed back to the original scale by exponentiation in order to provide treatment state geometric LS means and 95% CI for

geometric LS means for the 2 treatment states, point estimates of the geometric LS mean ratios of treatment states (niraparib fed versus fasted), and 90% CI for these ratios.

An absence of a food effect on BA was established if the 90% CI for the ratio of the population geometric means fell between fed and fasted states was contained in the equivalence limits of 0.8000 – 1.2500 (80% to 125%) for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}. Based on the results of a food effect study conducted using the capsule formulation, an effect of a high-fat meal on C_{max} was possible. AUC_{0-t} and $AUC_{0-\infty}$ are the primary parameters for assessment.

Safety:

The Safety Population was used for all safety analyses.

All AEs were classified by System Organ Class (SOC) and preferred term (PT) using Version 24.1 of Medical Dictionary for Regulatory Activities. A TEAE was any event that was not present prior to the initiation of study drug, or any event already present that worsened in either intensity or frequency following exposure to study drug. An adverse event of special interest (AESI) was any AE (serious or nonserious) that was of scientific and medical concern specific to the study drug, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor was appropriate.

Any AEs recorded in the database that occurred from the time of informed consent form to first dose were listed only and not included in safety analyses. AEs were classified into Period 1, Period 2, or Safety Follow-up/Extension Screening Period.

The number and percentage of patients with TEAEs, related TEAEs, treatment-emergent serious adverse events (SAEs), related treatment-emergent SAEs, TEAEs with Common Terminology Criteria for Adverse Events (CTCAE) toxicity Grade 3 or above, related TEAEs with CTCAE toxicity Grade 3 or above, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to death, and treatment-emergent AESI were summarized.

Laboratory data, vital signs measurements, physical examination findings, and electrocardiogram results were presented in listings. Prior and concomitant medications, transfusions, and growth factors were summarized.

SUMMARY

Disposition and Demographics:

A total of 35 unique patients were screened for Stage 3 PK Phase of the study, and 28 patients were randomized and received at least one dose of the study drug. A total of 7 patients discontinued, and 21 patients completed the Stage 3 PK Phase. Twenty-three (23) patients entered into the Extension Phase from Stage 3.

In the Stage 3 Safety Population, the median age for all patients was 63.5 years (range: 36 to 76 years), and 17.9% of patients were ≥75 years of age. Most patients (64.3%) were White; 60.7% of patients were male, and 14.3% of patients were Hispanic or Latino. The

median weight, height, and BMI for all patients was 78.3 kg (range: 54 to 131 kg), 173.0 cm (range: 157 to 188 cm), and 26.1 kg/m^2 (range: 17 to 46 kg/m^2), respectively. The demographic and baseline characteristics of the FE Evaluable population were similar to the Safety Population.

The Safety Population included all 28 patients. The PK Evaluable Population included 24 patients and the FE Evaluable population included 19 patients.

Pharmacokinetics Results:

- The mean niraparib PK profiles were similar following administration of the tablet formulation in the fasted state and following a high-fat meal, with an overall trend of slightly higher concentrations with food.
- There was a modest increase in niraparib exposures following fed dosing compared to fasted state (geometric mean AUC_{0-t} values were 25990 and 20100 ng•hr/mL, and geometric mean $AUC_{0-\infty}$ values were 29770 and 23600 ng•hr/mL for fed and fasted states, respectively). Average peak concentrations were also higher in the fed state and were observed approximately an hour later compared to fasted state (geometric mean C_{max} values were 774.6 and 704.1 ng/mL, and median t_{max} was 5.97 and 4.88 hours, for fed and fasted states, respectively). The difference in t_{max} was not statistically significant. Niraparib $t_{1/2}$ was similar in both treatments. The food effect was variable, with a decrease in exposure observed in some patients with a high-fat meal. Overall, inter-subject variability was moderate, and appeared slightly reduced with a high-fat meal. For the key PK parameters of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, CV% ranged from 57.0% to 78.5% following fasted dosing, and from 47.2% to 65.2% following a high-fat meal.
- The geometric LS means ratios for the fed to fasted comparison were 1.1129, 1.3154, and 1.2771 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, indicating a modest increase in exposure following a high-fat meal. The 90% CIs were outside the predefined limits of 0.8 to 1.25 for all 3 parameters. The intra-subject variability (CV%) ranged from 17.5% to 30.0%.
- A sensitivity analysis was done excluding one patient who had an ongoing condition of "abdominal fullness", which the site confirmed, after the patient completed the PK Phase, to be suspected constipation and potentially gastroparesis. This patient has been included in the primary FE Evaluable Population. When this patient's PK data was excluded, the food effect on 3 key parameters was reduced: C_{max} from 11% to 6%, AUC_{0-t} from 31% to 26% and $AUC_{0-\infty}$ from 28% to 22%, respectively.

Safety Results:

No new safety concerns were observed in this study compared with previous niraparib clinical studies. Due to the limitations of the single dose crossover study design and the small number of patients in the study, no conclusions can be drawn regarding relative safety between the fed and fasted states

In Stage 3 overall summary of TEAEs were as follows:

- A total of 20 (71.4%) patients experienced at least 1 TEAE. The TEAEs reported in ≥10% of patients overall were nausea [4 (14.3%) patients], abdominal pain, vomiting, anemia, and platelet count decreased [each TEAE experienced by 3 (10.7%) patients]. Overall, 9 (32.1%) patients had treatment-related TEAEs, and 6 (21.4%) patients had TEAEs with CTCAE toxicity Grade ≥3 – none of them were assessed as related to the study drug.
- TEAEs were reported following dosing in a fasted state for 8 (30.8%) patients and 12 (48.0%) patients following dosing in a fed state. The proportion of patients with specific TEAEs was similar following dosing in a fed and fasted state.
- A total of 6 (21.4%) patients had serious TEAEs and none of which were assessed as related to the study drug.
- Two (7.1%) patients had TEAEs leading to treatment discontinuation, one patient had TEAE leading to death (during the safety follow-up), and no AESIs were reported during the PK Phase of the Stage 3.
- No COVID-19 related adverse events were reported during Stage 3.

Conclusions:

A modest food effect was observed on niraparib exposure. Niraparib C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 11%, 32% and 28% higher, respectively, compared to exposures in the fasted state. The food effect was variable, with a decrease in exposure observed in some patients with a high-fat meal. The magnitude of the food effect observed was notably lower than the inter-subject variability (57.0% to 78.5%) observed in the three key niraparib pharmacokinetic parameters.

No new safety concerns were observed in this study compared with previous niraparib clinical studies. Due to the limitations of the single dose crossover study design and the small number of patients in the study, no conclusions can be drawn regarding relative safety between the fed and fasted states.

Effective Date: 08 JUN 2022

2. SYNOPSIS

Name of Sponsor/Company: TESARO, Inc. **Name of Finished Product:** niraparib **Name of Active Ingredient:** niraparib tosylate monohydrate	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:

An Open-Label, Randomized-Sequence, Multicenter, Single-Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Formulation Compared to Niraparib Capsule Formulation in Patients with Advanced Solid Tumors

Coordinating Investigator:

The coordinating investigator for this study is Dr. Gerald S. Falchook from the Sarah Cannon Research Institute at HealthONE in Denver, Colorado, USA.

Study Center(s):

16 study sites in the United States

Publications (Reference):

None

Study Period (Years):	**Phase of Development:**
Date first patient enrolled (signed informed consent for Stage 2): 02 January 2019 Date last patient completed (Stage 2): 02 January 2020	1

Objectives:

Primary Objectives:

- Stage 1: To obtain preliminary assessment of the relative bioavailability (BA) of 300 mg niraparib administered as a tablet versus capsule formulation and to estimate the intrasubject variability of niraparib pharmacokinetics (PK)
- Stage 2: To evaluate if the tablet formulation (1×300 mg) of niraparib is bioequivalent to the capsule formulation (3×100 mg)

Secondary Objectives:

- Stage 1 and Stage 2: To evaluate the safety of single-dose niraparib when administered as a tablet or capsule formulation in patients with advanced solid tumors
- Extension Phase: To evaluate the safety of continuously dosed niraparib in patients with advanced solid tumors

Exploratory Objective:

CCI [redacted]

Methodology:

This is a multicenter, open-label, 2-stage, randomized-sequence, single-crossover study to assess the relative BA and bioequivalence (BE) of niraparib tablet formulation relative to the capsule formulation in patients with advanced solid tumors. The methods, analyses, and results presented in this clinical study report (CSR) are those for the completed Stage 2 PK Phase of the study. The investigational plan and results for the completed Stage 1 PK Phase were previously reported in a separate CSR. The Extension Phase of the study is ongoing, and the results from the Extension Phase will be reported separately.

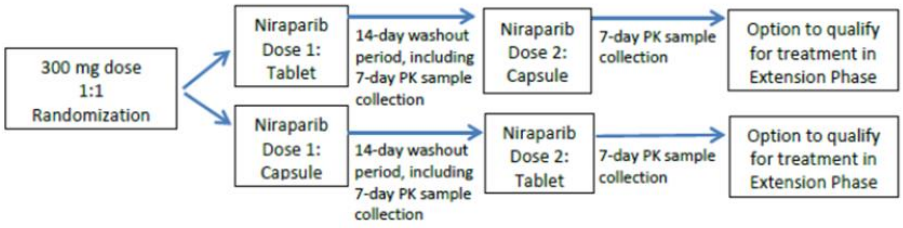
Stage 2 of the study consisted of a Screening Period (Day -21 to Day -1), a PK Phase (Study Drug and Washout/PK Period 1 and Study Drug and PK Period 2), an End of Treatment (EOT) Visit, and a Safety Follow-up Visit. When patients completed the PK Phase of the study, they had the option to enter an Extension Phase of the study, provided the required screening assessments were performed and they were deemed eligible.

Patients were randomized 1:1 to receive the tablet formulation in Period 1 followed by capsule formulation in Period 2 or the capsule formulation in Period 1 followed by the tablet formulation in Period 2. Following an 8-hour fast on Day 1, patients received a single dose of niraparib (tablet [1×300 mg] or capsule [3×100 mg]) followed by a 14 (±4)-day Washout/PK Period 1. After the washout period, patients received a dose of the alternate formulation also in a fasted state, followed by a 7-day Washout/PK Period 2. Extensive PK sampling was carried out after niraparib dosing.

Patients were administered niraparib on Day 1 in PK Period 1 and returned to the clinic on Days 2, 3, 4, 5, 6, and 8 for PK sample collection. On Day 15, patients were administered niraparib in PK Period 2 and returned to the clinic on Days 16, 17, 18, 19, 20, and 22 for PK sample collection. Blood was collected for PK assessments at the following time points relative to niraparib dosing: predose (30 minutes prior to dosing) and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, and 168 hours postdose. Patients meeting certain criteria were discontinued from the PK Phase and were allowed to be screened for the Extension Phase.

Patients who did not participate in the Extension Phase of the study had an EOT Visit followed by a Safety Follow-up Visit. Patients who participated in the Extension Phase proceeded into screening for the Extension Phase directly after completing the PK period. The EOT Visit occurred within 7 days of the decision to discontinue study treatment for any reason. If the first dose of a new anticancer therapy occurred within 14 days of the decision to discontinue study treatment, all assessments required for the Safety Follow-up Visit occurred at the EOT Visit, and this visit was considered the Safety Follow-up Visit. If the first dose of the new anticancer therapy occurred >14 days of the decision to discontinue study, the Safety Follow-up Visit occurred 30+7 days after the last dose of the study drug or at the start of any new anticancer therapy, whichever occurred first.

Study Design: Single-Crossover Study - Stage 2 (Completed)



Abbreviation: PK=pharmacokinetics.
Notes: Stage 1 of the study is complete and was reported previously in a separate clinical study report. The Extension Phase is ongoing; the results of the Extension Phase will be reported separately.

Number of Patients (Planned and Analyzed):

Approximately 170 patients were planned to be enrolled in Stage 2 to ensure 100 evaluable patients for BE analysis.

A total of 209 patients were screened, 179 patients were randomized, and 168 patients received study drug.

Diagnosis and Main Criteria for Inclusion:

Patients had histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that failed to respond to standard therapy, had progressed despite standard therapy, or for which no standard therapy exists, and who may have benefited from treatment with a poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor as assessed by the Investigator.

Patients enrolled in Stage 2 of the study were at least 18 years of age, had an Eastern Cooperative Oncology Group performance status of 0 to 2, had adequate organ function, and had recovered to baseline or Grade 1 toxicity from prior cancer therapy. Both male and female patients must have adhered to contraception requirements.

Test Product, Dose and Mode of Administration, Batch Number:

Niraparib ([3S]-3-[4-phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, and highly selective PARP1 and PARP2 inhibitor. The study drug was supplied as 100-mg niraparib capsules and 300-mg niraparib tablets.

Patients received a single oral dose of niraparib 300 mg (tablet [1×300 mg] or capsule [3×100 mg]), followed by a 14-day (±4 days) Washout/PK Period, and then a dose of the alternate formulation.

Duration of Study Treatment:

A single oral dose of study drug was administered on Day 1 and then on Day 15.

Reference Therapy, Dose, and Mode of Administration:

None

Criteria for Evaluation:

Pharmacokinetics:

The PK parameters that were estimated for Stage 2 included maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{0-t}), area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), apparent systemic clearance (CL/F), first time to reach maximum observed plasma concentration (t_{max}), apparent terminal elimination half-life ($t_{1/2}$), apparent volume of distribution (Vz/F), and apparent terminal rate constant (λ_z). To conclude BE of the tablet formulation relative to the capsule formulation, the 90% confidence intervals (CIs) of the ratios of geometric least squares mean (LSM) of the test (tablet) to reference (capsule) product were to be within 0.800 to 1.250 for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}.

Safety:

Safety parameters evaluated during the conduct of the study included treatment-emergent adverse events (TEAEs), discontinuations due to adverse events (AEs), physical examinations, vital signs, clinical laboratory results, and use of concomitant medications.

Statistical Methods:

Analysis Populations:

The following population was defined for Stage 2 safety analyses:

- Safety Population in the Stage 2 PK Phase: All patients who received any amount of niraparib during the Stage 2 PK Phase of the study.

The following populations were defined for the Stage 2 PK analyses:

- PK Population: All patients who received at least 1 dose of niraparib (tablet or capsule) and have at least 1 measurable niraparib concentration.
- PK Evaluable Population: All patients who completed at least 1 PK period and had sufficient concentration data to accurately estimate at least 1 PK parameter, without significant niraparib predose concentration (predose concentration >5% of C_{max}) in at least 1 period, and without events or protocol deviations deemed to affect PK. Patients with significant niraparib predose concentration were excluded from the analysis of that period, but were included in the analysis of the other period, as appropriate and as data were available.
- BE Evaluable Population: All patients who completed both PK periods and had sufficient PK sample collection to accurately estimate PK parameters, without significant niraparib carryover (predose concentration >5% of C_{max}) in both PK periods, and without events or protocol deviations deemed to affect PK. Patients who had significant niraparib predose concentration in either period were completely excluded from the BE Evaluable Population.

Pharmacokinetics:

Individual patient niraparib concentration-time data were graphically presented on linear and semi-logarithmic scales. Individual patient PK parameter values were derived by noncompartmental methods using Phoenix WinNonlin version 8.0. Actual elapsed time was used in parameter estimation. Plasma concentrations and PK parameters (with parameter-level exclusions) were summarized using descriptive statistics for each active treatment using the PK Evaluable Population and the BE Evaluable Population.

To assess BE between niraparib capsules (reference) and tablet (test), the log-transformed values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were evaluated with a linear mixed-effects model with fixed effects for sequence, period, and treatment, and a random effect for patient nested within sequence. This analysis was based on the BE Evaluable Population. The 90% CIs for the ratios of the geometric means of the test treatment (tablet) compared to the reference treatment (capsule) were obtained. BE was claimed if the 90% CI for the ratio of geometric means is between 0.800 and 1.250 for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}.

Safety:

The Safety Population was used for all safety analyses.

All AEs were classified by System Organ Class and preferred term using version 22.0 of Medical Dictionary for Regulatory Activities. A TEAE was any event that was not present prior to the initiation of study drug or any event already present that worsened in either intensity or frequency following exposure to study drug. An adverse event of special interest (AESI) was any AE (serious or nonserious) that was of scientific and medical concern specific to the study drug, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor was appropriate. Any AEs recorded in the database that occurred from the time of informed consent form to first dose were listed only and not included in safety analyses. AEs were classified into Period 1, Period 2, or Safety Follow-up/Extension Screening Period.

The number and percentage of patients with TEAEs, related TEAEs, treatment-emergent serious adverse events (SAEs), related treatment-emergent SAEs, TEAEs with Common Terminology Criteria for Adverse Events (CTCAE) toxicity Grade 3 or above, related TEAEs with CTCAE toxicity Grade 3 or above, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to death, and treatment-emergent AESI were summarized.

Laboratory data, vital signs measurements, physical examination findings, and electrocardiogram results were presented in listings. Prior and concomitant medications, transfusions, and growth factors were summarized.

SUMMARY – CONCLUSIONS

DISPOSITION AND DEMOGRAPHICS:

A total of 209 patients were screened, 179 patients were randomized, and 168 patients received study drug. Thirty-eight patients discontinued from the Stage 2 PK Phase; 138 patients continued on to the Extension Phase.

In the Stage 2 Safety Population (N=168), the median age for all patients was 65.5 years (range: 26 to 87 years), and 16.7% of patients were ≥75 years of age. Most patients (74.4%) were White; 57.1% of patients were female; 82.7% of patients were not Hispanic or Latino; and 6.0% of patients were Hispanic or Latino. The median weight, height, and body mass index for all patients was 79.6 kg (range: 38 to 147 kg), 168.0 cm (range: 142 to 196 cm), and 27.7 kg/m^2 (range: 17 to 49 kg/m^2), respectively.

The Safety Population and PK Population included all 168 patients. The PK Evaluable Population included a total of 142 patients who received the tablet formulation and 126 patients who received the capsule formulation. The BE Evaluable Population included 108 patients.

PHARMACOKINETICS RESULTS (STAGE 2):

Niraparib PK in Stage 2 of this study was found to be consistent with the values reported in Stage 1 and other studies where niraparib PK was assessed. Peak niraparib concentrations were reached within approximately 5 hours postdose following both tablet and capsule administration, indicating a relatively slow absorption profile. Niraparib had a long half-life of approximately 50 hours, in agreement with previously reported values.

Overall, intersubject variability was moderate but comparable between the 2 formulations and was similar to the intersubject variability observed for niraparib in Stage 1 and other studies of niraparib. For the key PK parameters of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, %CV ranged from 50.0% to 60.3% following tablet administration and from 44.3% to 54.2% following capsule administration.

BE was established between the niraparib tablet (1×300 mg) and capsule (3×100 mg) formulations using the BE Evaluable Population, which included patients with data in both PK Periods, as predefined in the protocol and the SAP. The 90% CIs of the geometric LSM ratios for tablet compared to capsules fell within the limits of 0.800 and 1.250 for all 3 primary niraparib PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$). Intrasubject variability was low, ranging from 18.1% to 23.7% for the key PK parameters. Similar results were observed using the PK Evaluable Population.

SAFETY RESULTS (STAGE 2):

Taking into consideration the limitations of a single-dose crossover study, no new safety concerns were observed in this study compared with previous niraparib clinical studies.

In Stage 2, observations related to TEAEs were as follows:

- A total of 125 (74.4%) patients experienced at least 1 TEAE. The TEAEs reported in ≥10% of patients overall were constipation (32 [19.0%] patients), nausea (31 [18.5%] patients), anemia (19 [11.3%] patients), fatigue (18 [10.7%] patients), and vomiting (17 [10.1%] patients).
- Overall, 60 (35.7%) patients had treatment-related TEAEs, 36 (21.4%) patients had TEAEs with CTCAE toxicity Grade ≥3, and 8 (4.8%) patients had treatment-related TEAEs with CTCAE toxicity Grade ≥3. The TEAEs assessed as related to study drug by the Investigator in ≥5% of patients overall were nausea (21 [12.5%] patients), constipation (12 [7.1%] patients), vomiting (10 [6.0%] patients), and fatigue (9 [5.4%] patients).
- A total of 26 (15.5%) patients had serious TEAEs, 5 (3.0%) patients had TEAEs leading to treatment discontinuation, 3 (1.8%) patients had TEAEs leading to death, and no AESIs were reported.
- One patient experienced a TEAE in the Stage 2 PK Phase that led to the dose being reduced in the Extension Phase; the dose reduction could not be implemented in the Stage 2 PK Phase because only a single administered dose of niraparib tablet or capsule was allowed during this phase of the study. Two patients experienced TEAEs in the Stage 2 PK Phase that led to dose interruption. These patients had their study treatment delayed; one of whom eventually discontinued treatment due to disease progression.

CONCLUSION:

- BE was established between the niraparib tablet (1×300 mg) and capsule (3×100 mg) formulations. The 90% CIs of the geometric LSM ratios for tablet compared to capsules fell within the limits of 0.800 and 1.250 for all 3 primary niraparib PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$).
- Niraparib concentration-time profiles and parameter estimates were consistent with those observed in Stage 1 of the study and other studies with niraparib.
- Overall PK intersubject variability was moderate and comparable between the 2 formulations. Intrasubject variability was low for all 3 key PK parameters.
- Taking into consideration the limitations of a single-dose crossover study, no new safety concerns were observed in this study compared with previous niraparib clinical studies.

Date of the report: 18 May 2020

2. SYNOPSIS

Name of Sponsor/Company: TESARO, Inc. **Name of Finished Product:** niraparib **Name of Active Ingredient:** niraparib tosylate monohydrate	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:

An Open-Label, Randomized-Sequence, Multicenter, Single-Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Formulation Compared to Niraparib Capsule Formulation in Patients with Advanced Solid Tumors

Coordinating Investigator:

The coordinating investigator for this study is Amita Patnaik, MD, FRCP(C), South Texas Accelerated Research Therapeutics, LLC, 4383 Medical Drive, San Antonio, TX 78229, USA

Study Center(s):

4 study sites in the United States

Publications (reference):

None

Study Period (years):	**Phase of Development:**
Date first patient enrolled (signed informed consent): 29 November 2017 Date last patient completed (Stage 1): 14 May 2018	1

Objectives:

Primary Objective:

- Stage 1: To obtain preliminary assessment of the relative bioavailability (BA) of 300 mg niraparib administered as a tablet versus capsule formulation and to estimate the intrasubject variability of niraparib pharmacokinetics (PK)
- Stage 2: To evaluate if the tablet formulation (1×300 mg) of niraparib is bioequivalent (BE) to the capsule formulation (3×100 mg)

Secondary Objectives:

- Stage 1 and Stage 2: To evaluate the safety of single-dose niraparib when administered as a tablet or capsule formulation in patients with advanced solid tumors
- Extension Phase: To evaluate the safety of continuously dosed niraparib in patients with advanced solid tumors

Exploratory Objectives:

CCI [redacted]

Methodology:

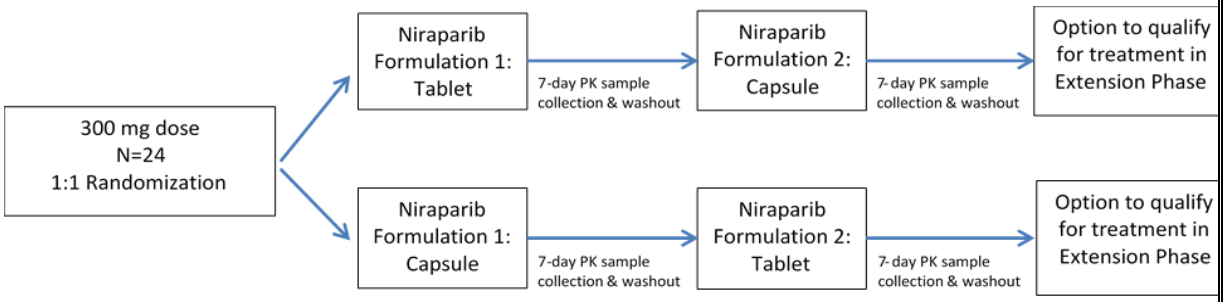
This is a multicenter, open-label, 2-stage, randomized-sequence, single-crossover study to assess the relative BA and BE of niraparib tablet formulation relative to the capsule formulation in patients with advanced solid tumors. The methods, analyses, and results presented in this Clinical Study Report are those for the completed Stage 1 PK Phase of the study; the investigational plan and the results for the ongoing Stage 2 and the Extension Phases will be reported separately.

Stage 1 of the study consisted of a Screening Period (Day -21 to Day -1), a PK Phase (Study Drug and Washout/PK Period 1 and Study Drug and PK Period 2), an End of Treatment (EOT) Visit, and a Safety Follow up Visit. When patients completed the PK Phase of the study (at least 7 days after the beginning of PK Period 2), they were eligible to participate in an Extension Phase prior to the EOT and Safety Follow up Visits, following review of the Extension Phase inclusion criteria and completion of the required screening assessments.

Patients were randomized 1:1 to receive the tablet formulation in Period 1 followed by capsule formulation in Period 2 or the capsule formulation in Period 1 followed by the tablet formulation in Period 2. Following an 8-hour fast on Day 1, patients received a single dose of niraparib (tablet [1 × 300 mg] or capsule [3 × 100 mg]) followed by a 7 (+1)-day Washout/PK Period 1. After the washout period, patients received a dose of the alternate formulation also in a fasted state, followed by a 7-day Washout/PK Period 2. Extensive PK sampling was carried out after niraparib dosing.

All patients who completed the Stage 1 PK phase of the study had an EOT visit within 7 days of the decision to discontinue study drug for any reason and a Safety Follow-up Visit occurring 30 + 7 days after the last dose of study drug. Patients who did not participate in the Extension Phase of the study proceeded to the Safety Follow-up Visit. Patients who completed the Extension Phase proceeded to the Safety Follow-up Visit.

Study Design: Single-Crossover Study - Stage 1 (completed)



Abbreviations: PK=pharmacokinetics.

Number of Patients (planned and analyzed):

Approximately 24 patients were planned to be enrolled in Stage 1.

A total of 35 patients were screened, and 29 patients were randomized and received study drug.

Diagnosis and Main Criteria for Inclusion:

Patients had histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that failed to respond to standard therapy, had progressed despite standard therapy, or for which no standard therapy exists, and who may have benefited from treatment with a poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor as assessed by the Investigator.

Patients enrolled in Stage 1 of the study were at least 18 years of age, had an Eastern Cooperative Oncology Group performance status of 0 to 2, had adequate organ function, and had recovered to

Grade 1 toxicity from prior cancer therapy. Both male and female patients must have adhered to contraception requirements.

Test Product, Dose and Mode of Administration, Batch Number:

Niraparib ([3S]-3-[4-phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP1 and PARP2 inhibitor. The study drug was supplied as 100 mg niraparib capsules and 300 mg tablets.

Patients received a single oral dose of niraparib 300 mg (tablet [1 × 300 mg] or capsule [3 × 100 mg]), followed by a 7(+1)-day Washout/PK Period, and then a dose of the alternate formulation.

Duration of Study Treatment:

A single oral dose of study drug was administered on Day 1 and then on Day 8.

Reference Therapy, Dose, and Mode of Administration:

None

Criteria for Evaluation:

Pharmacokinetics:

In Stage 1, plasma samples for PK assessments were analyzed for concentrations of niraparib and CCI. The PK parameters included area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{0-t}), area under the concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), maximum observed plasma concentration (C_{max}), time to reach maximum observed plasma concentration (t_{max}), terminal elimination half-life ($t_{1/2}$), time of the last value not below the limit of quantification (t_{last}), terminal elimination rate constant (kel), apparent total body clearance (CL/F; niraparib only), apparent terminal volume of distribution (Vz/F; niraparib only), and BA of the tablet formulation relative to the capsule formulation based on AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}.

Safety:

Safety parameters evaluated included treatment-emergent adverse events (TEAEs), discontinuations due to adverse events (AEs), physical examinations, vital signs, clinical laboratory results, and use of concomitant medications.

Statistical Methods:

Analysis Populations:

The following population was defined for the Stage 1 safety analysis:

- Safety Population in the Stage 1 PK Phase: All patients who received any amount of niraparib during the Stage 1 PK Phase of the study.

The following populations were defined for the Stage 1 PK analysis of niraparib:

- PK Population: All patients who received at least 1 dose of niraparib and have at least 1 measurable concentration.
- PK Evaluable Population: All patients who completed at least 1 Study Drug and Washout/PK Period and had sufficient concentration data to accurately estimate PK parameters without significant niraparib carryover (baseline concentration > 5% of C_{max}) in at least 1 Period.

Patients with carryover were excluded from the analysis of PK Period 2, but were included in the analysis of PK Period 1, as data were available.

- BA Evaluable Population: All patients who completed both Study Drug and Washout/PK Periods and had sufficient PK sample collection to accurately estimate PK parameters, without significant niraparib carryover (baseline concentration > 5% of C_{max}) in both PK Periods. Patients who had significant niraparib carryover from PK Period 1 in PK Period 2 were completely excluded from the BA Evaluable Population.

The following populations were defined for the Stage 1 PK analysis of CCI (PK Analysis Plan; CCI is analyzed in Stage 1 only):

- CCI PK Population: All patients who received at least 1 dose of niraparib and had at least 1 measurable CCI concentration.
- CCI PK Evaluable Population: All patients who completed at least 1 Study Drug and Washout/PK Period and had sufficient CCI concentration data to accurately estimate PK parameters.

Pharmacokinetics:

Individual and mean plasma niraparib and CCI concentrations over time were plotted using the BA Evaluable and PK Evaluable Populations for the niraparib analysis and the CCI PK Population for the CCI analysis.

The PK parameters were derived by noncompartmental methods using actual sampling times and were summarized descriptively, including the number of observations, arithmetic mean, median, standard deviation, coefficient of variation (CV), minimum, maximum, geometric mean, and geometric CV%. PK parameters were summarized for the BA Evaluable and PK Evaluable Populations for niraparib and for the CCI PK Evaluable Population for CCI The intrasubject variability of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ was assessed as well as the number of patients with carryover from Period 1 to Period 2.

The primary PK parameters for determining the relative BA in Stage 1 were AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for niraparib. The niraparib capsules served as the reference treatment, and niraparib tablets served as the test. All other PK parameters were regarded as secondary and were not subjected to inferential statistical analysis.

A comparison of the logarithmically transformed niraparib PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) was carried out to evaluate the relative BA between treatments (test versus reference) by performing an analysis of variance (ANOVA) model, accounting for sources of variation. Geometric least-squares mean (LSM), geometric mean ratios, and 90% CIs were presented. The BA Evaluable Population was used for the relative BA analysis.

Safety:

The Safety Population was used for all safety analyses.

All AEs were classified by SOC and PT using version 20.0 of MedDRA. TEAEs were defined as any AEs collected with a start date on or after the first dose of study drug or an AE that worsened in either intensity or frequency following exposure to study drug. Any AEs recorded in the database that occurred from the time of ICF to first dose were listed only and not included in safety analyses. AEs were classified into Period 1, Period 2, or Safety Follow-up/Extension Screening Period.

The number and percentage of patients with TEAEs, related TEAEs, treatment-emergent SAEs, related treatment-emergent SAEs, TEAE with CTCAE toxicity Grade 3 or above, related TEAE with

CTCAE toxicity Grade 3 or above, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to death, and treatment-emergent AESI were summarized.

Laboratory data, vital signs measurements, physical examination findings, and electrocardiograms were presented in listings. Prior and concomitant medications, transfusions, and growth factors were summarized.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS RESULTS (STAGE 1):

Niraparib concentration-time profiles and PK parameter estimates following administration of the tablet and capsule formulations were similar, although exposures tended to be slightly lower following tablet administration. Overall, parameter estimates were consistent with previously reported values. Niraparib C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ exhibited moderate intersubject variability, with %CV estimates of approximately 40% to 50% for PK parameter estimates following both formulations. Intrasubject variability was considerably lower, ranging from 12.4% to 21.9%. The median t_{max} was approximately 4 hours for both formulations, indicating comparable absorption following tablet and capsule administration. The mean $t_{1/2}$ was 48.4 hours for the tablet formulation and 44.9 hours for the capsule formulation and was consistent with previously reported estimates. Comparable performance of the capsule and tablet formulations was demonstrated; the 90% CIs of the geometric LSMs for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the 0.80 to 1.25 limits.

SAFETY RESULTS (STAGE 1):

In the Stage 1 PK Phase, observations related to TEAEs were as follows:

- Two (6.9%) patients had dose reductions due to TEAEs. The TEAEs that led to dose reduction occurred during the PK Phase, and the dose reduction was implemented at the first dose of the Extension Phase. The events leading to dose reduction were increased AST (Grade 3) and increased ALT (Grade 2) in 1 patient and increased AST (Grade 3) in 1 patient; these 3 events were considered by the Investigator as related to study drug and were transient in nature, as they eventually resolved.
- A total of 19 (65.5%) patients experienced at least 1 TEAE. TEAEs reported in more than 1 patient in total, were nausea (7 [24.1%] patients); vomiting (4 [13.8%] patients); fatigue (3 [10.3%] patients); and AST increased, back pain, and hypomagnesaemia (2 [6.9%] patients each).
- Overall, related TEAEs were reported for 7 (24.1%) patients. The only TEAEs assessed as related to study drug by the Investigator in more than 1 patient in total were nausea (6 [20.7%] patients), vomiting (3 [10.3%] patients), and AST increased (2 [6.9%] patients).
- In the Stage 1 PK Phase there were no deaths, SAEs, discontinuations due to AEs, or AESIs reported.

CONCLUSION:

Overall, comparable performance of the capsule and tablet formulations was demonstrated; the 90% CIs of the geometric LSMs for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the 0.80 to 1.25 limits.

No new safety issues were observed in this study compared with previous niraparib clinical studies.

Date of the report: 07 February 2020