Clinical Therapeutics xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Therapeutics

journal homepage: www.elsevier.com/locate/clinthera

Original Research

A Relative Bioavailability, Bioequivalence, and Food Effect Study of Niraparib Tablets in Patients with Advanced Solid Tumors

Gerald Falchook, MD[1], Amita Patnaik, MD[2], Debra L. Richardson, MD, FACS, FACOG[3,4], R. Donald Harvey, PharmD[5], Manish R. Sharma, MD[6], Navid Hafez, MD, MPH[7], Erika Hamilton, MD[8], Sarina A. Piha-Paul, MD[9], Minal Barve, MD[10], Trisha Wise-Draper, MD, PhD[11], Manish R. Patel, MD[12,13], Afshin Dowlati, MD[14], Joseph Pascuzzo, DO[15], Shou-Ching Tang, MD, PhD, FACP, FRCPC[16], Christina Faltermeier, PhD[17], Izabela A. Malinowska, MD, PhD[18], Luda Shtessel, PhD[18], Alina Striha, MSc[19], Elizabeth Potocka, PhD[20,*]

[1] *Sarah Cannon Research Institute at HealthONE, Denver, Colorado*
[2] *START San Antonio, San Antonio, Texas*
[3] *Gynecologic Oncology, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma*
[4] *Sarah Cannon Research Institute, Oklahoma City, Oklahoma*
[5] *Emory University School of Medicine, Atlanta, Georgia*
[6] *START Midwest, Grand Rapids, Michigan*
[7] *Yale Cancer Center, New Haven, Connecticut*
[8] *Sarah Cannon Research Institute at Tennessee Oncology, Nashville, Tennessee*
[9] *Investigational Cancer Therapeutics, University of Texas MD Anderson Cancer Center, Houston, Texas*
[10] *Mary Crowley Cancer Research Center, Dallas, Texas*
[11] *University of Cincinnati Cancer Center, Cincinnati, Ohio*
[12] *Florida Cancer Specialists, Sarasota, Florida*
[13] *Sarah Cannon Research Institute, Sarasota, Florida*
[14] *University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, Ohio*
[15] *Medical Oncology, California Cancer Associates for Research and Excellence, San Diego, California*
[16] *Cancer Center and Research Institute, University of Mississippi Medical Center, Jackson, Mississippi*
[17] *Pharmacokinetics, IQVIA, Kansas City, Missouri*
[18] *Oncology Clinical Development, GSK, Waltham, Massachusetts*
[19] *Plus-Project Partnership Ltd, Knutsford, UK*
[20] *Clinical Pharmacology Modeling and Simulation, GSK, Waltham, Massachusetts*

ARTICLE INFO

Key words:
Bioequivalence
Food effect
Niraparib
Pharmacokinetics
Relative bioavailability
Solid tumors

ABSTRACT

Purpose: The poly (ADP-ribose) polymerase inhibitor niraparib is indicated as maintenance treatment in patients with certain subtypes of advanced ovarian cancer, and is being investigated in patients with other solid tumors. Niraparib is available in 100-mg capsules with a starting dosage of 200 or 300 mg/d. This study assessed the relative bioavailability (BA) and bioequivalence (BE) between a 1 × 300-mg tablet relative to 3 × 100-mg niraparib capsules. In addition, the food effect (FE) of a high-fat meal on the pharmacokinetic (PK) properties of tablet-formulated niraparib was investigated.

Methods: This was a US-based, 3-stage, open-label, multicenter, single-crossover, randomized-sequence study. Enrolled patients were 18 years and older, with histologically or cytologically confirmed advanced solid tumors (metastatic or local) and disease progression despite standard therapy. Patients were randomly assigned 1:1 to receive niraparib 1 × 300-mg tablet or 3 × 100-mg capsules in the BA and BE stages or 1 × 300-mg tablet in a fasted or fed (high-fat meal) state in the FE stage. Across all study stages, PK parameters were assessed for 7 days after each dose (tablet or capsule) or prandial state (fasted or fed). In the BA stage, patients crossed over

* Address correspondence to: Elizabeth Potocka, PhD, Clinical Pharmacology Modeling and Simulation, GSK, 1000 Winter Street, Waltham, MA 02451.
E-mail address: ella.x.potocka@gsk.com (E. Potocka).

https://doi.org/10.1016/j.clinthera.2024.01.004
Accepted 4 January 2024
Available online xxx

Please cite this article as: G. Falchook, A. Patnaik, D.L. Richardson et al., A Relative Bioavailability, Bioequivalence, and Food Effect Study of Niraparib Tablets in Patients with Advanced Solid Tumors, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2024.01.004

to the other treatment after a 7-day washout period, which was extended to 14 days in the BE and FE stages. Tolerability was assessed for patients who received any amount of niraparib.

Findings: The BA-, BE-, and FE-evaluable populations comprised 23, 108, and 19 patients, respectively, who completed both treatment periods in each study stage, had sufficient concentration data to accurately estimate PK parameters without niraparib carryover, and did not experience disqualifying events. PK parameters were similar after dosing with tablet or capsule formulations; the 90% CIs of the geometric least square means for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the 0.80 to 1.25 BE limits. In the FE stage, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 11%, 32%, and 28% higher, respectively, in the fed versus fasted state. The safety population included 29, 168, and 28 patients in the BA, BE, and FE stages, respectively, who received niraparib. No new safety signals were identified.

Implications: Niraparib tablets were found to be bioequivalent to capsules. A modest (≤32%) FE was observed with a high-fat meal, but was not considered to be clinically meaningful, given niraparib's PK variability. ClinicalTrials.gov identifier: NCT03329001. (*Clin Ther*. 2024;46:XXX–XXX) © 2024 Elsevier HS Journals, Inc.

Introduction

Poly (ADP-ribose) polymerase enzymes (PARPs) are a family of proteins involved with DNA repair, genomic stability, and apoptosis. PARP inhibitors (PARPi) prevent DNA single-strand break repair, which leads to the accumulation of double-strand breaks and cell death through synthetic lethality in the presence of defects in homologous recombination repair (through mutations in breast cancer gene [*BRCA1* or *BRCA2*] or due to other defects).[1] Niraparib is a PARPi treatment approved for the first-line maintenance therapy of adults with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (collectively termed *advanced epithelial ovarian cancer*) after first-line platinum-based chemotherapy.[2,3] Niraparib is also approved in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (restricted to patients with deleterious or suspected deleterious germline *BRCA*-mutated in the United States) who experienced a complete or partial response to platinum-based chemotherapy.[2,3]

Niraparib has a high tissue distribution[4] and a prolonged estimated half-life of approximately 50 hours.[3] The solubility of niraparib is pH-independent, with an aqueous free base solubility of 0.7 to 1.1 mg/mL across the physiologic pH range; the absolute bioavailability (BA) of the capsule formulation is 73%.[2,5] The Biopharmaceutical Classification System classifies niraparib as a class I drug (high permeability and high solubility) when administered at 200 mg and class II (high permeability and low solubility) when administered at 300 mg.[6,7] Researchers have reported that food intake did not affect the pharmacokinetic (PK) profile of niraparib when administered as capsules at a 300-mg dose to patients with advanced epithelial ovarian cancer.[8]

The recommended dosages of niraparib for the first-line maintenance treatment of advanced epithelial ovarian cancer[2,3] are (1) 200 mg (2 × 100-mg capsules) once daily for patients weighing <77 kg or with a platelet count <150,000/μL and (2) 300 mg (3 × 100-mg capsules) once daily for patients weighing ≥77 kg and with a platelet count ≥150,000/μL.

For maintenance treatment of relapsed or recurrent advanced epithelial ovarian cancer, the recommended dose is 300 mg (3 × 100-mg capsules) once daily for all patients.[2,3]

Although niraparib was first approved as a capsule formulation, tablets enable greater scalable manufacturing due to their smaller size, and would provide patients with an easier to swallow treatment. In addition, given that previous research on the food effect (FE) of niraparib was limited to a capsule formulation only,[8] assessment of the FE with niraparib tablets was required according to current US Food and Drug Administration (FDA) guidelines.[9] Finally, as PARPi therapies have the potential to be genotoxic in humans,[3] and have been found to be associated with myelosuppression and hematologic toxicities,[10] assessment of the bioequivalence (BE) or FE of niraparib in healthy volunteers could not be justified.[11] The present study evaluated the relative BA and BE of the niraparib tablet formulation compared with the approved capsule formulation. In addition, the FE on the PK parameters of niraparib tablets in patients with advanced solid tumors was evaluated.

Methods

Study Design

This was a US-based, open-label, multicenter, single-cohort, randomized-sequence, single-crossover study in patients with advanced solid tumors (ClinicalTrials.gov identifier: NCT03329001). The study consisted of 3 stages (ie, BA, BE, and FE), as illustrated in Figure 1. The BA stage assessed the relative BA of the niraparib 1 × 300-mg tablet and 3 × 100-mg capsule formulations and determined the sample size for the BE stage. The BE stage provided the primary clinical evidence of the BE of the 2 formulations. The FE stage evaluated the effect of a high-fat meal on the PK parameters of the niraparib tablet formulation. This study followed FDA guidance for BE and FE studies of oral therapies[9,11] and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines after approval from the Ethics Committees and Institutional Review Boards at each study site. All patients provided written informed consent.[9,11]

Treatment

In the BA and BE stages, patients were randomly assigned 1:1 to receive a single niraparib dose (tablet or capsules) after an 8-hour fast. After baseline sample collection and once patients had received their initial treatment, PK samples were collected for 7 days before patients were crossed over to receive the other formulation. In the BA stage, patients underwent a 7-day washout period (approximately 3 niraparib half-lives), which included PK sample collection time between niraparib formulations. In the BE and FE stages, a 14-day washout period (approximately 5 niraparib half-lives), which included PK sample collection time, was used between niraparib formulation and prandial states, respectively.

In the FE stage, patients were randomly assigned 1:1 after a ≥10-hour overnight fast to receive a single niraparib tablet either fasted or with a high-fat meal, as specified by FDA guidelines[9] (see high-fat meal example in Supplemental Table I). PK samples were collected over 7 days and, once patients had completed the 14-day washout period, they were then crossed over to the alternative prandial state. Patients taking niraparib with a high-fat meal had up to 30 minutes to consume the entire meal and took niraparib with 240 mL of water within 5 minutes of finishing the meal. Patients in the fasted state took niraparib with 240 mL of water only. All patients were required to fast for 4 hours post dose. After completion of both treatment periods, patients were allowed to receive daily niraparib administration in an extension phase of this study; data from this phase are not presented.

PK Assessments

In the BA stage, blood samples were collected for PK assessments at the following time points relative to niraparib dosing: pre dose (within

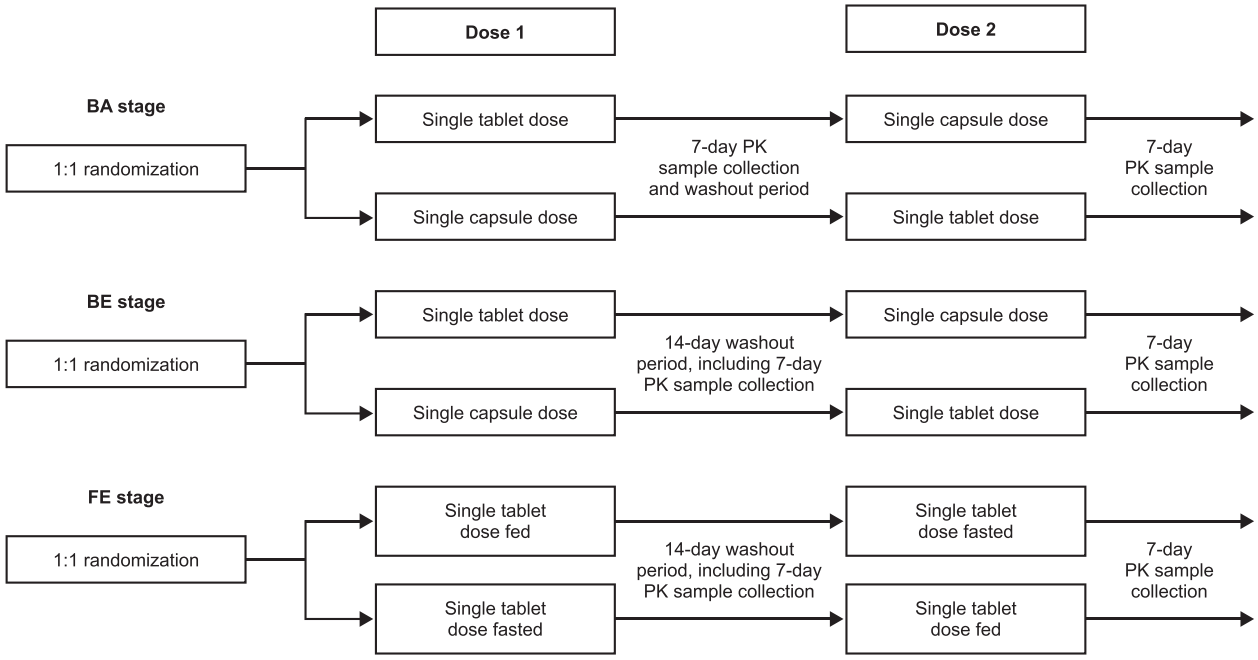


Figure 1. Overall study design. BA = bioavailability; BE = bioequivalence; FE = food effect, PK = pharmacokinetic.

0.5 hours before dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 168 hours post dose. In the BE and FE stages, PK sampling time points relative to niraparib dosing were pre dose (within 0.5 hours before dosing) and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, and 168 hours post dose. Samples were analyzed for plasma niraparib concentration using a validated liquid chromatography coupled to tandem mass spectrometry bioanalytical method,[12] with an analytical range of 5 to 2500 ng/mL. The following PK parameters were assessed for all 3 study stages: (1) C_{max}, (2) $AUC_{0\text{-}t,}$ (3) $AUC_{0\text{-}\infty,}$ (4) CL/F, (5) T_{max}, (6) $t_{\frac{1}{2}}$, and (7) apparent volume of distribution (Vd/F).

Safety Assessments

Tolerability assessments were conducted throughout the study and for 30 days after the last dose of niraparib (90 days for serious adverse events [SAEs]). Safety profile included treatment-emergent adverse events (TEAEs), SAEs, and discontinuations due to AEs. AEs for the BA, BE, and FE stages were classified per *Medical Dictionary for Regulatory Activities* (versions 20.0, 22.0, and 24.1, respectively).[13–15] Investigators assessed all AEs for severity according to *Common Terminology Criteria for Adverse Events*, version 4.03.[16]

Eligibility

Eligible patients were ≥18 years of age with histologically or cytologically confirmed advanced solid tumors (metastatic or local) who had failed to respond to standard therapy or for whom no standard therapy exists. Eligible patients also had disease progression despite standard therapy or were considered as those who may benefit from PARPi treatment, as determined by the investigator. Patients had an Eastern Cooperative Oncology Group Performance Status of 0 to 2 and adequate organ function, defined as absolute neutrophil count ≥1500 μL, platelet ≥100,000 μL, hemoglobin ≥9 g/dL, serum creatinine ≤1.5 × the upper limit of normal (ULN) or a calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation or 24-hour urine creatinine clearance, total bilirubin ≤1.5 × ULN (except in patients with Gilbert's syndrome who were enrolled if direct bilirubin was ≤1.5 × ULN), and aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN unless liver metastases were present, in which case, they must have been ≤5 × ULN. Patients eligible for the FE stage were required to be able to eat a high-fat meal, fast for a minimum of 10 hours before and 4 hours after dosing, and meet the central nervous system inclusion criteria based on magnetic resonance screening (ie, no evidence of brain metastases or untreated or previously treated metastases that did not require local therapy). Full inclusion and exclusion criteria are listed in Supplemental Table II.

Statistical Analysis

Sample Size Considerations

No formal sample size calculation was performed for the BA stage. A sample size of 24 patients was considered adequate for preliminary assessments of the relative BA and estimation of the intra-patient %CV after accounting for patient dropouts and potential carryover.

The BE sample size was estimated on the basis of assumptions of intra-patient %CV of 25% and true ratio of means of 0.89, as determined in the BA stage; 100 patients were considered sufficient to allow 90% power to indicate BE. Target enrollment for the BE stage was therefore set at 170 patients, assuming a 35% nonevaluability rate during study conduct and 10% nonevaluability rate during PK analysis.

The FE sample size was determined under the assumption that the true ratio of means was 1 and the intra-patient %CV was 20% for AUC_{0-t} and $AUC_{0-\infty}$; therefore, with 16 evaluable patients, there was approximately 83% probability that the 90% CI of the ratio of geometric least square means (LSM) would be within 0.800 and 1.250 (80%–125%). Target enrollment for the FE stage was therefore set at approximately 20 patients to ensure 16 evaluable patients.

Analysis Populations

The BA-evaluable, BE-evaluable, and FE-evaluable populations consisted of patients who completed both treatment and washout periods, had sufficient concentration data to accurately estimate PK parameters without niraparib carryover (ie, pre-dose concentration >5% of C_{max} based on FDA guidance[11]), and did not have event or protocol deviations affecting PK parameters.

For each study stage, the safety population consisted of patients who received any amount of niraparib.

Considerations for PK Parameter Analysis

Descriptive statistics were used to summarize continuous variables. PK summary parameters also included %CV, geometric mean, and geometric %CV, when applicable, except for t_{max}, which was summarized with number of patients, median, minimum, and maximum. PK parameters were calculated from the plasma concentration–time profiles for patients using noncompartmental methods (Phoenix WinNonlin [Certara, Princeton, NJ], version 7.0 or higher for the BA stage, version 8.0 for the BA and FE stages). During the PK analysis, the following rules were applied: if the pre-dose sample concentration was >5% of C_{max}, the profile was excluded from the PK concentration summary, the PK parameters summary, and inferential statistics; if adjusted R^2 was <0.800, then $AUC_{0-\infty}$, CL/F, Vd/F, and $t_{1/2}$ were excluded from descriptive and inferential statistics; if $AUC_{0-t}/AUC_{0-\infty}$ was <0.8000 (ie, $AUC_{0-\infty}$ was extrapolated >20%), then $AUC_{0-\infty}$, CL/F, and Vd/F were excluded from descriptive and inferential statistics.

A linear mixed-effects model was applied to the log-transformed values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, with fixed effects for sequence, period, and treatment, and a random effect for patient nested within sequence. This analysis assessed the BA and BE of niraparib capsule and tablet formulations and the FE on niraparib tablets; the 90% CIs for ratios of geometric means of the tablet compared with the capsule formulation (for BA and BE) and of the fed compared with the fasted state (for FE) were determined. BE between the tablet versus capsule formulation in the BE stage and absence of an FE between the prandial states in the FE stage were considered to be achieved if the 90% CI for the ratios of LSM were between 0.800 and 1.250 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. In the FE stage, a statistical comparison of the median t_{max} for each prandial state and the median of the differences between states (fed minus fasted) was provided using the FE-evaluable population. A nonparametric analysis was used to produce the median (90% CI [exact]) difference between prandial states (Hodges–Lehmann estimates), and *P* values were calculated using the Wilcoxon signed rank test.

Results

Patient Demographic Characteristics

Patient flow charts, denoting the total number of patients screened and included for each subpopulation, are provided in Figure 2. In total, the number of patients who received at least 1 niraparib dose and were included in the safety profile populations was 29 patients in the BA stage, 168 patients in the BE stage, and 28 patients in the FE stage. Baseline demographic and patient characteristics of the safety profile populations for patients in each stage by formulation (BA and BE) or prandial state (FE) sequence are shown in Table 1.

The BA-, BE-, and FE-evaluable populations, which were the primary analysis populations, consisted of 23 patients in the BA stage, 108 patients in the BE stage, and 19 patients in the FE stage. Baseline demographic characteristics for these populations are described in Supplemental Table III, and reasons for nonevaluability of excluded patients are detailed in Supplemental Table IV. In brief, for the BE-evaluable population, the 2 most common reasons for excluding patients were (1) discontinuation from study due to death, progressive disease, SAE, or other reason and thus did not have evaluable PK data for both treatment periods (n = 18) and (2) dosing error (n = 13; see Supplemental Table IV footnotes).

Assessments

BA Stage

In the BA-evaluable population, the mean concentration–time profile was similar between a single dose of niraparib tablet and the capsule formulation (Figure 3A). Niraparib peak and overall exposures were slightly lower after tablet administration compared with the capsule formulation (Table 2). The median t_{max} was similar after both formulations, suggesting that the rate of absorption did not differ, and niraparib mean $t_{1/2}$ (%CV) was also similar between the 2 formulations (48.4 [23.3%] and 44.9 [23.1%] hours, respectively). Overall, inter-patient variability was moderate and similar between the 2 formulations.

Statistical evaluation of PK parameters found similar BA between the tablet and capsule formulations, as shown in Table 3. The geometric LSM ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 0.948 (90% CI, 0.849–1.059), 0.911 (90% CI, 0.855–0.971), and 0.922 (90% CI, 0.863–0.984), and the 90% CI fell within the prespecified range of 0.800 to 1.250.

Tolerability results for the BA stage are reported for 29 patients who received at least 1 dose of niraparib in the tablet formulation and 29 patients in the capsule formulation. In total, 3.4% of patients (1/29) experienced a treatment-related TEAE when receiving the tablet formulation and 17.2% of patients (5/29) experienced a treatment-related TEAE when receiving the capsule formulation (Table 4). The most common treatment-related TEAEs were nausea (tablet formulation, 3.4% [n = 1/29]; capsule formulation, 13.8% [4/29]) and vomiting (tablet formulation, 3.4% [1/29]; capsule formulation, 3.4% [1/29]). No treatment-related grade ≥3 or SAEs were reported. All TEAEs for the BA stage safety profile population are reported in Supplemental Table V.

BE Stage

In the BE-evaluable population, a single dose of the niraparib tablet or capsule formulations had nearly identical mean concentration–time profiles (Figure 3B). Similarly, there were no notable differences in PK characteristics between the 2 formulations (Table 2). Maximum niraparib concentrations were reached within approximately 5 hours post dose (t_{max}) regardless of formulation type, indicating no apparent difference in absorption rate between the 2 formulations. Niraparib $t_{1/2}$ was also similar between formulations; mean $t_{1/2}$ (%CV) was 49.6 hours (28.2%) and 51.9 hours (27.1%) for tablet and capsule formulations, respectively.

The 2 formulations had moderate and similar inter-patient variability; the geometric %CV of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ ranged from 50.0% to 60.3% after tablet administration and from 44.3% to 54.2% after capsule administration.

Statistical assessment of niraparib BE was performed between the tablet and capsule formulations by analyzing C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (Table 3). The geometric LSM ratios were 0.962 (90% CI, 0.912–1.014), 0.959 (90% CI, 0.920–1.001), and 0.957 (90% CI, 0.916–0.999), respectively, indicating BE between tablet and capsule formulations, as the 90% CI fell within the prespecified BE range from 0.800 to 1.250.

Tolerability results for the BE stage are reported for 156 patients who received at least 1 dose of niraparib in the tablet formulation and 152 patients in the capsule formulation. In total, 24.4% of patients (38/156) experienced a treatment-related TEAE when receiving the tablet formulation and 19.1% of patients (29/152) when receiving the capsule formulation (Table 4). The most common treatment-related TEAEs were nausea (tablet formulation, 7.1% [11/156]; capsule formulation, 5.9% [9/152]), constipation (tablet formulation, 4.5% [7/156]; capsule formulation, 3.3% [5/152]), and vomiting (tablet formulation, 4.5% [7/156]; capsule formulation, 3.3% [5/152]). Grade ≥3 treatment-related TEAEs occurred in 1.3% of patients (2/156) when receiving the tablet formulation and 2.6% of patients (4/152) when receiving the capsule formulation. Treatment-related SAEs occurred in 1 of the 152 patients (0.7%) when receiving the capsule formulation; the patient reported nausea and vomiting; no treatment-related SAEs were reported for patients when receiving the tablet formulation. All TEAEs for the BE stage safety profile population are reported in Supplemental Table VI.

FE Stage

In the FE-evaluable population, the mean concentration–time profile indicated a slight increase in exposure after administration of niraparib in the fed state compared with the fasted state (Figure 3C). Similarly, an

Table 1
Baseline patient demographic characteristics and characteristics of bioavailability, bioequivalence, and food effect safety populations.

Characteristic	BA Stage			BE Stage			FE Stage		
	Sequence Tablet/Capsule (n = 15)	Sequence Capsule/Tablet (n = 14)	Overall (N = 29)	Sequence Tablet/Capsule (n = 85)	Sequence Capsule/Tablet (n = 83)	Overall (N = 168)	Sequence Fasted/Fed* (n = 14)	Sequence Fed*/Fasted (n = 14)	Overall (N = 28)
Age (y), median (minimum, maximum)	67.0 (42, 88)	64.5 (28, 83)	66.0 (28, 88)	64.0 (26, 87)	66.0 (29, 85)	65.5 (26, 87)	65.0 (36, 76)	54.5 (28, 79)	63.5 (28, 79)
Age group, n (%)									
18 to <65 y	5 (33.0)	7 (50.0)	12 (41.4)	43 (50.6)	38 (45.8)	81 (48.2)	6 (42.9)	9 (64.3)	15 (53.6)
65 to <75 y	9 (60.0)	4 (28.6)	13 (44.8)	27 (31.8)	32 (38.6)	59 (35.1)	7 (50.0)	1 (7.1)	8 (28.6)
≥75 y	1 (6.7)	3 (21.4)	4 (13.8)	15 (17.6)	13 (15.7)	28 (16.7)	1 (7.1)	4 (28.6)	5 (17.9)
Sex, n (%)									
Male	6 (40.0)	5 (35.7)	11 (37.9)	37 (43.5)	35 (42.2)	72 (42.9)	9 (64.3)	8 (57.1)	17 (60.7)
Female	9 (60.0)	9 (64.3)	18 (62.1)	48 (56.5)	48 (57.8)	96 (57.1)	5 (35.7)	6 (42.9)	11 (39.3)
Race, n (%)									
White	14 (93.3)	14 (100.0)	28 (96.6)	63 (74.1)	62 (74.7)	125 (74.4)	8 (57.1)	10 (71.4)	18 (64.3)
African American	1 (6.7)	0	1 (3.4)	11 (12.9)	11 (13.3)	22 (13.1)	5 (35.7)	0	5 (17.9)
Asian	0	0	0	5 (5.9)	3 (3.6)	8 (4.8)	0	0	0
American Indian or Alaska Native	0	0	0	2 (2.4)	0	2 (1.2)	0	0	0
Not reported	0	0	0	4 (4.7)	7 (8.4)	11 (6.5)	1 (7.1)	4 (28.6)	5 (17.9)
Ethnicity, n (%)									
Hispanic or Latino	8 (53.3)	5 (35.7)	13 (44.8)	6 (7.1)	4 (4.8)	10 (6.0)	1 (7.1)	3 (21.4)	4 (14.3)
Not Hispanic or Latino	7 (46.7)	9 (64.3)	16 (55.2)	70 (82.4)	69 (83.1)	139 (82.7)	12 (85.7)	11 (78.6)	23 (82.1)
Unknown	0	0	0	1 (1.2)	4 (4.8)	5 (3.0)	0	0	0
Not reported	0	0	0	8 (9.4)	6 (7.2)	14 (8.3)	1 (7.1)	0	1 (3.6)
Weight (kg), mean (SD)	76.4 (18.72)	80.1 (22.47)	78.2 (20.32)	80.4 (18.8)	83.6 (21.7)	82.0 (20.3)	75.6 (20.8)	89.5 (19.5)	82.5 (21.0)
BMI, mean (SD)	27.3 (5.24)	29.3 (7.24)	28.3 (6.25)	28.2 (6.4)	29.0 (6.8)	28.6 (6.6)	25.4 (7.5)	31.0 (7.3)	28.1 (7.8)
ECOG PS, n (%)									
0	4 (26.7)	4 (28.6)	8 (27.6)	20 (23.5)	18 (21.7)	38 (22.6)	2 (14.3)	7 (50.0)	9 (32.1)
1	11 (73.3)	10 (71.4)	21 (72.4)	61 (71.8)	60 (72.3)	121 (72.0)	11 (78.6)	7 (50.0)	18 (64.3)
2	0	0	0	4 (4.7)	5 (6.0)	9 (5.4)	1 (7.1)	0	1 (3.6)
Cancer stage (most recent), n (%)									
Locally advanced	0	1 (7.1)	1 (3.4)	3 (3.5)	2 (2.4)	5 (3.0)	0	0	0
Metastatic	15 (100.0)	13 (92.9)	28 (96.6)	82 (96.5)	81 (97.6)	163 (97.0)	14 (100)	14 (100)	28 (100)
No. of prior lines of therapy, median (range)	3 (2–9)	2 (1–11)	3 (1–11)	4 (0–12)	3 (1–12)	3 (0–12)	3 (1–19)	3.5 (1–7)	3 (1–19)
Any prior radiotherapy, n (%)	9 (60.0)	6 (42.9)	15 (51.7)	49 (57.6)	44 (53.0)	93 (55.4)	4 (28.6)	7 (50.0)	11 (39.3)
5 most common tumor types, n (%)†									
Pancreatic adenocarcinoma	0	1 (7.1)	1 (3.4)	13 (15.3)	13 (15.7)	26 (15.5)	5 (37.5)	2 (14.3)	7 (25.0)
Prostate cancer	3 (20.0)	1 (7.1)	4 (13.8)	9 (10.6)	9 (10.8)	18 (10.7)	0	2 (14.3)	2 (7.1)
Colon cancer	3 (20.0)	2 (14.3)	5 (17.2)	10 (11.8)	5 (6.0)	15 (8.9)	5 (37.5)	4 (28.6)	9 (32.1)
Endometrial cancer	1 (6.7)	0	1 (3.4)	4 (4.7)	9 (10.8)	13 (7.7)	0	0	0
Ovarian cancer, serous histology	2 (13.3)	1 (7.1)	3 (10.3)	7 (8.2)	6 (7.2)	13 (7.7)	0	0	0
Other cancer types	6 (40.0)	9 (64.2)	15 (51.7)	42 (49.4)	41 (49.4)	83 (49.4)	1 (7.1)	5 (35.7)	6 (21.4)

BA = bioavailability; BE = bioequivalence; BMI = body mass index (calculated as kg / m^2); ECOG PS = Eastern Cooperative Oncology Group Performance Status; FE = food effect.

* Fed with a high-fat meal.

† Based on patients included in the BE stage.

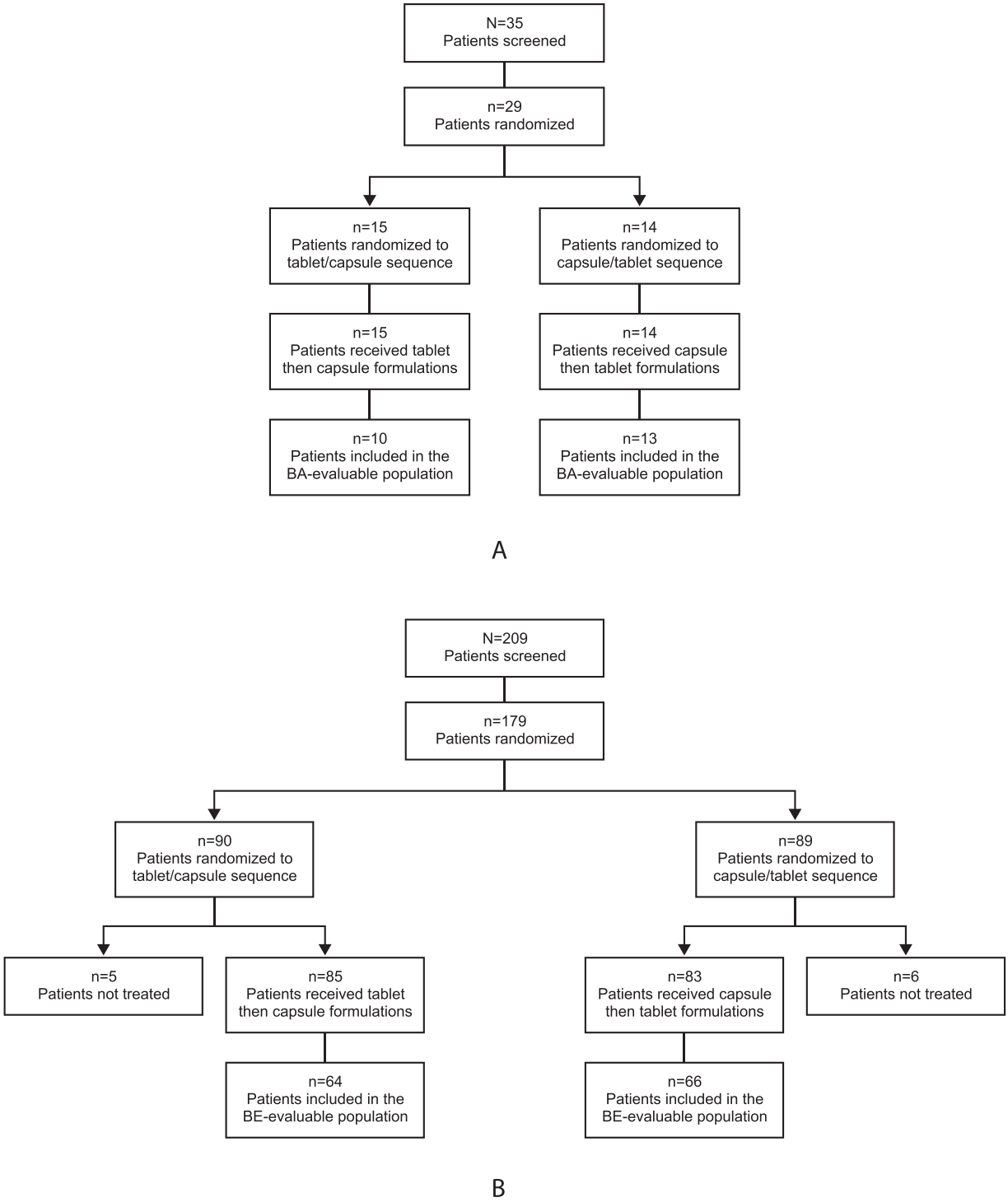
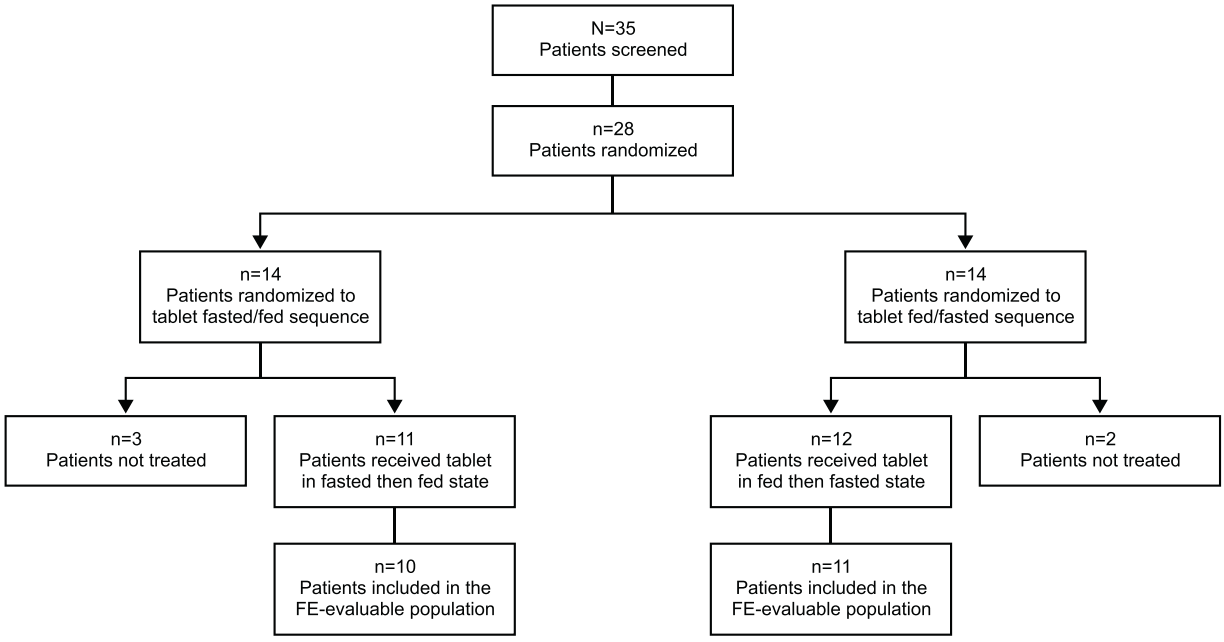


Figure 2. Patient flow diagram for the (A) bioavailability (BA), (B) bioequivalence (BE), and (C) food effect (FE) stages.

overall slightly higher trend in PK parameters was observed in the fed state compared with the fasted state (Table 2). Peak niraparib concentrations were reached within approximately 6 hours and 5 hours post dose (t_{max}) for the fed and fasted states, respectively, and the difference between t_{max} values did not reach statistical significance ($P = .185$). The $t_{1/2}$ of niraparib was similar; mean $t_{1/2}$ (%CV) was 47.3 hours (21.7%) for the fasted state and 47.2 hours (23.2%) for the fed state. Inter-patient variability was moderate to high and slightly reduced in the fed state; the geometric %CV of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ ranged from 47.2% to 65.2% in the fed state and from 57.0% to 78.5% in the fasted state.

Statistical assessment of the 3 key PK parameters between the fed and fasted states is shown in Table 3. The geometric LSM ratios were 1.113 (90% CI, 0.941–1.316) for C_{max}, 1.315 (90% CI, 1.174–1.474) for AUC_{0-t}, and 1.277 (90% CI, 1.154–1.414) for $AUC_{0-\infty}$. Niraparib C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 11%, 32%, and 28% higher in the fed versus fasted state, indicating an increase in exposure with a high-fat meal.



C

Figure 2. Continued

Table 2
Summary of pharmacokinetic parameters by niraparib treatment in the bioavailability-, bioequivalence-, and food effect-evaluable populations.

Variable	BA-Evaluable Population			BE-Evaluable Population			FE-Evaluable Population		
	n	Tablet (Test)	Capsule (Reference)	n	Tablet (Test)	Capsule (Reference)	n	Fed* (Test)	Fasted (Reference)
C_{max} (ng/mL), mean (%CV)	23	494 (42.3)	521 (49.2)	108	581 (50.0)	595 (44.3)	19	855 (48.9)	799 (50.6)
t_{max} (h), median (minimum, maximum)	23	4.1 (2.0, 8.0)	4.0 (1.5, 25.0)	108	5.0 (1.6, 8.0)	5.0 (1.0, 23.8)	19	6.0 (1.0, 11.1)	4.9 (3.0, 7.1)
AUC_{0-t} (h/ng/mL), mean (%CV)	23	16,200 (42.4)	17,300 (40.9)	107†	19,800 (60.3)	20,190 (54.0)	16†	29,210 (51.9)	23,540 (59.8)
$AUC_{0-\infty}$ (h/ng/mL), mean (%CV)	23	17,700 (43.9)	18,600 (41.1)	98‡	20,450 (59.3)	20,990 (54.2)	18‡	35,760 (71.0)	30,360 (87.7)
CL/F (L/h), mean (%CV)	23	20.1 (39.7)	18.8 (38.8)	98‡	19.1 (47.4)	18.3 (48.0)	18‡	11.7 (50.3)	15.6 (64.1)
Vd/F (L), mean (%CV)	23	1370 (40.4)	1190 (39.3)	98‡	1258 (46.4)	1253(44.5)	18‡	729 (45.5)	1052 (70.6)
$t_{1/2}$ (h), mean (%CV)	23	48.4 (23.3)	44.9 (23.1)	108	49.6 (28.2)	51.9 (27.1)	19	47.2 (23.2)	47.3 (21.7)

BA = bioavailability; BE = bioequivalence; FE = food effect; PK = pharmacokinetic; Vd/F = apparent volume of distribution.
* Fed with a high-fat meal.
† Patients with AUC_{0-t} values collected outside the sample window were excluded from the analysis.
‡ Patients with $AUC_{0-\infty}$ values >20% were excluded from analysis along with CL/F and Vd/F per pharmacokinetic parameter analysis rules.

Tolerability results for the FE stage are reported for 25 patients who received at least 1 dose of niraparib in the fed state and 26 patients in the fasted state. In total, 24.0% of patients (6/24) experienced a treatment-related TEAE in the fed state and 11.5% of patients (3/26) experienced a treatment-related TEAE in the fasted state (Table 4). The most common treatment-related TEAEs were nausea (fed, 8.0% [2/25]; fasted, 3.8% [1/26]), vomiting (fed, 4.0% [1/25]; fasted, 3.8% [1/26]), and headache (fed state only, 8.0% [2/25]). No treatment-related grade ≥3 or SAEs were reported. All TEAEs for the FE stage safety profile population are reported in Supplemental Table VII.

Discussion

In this study, the niraparib tablet formulation was found to be bioequivalent to the capsule formulation. A modest (11%–32%) increase in the 3 key PK parameters (ie, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) was observed in the fed versus fasted state for the niraparib tablet, but the magnitude was lower than inter-patient variability in PK; therefore, this result was not considered clinically meaningful in the context of the PK variability of the niraparib formulation.

Niraparib capsule and tablet formulations had similar concentration–time profiles and PK parameters in both BA and BE stages. Overall, the geometric LSM ratios of the key niraparib PK parameters for the tablet versus capsule formulation had 90% CIs within the predefined limits of 0.800 and 1.250, indicating similar relative BA and BE. When the effect of a high-fat meal was assessed in the FE stage, an increase of 11%, 32%, and 28% was observed for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively. Studies of the FE of other PARPi therapies approved for use in ovarian cancer have also reported minor changes in PK parameters, including a statistically significant increase in $AUC_{0-\infty}$ for patients who received olaparib in the fed versus fasted state, and a fed to fasted geometric mean ratio of 120% (90% CI, 99.1%–146%) for C_{max} for patients who received rucaparib; however, neither were thought to be clinically relevant.[17,18] Of note, the increase in C_{max} for patients who received niraparib tablets in the fed versus fasted state deviated from the findings of a previous study that assessed FE on niraparib capsules.[8] Differences in study design and time-point selection may have contributed to this finding.

The safety profiles of the tablet and capsule formulations and between the fed and fasted states were found to be similar; no new safety

Table 3
Analysis of niraparib pharmacokinetic parameters in the bioavailability-, bioequivalence-, and food effect-evaluable populations.

Stage	Parameter	Treatment	n	Geometric LSM	Ratio	90% CI of Ratio of Geometric LSM	Intra-patient %CV
BA	C_{max} (ng/mL)	Tablet (test)	23	448.8	0.948	0.849–1.059	21.9
		Capsule (reference)	23	473.2	–	–	–
	AUC_{0-t} (h/ng/mL)	Tablet (test)	23	14,861	0.911	0.855–0.971	12.4
		Capsule (reference)	23	16,313	–	–	–
	$AUC_{0-\infty}$ (h/ng/mL)	Tablet (test)	23	16,119	0.922	0.863–0.984	12.9
		Capsule (reference)	23	17,490	–	–	–
BE	C_{max} (ng/mL)	Tablet (test)	108	518.1	0.962	0.912–1.014	23.7
		Capsule (reference)	108	538.6	–	–	–
	AUC_{0-t} (h/ng/mL)	Tablet (test)	107*	17,020	0.959	0.920–1.001	18.7
		Capsule (reference)	107*	17,740	–	–	–
	$AUC_{0-\infty}$ (h/ng/mL)	Tablet (test)	98†	17,620	0.957	0.916–0.999	18.1
		Capsule (reference)	98†	18,420	–	–	–
FE	C_{max} (ng/mL)	Fed‡ (test)	19	791.3	1.113	0.941–1.316	30.0
		Fasted (reference)	19	711.1	–	–	–
	AUC_{0-t} (h/ng/mL)	Fed‡ (test)	16	26,530	1.315	1.174–1.474	18.2
		Fasted (reference)	16	20,170	–	–	–
	$AUC_{0-\infty}$ (h/ng/mL)	Fed‡ (test)	18	30,240	1.277	1.154–1.414	17.5
		Fasted (reference)	18	23,680	–	–	–

BA = bioavailability; BE = bioequivalence; FE = food effect; LSM = least squares mean.
* Patients with AUC_{0-t} values collected outside the sample window were excluded from the analysis.
† Patients with $AUC_{0-\infty}$ values extrapolated >20% were excluded from analysis along with CL/F and Vd/F per pharmacokinetic parameter analysis rules.
‡ Fed with a high-fat meal.

Table 4
Treatment-related treatment-emergent adverse events in all patients (bioavailability and food effect) and ≥2% (bioequivalence) of patients in the bioavailability-, bioequivalence-, and food effect-safety populations.

Variable	BA Stage		BE Stage		FE Stage	
	Tablet* (n = 29)	Capsule* (n = 29)	Tablet* (n = 156)	Capsule* (n = 152)	Fed*† (n = 25)	Fasted* (n = 26)
All treatment-related TEAEs, n (%)	1 (3.4)	5 (17.2)	38 (24.4)	29 (19.1)	6 (24.0)	3 (11.5)
Treatment-related TEAEs,‡ n (%)						
Nausea	1 (3.4)	4 (13.8)	11 (7.1)	9 (5.9)	2 (8.0)	1 (3.8)
Constipation	–	–	7 (4.5)	5 (3.3)	–	–
Vomiting	1 (3.4)	1 (3.4)	7 (4.5)	5 (3.3)	1 (4.0)	1 (3.8)
Fatigue	–	–	6 (3.8)	4 (2.6)	–	–
Headache	–	–	5 (3.2)	1 (0.7)	2 (8.0)	–
Abdominal pain	–	–	–	–	1 (4.0)	–
Anemia	–	–	–	–	1 (4.0)	–
Iron deficiency anemia	–	–	–	–	1 (4.0)	–
Tumor pain	–	1 (3.4)	–	–	–	–
Breast swelling	–	1 (3.4)	–	–	–	–
Platelet count decreased	–	–	–	–	–	1 (3.8)
Any grade ≥3 treatment-related TEAE, n (%)	0	0	2 (1.3)	4 (2.6)	0	0
Any treatment-related serious TEAE, n (%)	0	0	0	1 (0.7)	0	0

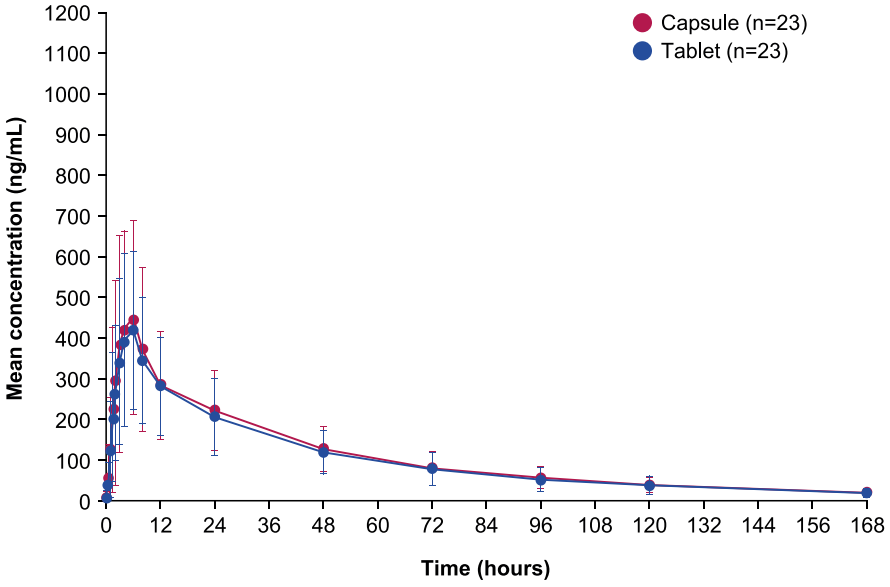
BA = bioavailability; BE = bioequivalence; FE = food effect; TEAE = treatment-emergent adverse event.
* Includes TEAEs with onset date in the treatment period.
† Fed with high-fat meal.
‡ Reported for either all patients (BA and FE) or ≥2% of patients for at least 1 formulation state (BE).

signals were observed during this study, as compared with previous niraparib clinical studies.[8,19,20] Due to the single-dose crossover study design in all 3 study stages, the safety data for niraparib in this study are limited compared with other niraparib studies in which niraparib was dosed continuously.

During the study, 2 protocol amendments were implemented after completion of the BA stage, with the aim of improving data capture. Initially, washout periods between formulations were 7 days; however, as niraparib levels remained notably above the predefined threshold (predose concentration >5% of C_{max}) before initiation of the second treatment period for some patients in the BA stage, the washout period was extended to 14 days for the BE and FE stages. After analysis of the BA data, the PK sampling scheme in the BE and FE stages was adjusted by means of removing the 0.5-hour time point post dose and adding 5- and 7-hour post-dose time points to better capture C_{max}.

After completion of the study, patients were able to enroll in an extension phase, where they could continue to receive daily niraparib if tolerable to the patient and if deemed beneficial by the investigator. The aim of the extension phase was to evaluate the safety of continuously dosed niraparib in patients with advanced solid tumors.

There are numerous challenges in conducting large clinical pharmacology studies in patients with advanced cancer. These include study design elements, such as multiple blood draws over an extended period, unrealistic dietary restrictions, and single treatment doses with long washout periods between treatments. These requirements are challenging for patients, making it difficult to enroll patients in studies of this nature. Due to multiple competing studies and the availability of approved niraparib and other PARPi therapies, we expanded enrollment to patients with more advanced disease to aid recruitment. Clinical trials in patients with advanced cancer often do not allow enrollment of



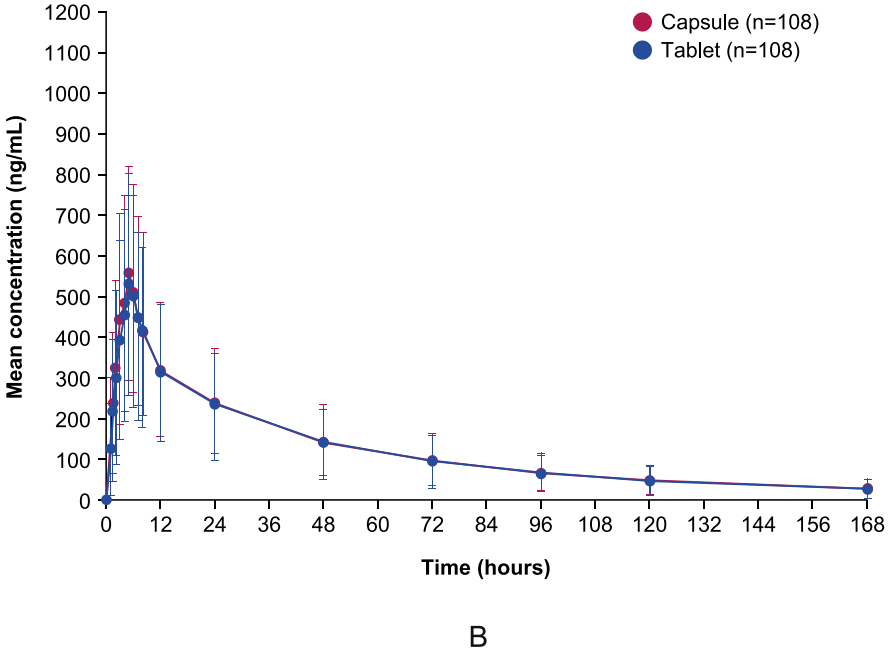
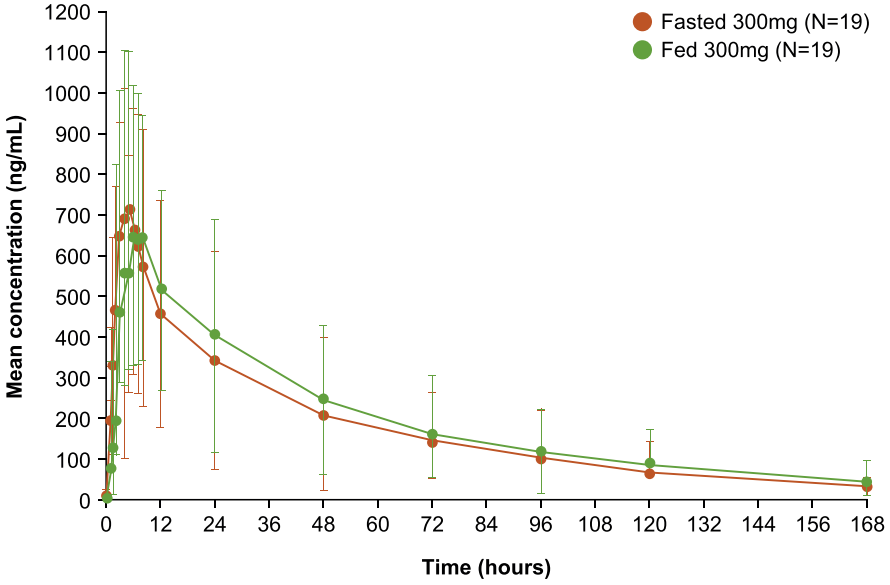


Figure 3. Mean (SD) niraparib concentration–time profiles for tablet and capsule formulation in the (A) bioavailability (BA)- (B) bioequivalence (BE)-, and (C) food effect (FE)-evaluable populations.

patients with Eastern Cooperative Oncology Group Performance Status ≥2,[21] tending to enroll healthier, lower-risk patients instead.[22] Here, patients with Eastern Cooperative Oncology Group Performance Status of 2 (n = 10) were eligible for inclusion in the study, increasing the available patient population, and generalizability of the data to clinic populations,[22] but also potentially contributing to increased frequency and severity of TEAEs, as well as the likelihood that patients would experience difficulties in adhering to the study restrictions and demands of a clinical pharmacology study. Unlike healthy volunteer studies, PK studies of patients with advanced cancer are more likely to result in a high nonevaluability rate, although they do enable relatively long duration use in patients who might not otherwise have access to study medications like niraparib in the extension phase of the study. It is important to consider that studies dependent on patients completing both treatment periods for the statistical evaluation, as in our study, are particularly difficult to conduct. Of note, a number of patients in the BE stage were excluded due to dosing administration from a different study stage being adopted in error. This was likely a consequence of running 2 very similar study stages within the same clinical center, and thus particular attention from personnel is required when conducting future complex study designs. In addition, conducting PK parameter studies with therapies that have long half-lives, including niraparib, may be particularly onerous, as the PK period requires several weeks of limited exposure to therapy, long days at the study site, and repeated visits for PK sample collection. In this study, several patients had disease progression and were subsequently switched to palliative care or died between study periods; consequently, although these data were analyzed and contributed to the overall understanding of the PK parameters of niraparib, they could not be included in the primary analysis. Given the overall challenges of conducting clinical pharmacology studies in patients



C

with advanced cancer, alternate study designs or assessments should be considered.

Conclusions

In summary, the niraparib tablet and capsule formulations were found to be bioequivalent. An 11% to 32% increase in niraparib exposure observed for the tablet formulation when taken with a high-fat meal was not considered clinically meaningful. No new safety signals were identified.

Declaration of competing interest

This study was funded by GSK (GSK study 213362). GSK contributed to the study design, implementation, data collection, interpretation, and analysis. All authors had full access to the data and had final responsibility for the decision to submit for publication. Medical writing support was provided by Nicholas Thomas, PhD, of Fishawack Indicia Ltd, UK, part of Avalere Health, and funded by GSK.

Acknowledgments

The authors would like to acknowledge Sujata Arora, Reginald Ewesuedo, Michelle Kneissl, and Scott Murphy for their contributions to this publication.

Data Availability

GSK is committed to sharing anonymized patient-level data from interventional trials as per GSK policies and as applicable. Requests for patient-level data should be done via the following GSK link: https://www.gsk-studyregister.com/en/.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2024.01.004.

References

1. Lord CJ, Ashworth A. PARP inhibitors: the first synthetic lethal targeted therapy. *Science*. 2017;355(6330):1152.
2. Niraparib prescribing information. US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208447s026lbl.pdf. Accessed April 26, 2023.
3. Niraparib summary of product characteristics (SmPC). European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf. Accessed April 26, 2023.
4. van Andel L, Zhang Z, Lu S, et al. Human mass balance study and metabolite profiling of (14)C-niraparib, a novel poly(ADP-Ribose) polymerase (PARP)-1 and PARP-2 inhibitor, in patients with advanced cancer. *Invest New Drugs*. 2017;35:751–765.
5. van Andel L, Rosing H, Zhang Z, et al. Determination of the absolute oral bioavailability of niraparib by simultaneous administration of a (14)C-microtracer and therapeutic dose in cancer patients. *Cancer Chemother Pharmacol*. 2018;81:39–46.
6. Committee for Medicinal Products for Human Use Assessment report: Zejula. European Medicines Agency. https://www.ema.europa.eu/en/documents/assessment-report/zejula-epar-public-assessment-report_en.pdf. Accessed April 26, 2023.
7. Sun K, Mikule K, Wang Z, et al. A comparative pharmacokinetic study of PARP inhibitors demonstrates favorable properties for niraparib efficacy in preclinical tumor models. *Oncotarget*. 2018;9:37080–37096.
8. Moore K, Zhang ZY, Agarwal S, Burris H, Patel MR, Kansra V. The effect of food on the pharmacokinetics of niraparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, in patients with recurrent ovarian cancer. *Cancer Chemother Pharmacol*. 2018;81:497–503.
9. US Food and Drug Administration. *Assessing the Effects of Food on Drugs in INDs and NDAs-Clinical Pharmacology Considerations. Guidance for Industry*. Center for Drug Evaluation and Research, US Food and Drug Administration; 2022.
10. LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. *Lancet Oncol*. 2019;20:e15–e28. doi:10.1016/S1470-2045(18)30786-1.
11. US Food and Drug Administration. *Guidance for industry: bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA*. US Food and Drug Administration; 2013.
12. Sandhu SK, Schelman WR, Wilding G, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. *Lancet Oncol*. 2013;14:882–892.
13. *Medical Dictionary for Regulatory Activities*, version 20.0. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2017.
14. *Medical Dictionary for Regulatory Activities,* version 22.0. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2019.
15. *Medical Dictionary for Regulatory Activities,* version 24.1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2021.
16. . Common Terminology Criteria for Adverse Events*, version 4.03*. National Cancer Institute; 2010.
17. Plummer R, Swaisland H, Leunen K, et al. Olaparib tablet formulation: effect of food on the pharmacokinetics after oral dosing in patients with advanced solid tumours. *Cancer Chemother Pharmacol*. 2015;76:723–729.

18. Shapiro GI, Kristeleit RS, Burris HA, et al. Pharmacokinetic Study of Rucaparib in Patients With Advanced Solid Tumors. *Clin Pharmacol Drug Dev*. 2019;8:107–118.
19. Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2019;381:2391–2402.
20. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med*. 2016;375:2154–2164.
21. Abi JJ, Kouzy R, Mainwaring W, et al. Performance Status Restriction in Phase III Cancer Clinical Trials. *J Natl Compr Canc Netw*. 2020;18:1322–1326.
22. Jin S, Pazdur R, Sridhara R. Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015. *J Clin Oncol*. 2017;35:3745–3752.