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A Phase 1 Randomized Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Escalating Oral Doses of Dordaviprone and the Effects of Food on the Bioavailability of Dordaviprone in Healthy Adult Subjects

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Abstract

Dordaviprone (ONC201) is a novel, small molecule imipridone with antitumor effects in glioma patients. This study evaluated the pharmacokinetics and safety of dordaviprone following single escalating doses (Part A), as a capsule content mixed with applesauce or Gatorade (sports drink) [Part B1]), and with or without food [Part B2]. The most common treatment-emergent adverse events pooled across study parts (Parts A, B1, and B2) were headache, dizziness, and headache, respectively; all were mild. Systemic dordaviprone exposure increased dose proportionally following administration of 125-625 mg of dordaviprone. Following dordaviprone capsule contents sprinkled on applesauce or dissolved in sports drink, the geometric mean ratios, and 90% confidence intervals (CIs) of the dordaviprone area under the concentration versus time curve (AUC) fell within the bioequivalence (BE) limits of 80.00%-125.00%; however, for C_{max} the 90% CI lower limit (0.70) fell below BE limits when sprinkled on applesauce. The geometric mean ratios and 90% CIs of dordaviprone administered under fed versus fasted conditions fell within BE limits of 80.00%-125.00% for the AUC, indicating no food effect on total exposure; however, maximum concentration (C_{max}) (90% CI 0.55, 0.67) fell below BE limits.

Keywords

dordaviprone, dose escalation, food effect, ONC201, pharmacokinetics

Dordaviprone (ONC201) is the first member of a class of anticancer compounds called imipridones. The antitumor effects of dordaviprone have been demonstrated in multiple in vitro, ex vivo, and in vivo models across multiple tumor types.[1–6]

Dordaviprone is a brain-penetrant, small molecule agonist of mitochondrial caseinolytic protease P (ClpP) and an antagonist of G protein-coupled dopamine receptor D2 (DRD2). ClpP and DRD2 are overexpressed in a number of tumor types and have been tied to lower overall survival in patients[7] (Nouri, Cole, Przystal).[7–9] ClpP expression is essential for dordaviprone anticancer activity in vitro. Allosteric agonism of ClpP by dordaviprone results in enlargement of the enzyme substrate pore, leading to increased degradation of the mitochondrial enzymes that regulate oxidative phosphorylation. This degradation results in activation

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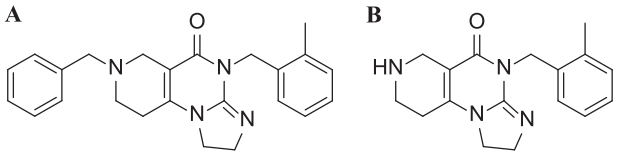

Figure 1. Chemical structures of (A) dordaviprone and (B) metabolite ONC207.

of the integrated stress response, ultimately leading to apoptosis in tumor cells.[10,11] Recent studies have demonstrated that the metabolic alterations induced by ClpP agonism can impact histone demethylases, resulting in reversal of H3 K27me3-loss in H3 K27M-mutant glioma cells that is the central hallmark of the disease.[12]

After oral administration of radiolabeled dordaviprone to humans, dordaviprone was largely cleared as oxidative metabolites in urine (71% of the dose) and feces (20% of the dose). The major circulating metabolite was ONC207 (Figure 1), contributing approximately a third of the total circulating radioactivity area under the plasma concentration–time curve (AUC).[13] ONC207 was shown to be inactive in in vitro studies, causing a minimal (~10%) reduction in cell viability at the dordaviprone half maximal inhibitory concentration (IC_{50}) (2.5 μM).[14] In vitro, dordaviprone was primarily eliminated by metabolism via CYP3A4, which was confirmed clinically by the large increase in dordaviprone AUC (~4-fold) after coadministration with the strong CYP3A4 inhibitor itraconazole.[15] Currently, dordaviprone is being evaluated in a large phase 3 trial for the treatment of diffuse gliomas harboring the H3 K27M mutation (NCT05580562).[16] Because safety and pharmacokinetic (PK) data collected in previous patient studies are confounded by disease-related symptoms, potential underlying organ dysfunction, concomitant medications, in addition to limitations associated with sparse pharmacokinetic sampling, this study was designed to fully characterize the PKs of dordaviprone and its metabolite, ONC207. This study was divided into 3 parts. In Part A, the safety and PKs of dordaviprone after single escalating doses administered with fasting were evaluated in healthy volunteers. In Part B1, the study compared the bioavailability of dordaviprone when capsule contents were sprinkled on applesauce or dissolved in extemporaneous compounding liquid (ie, Gatorade, a sports drink) to that of dordaviprone administered as an intact capsule. This was done to evaluate potential dosing recommendations in pediatric patients or adult patients unable to swallow capsules. Part B2 evaluated the effect of a high-fat meal on the plasma PKs of dordaviprone.

Subjects and Methods

This study was conducted at New Zealand Clinical Research (Christchurch, New Zealand) in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonization Good Clinical Practice Guidelines, and other applicable laws and regulations.

The protocol, protocol amendments, informed consent forms, Investigator Brochure, and other relevant documents (eg, advertisements) were submitted to an independent ethics committee (IEC; Health and Disability Ethics Committees, Wellington, New Zealand) by the investigator and were reviewed and approved by the IEC before the study was initiated. Any amendments to the protocol required IEC approval before implementation of changes made to the study design.

Study Design

This phase 1, open-label, 3-part study of dordaviprone was conducted in healthy adult participants at a single center. Participants were only permitted to participate in 1 study part: A, B1, or B2. Part A evaluated the PKs of escalating single doses of dordaviprone administered orally after an overnight fast of at least 10 hours. All participants received dordaviprone during 3 periods in sequential, escalating doses: 125 mg in period 1, 375 mg in period 2, and 625 mg in period 3.

Part B1 was a 3-period, single-dose, randomized, crossover design to evaluate the effect of administering 125 mg of dordaviprone as an intact capsule, capsule contents sprinkled on 4 ounces of applesauce, or capsule contents dissolved in 15 mL of extemporaneous compounding liquid (ie, sports drink) on dordaviprone plasma PK parameters. Participants were randomized in a 1:1:1 ratio to 1 of 3 treatment sequences. Due to the possibility of higher exposure under different dosing conditions, the safety of 375 mg in Part A was confirmed prior to initiation of Part B1 with 125 mg.

Part B2 used a 2-period, crossover design to evaluate the effect of food (fasted vs. fed) on dordaviprone PK parameters after administration of single 625-mg doses. Part B2 was started after the safety and tolerability of 625 mg of dordaviprone had been assessed in Part A. Participants were randomized to the order in which they received each treatment. In 1 period, dordaviprone was administered after an overnight fast (nothing but water) for a minimum of 10 hours, and in the other period, dordaviprone was administered after participants had completed the same overnight fast and within approximately 10 minutes of the

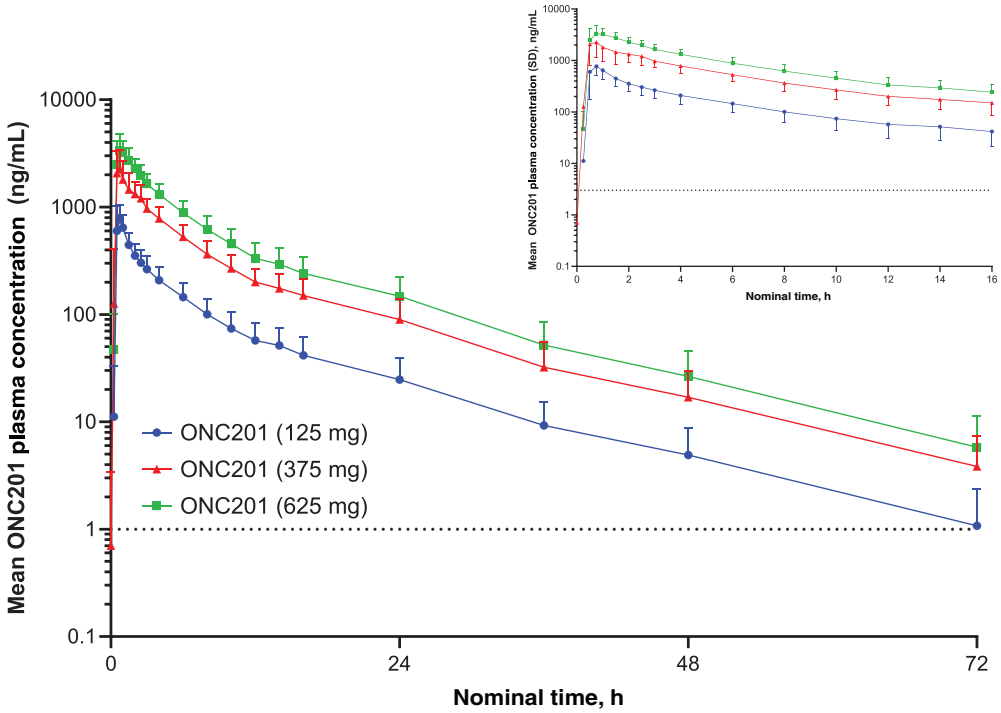

Figure 2. Mean (± standard deviation) dordaviprone plasma concentration–time profile after a single dose escalation of dordaviprone to healthy adults (Part A).

participant consuming in entirety a high-fat meal (~50% fat, 800-1000 calories) for breakfast.

Study Subjects

Healthy male and female participants of non-childbearing potential who were 18-55 years of age (inclusive), with a body mass index (BMI) of 18-32 kg/m^2 and normal renal function (defined as creatinine clearance ≥80 mL/min) were enrolled to respective parts of the study.

The main exclusion criteria included current history of heavy tobacco/nicotine use, clinically significant laboratory values outside of the normal reference ranges, or a history or symptoms of cardiovascular disease, including but not limited to coronary artery disease, hypertension, congestive heart disease, and clinically significant cardiac arrhythmia or conduction disorder, or an abnormal electrocardiogram (ECG) thought to be potentially clinically significant by the investigator at screening or day −1, or Fridericia's correction formula (QTcF) >450 ms for males and >470 ms for females.

Participant Demographics

A total of 62 male and 1 female participant were enrolled across all 3 parts of the study, with 61 participants (96.8%) completing the study. Two participants discontinued early due to personal reasons, with no participants discontinuing due to adverse events (AEs). The median age was 29 years (range 18-53 years); the majority of participants were White (76.2%), male (98.4%), and not Hispanic or Latino (84.1%). The demographics for individual Parts A, B1, and B2 are presented in Tables S1–S3, respectively.

Bioanalysis and PK

Blood samples for quantification of drug concentrations in plasma were collected in Parts A, B1, and B2 at predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72, and 144 hours postdose during each treatment period. Dordaviprone and ONC207 were extracted from plasma with acetonitrile (ACN) containing isotopically labeled internal standards (d7-dordaviprone and d7-ONC207) from K2-EDTA human plasma (0.025 mL). The supernatant was evaporated to dryness at ~35 °C and reconstituted with 0.300 mL of methanol/water (20:80, v/v). Chromatographic separation for dordaviprone and ONC207 was performed using an Atlantis dC18 HPLC column (50 × 2.1 mm, 3 um). Dordaviprone and ONC207 were eluted using mobile phase A consisting of 0.2% formic acid (FA) (aq)/ACN, pH 7.0 (90:10) and mobile phase B consisting of ACN/methanol (50:50) at 0.600 mL/min flow rate. The same plate was injected twice: once each for dordaviprone and ONC207. The total run time for each injection was 3 minutes. Dordaviprone and its internal standard were analyzed by tandem mass spectrometric detection with multiple reaction monitoring

Table 1. Single-dose Plasma PK Parameters for Dordaviprone and Metabolite ONC207 After Oral Administration of 125, 375, and 625 mg of Dordaviprone to Healthy Adults

	Dordaviprone			ONC207		
Administered dordaviprone dose	125 mg	375 mg	625 mg	125 mg	375 mg	625 mg
n	15	15	15	15	15	15
C_{max} (ng/mL)						
Mean (SD)	872 (255)	2654 (929)	3971 (1018)	195 (46.7)	484 (107)	742 (142)
GM (%CV)	829 (36.6)	2501 (37.6)	3830 (29.7)	189 (27.9)	472 (23.5)	729 (19.6)
AUC_{last} (h•ng/mL)						
Mean (SD)	3112 (1096)	11002 (3340)	18137 (5390)	4279 (1191)	13034 (2848)	21848 (5208)
GM (%CV)	2909 (41.5)	10498 (33.5)	17354 (32.3)	4131 (27.9)	12740 (22.6)	21280 (24.2)
AUC_{inf} (h•ng/mL)						
Mean (SD)	3151 (1110)	11076 (3380)	18250 (5444)	4596 (1128)	13478 (2947)	22499 (5356)
GM (%CV)	2946 (41.5)	10564 (33.7)	17458 (32.3)	4472 (24.4)	13176 (22.5)	21916 (24.1)
$t_{1/2}$ (hours)						
Mean (SD)	10.8 (3.60)	10.3 (2.56)	10.2 (2.60)	28.1 (5.18)	27.9 (3.72)	27.4 (5.15)
GM (%CV)	10.3 (31.6)	9.96 (26.2)	9.93 (26.2)	27.6 (19.8)	27.7 (13.8)	26.9 (19.2)
T_{max} (hours)	0.750	0.750	0.750	0.750	0.750	1.5
Median (Range)	(0.500, 1.50)	(0.500, 2.50)	(0.500, 2.00)	(0.500, 8.00)	(0.500, 8.12)	(0.500, 8.00)
Cl/F (L/h)						
Mean (SD)	46.0 (21.4)	37.4 (13.4)	37.6 (12.6)	NC	NC	NC
GM (%CV)	42.4 (41.5)	35.5 (33.7)	35.8 (32.3)			
M/P ratio C_{max}						
Mean (SD)	NA	NA	NA	0.246 (0.111)	0.198 (0.0691)	0.201 (0.0681)
GM (%CV)				0.228 (40.5)	0.189 (30.5)	0.190 (34.0)
M/P ratio AUC_{inf}						
Mean (SD)	NA	NA	NA	1.59 (0.511)	1.27 (0.271)	1.28 (0.256)
GM (%CV)				1.52 (32.2)	1.25 (21.4)	1.26 (21.4)

AUC_{inf}, area under the plasma concentration versus time curve from time zero to infinity; AUC_{last}, area under the plasma concentration–time curve from time zero to time of last measurable plasma concentration; Cl/F, apparent clearance of drug from plasma after extravascular administration; C_{max}, peak (maximum) plasma concentration of the drug; GM (%CV), geometric mean (percentage coefficient of variation); NA, not applicable; NC, not calculated; M/P, metabolite to parent ratio (not corrected for molecular weight differences); SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to peak (maximum) plasma concentration.

using positive ESI ion electrospray utilizing ion transitions from m/z 387.1 to m/z 268.3 and m/z 394.2 to 268.3, respectively. ONC207 and its internal standard utilized ion transitions from m/z 297.3 to m/z 105.1 and 304.2 and m/z 275.2, respectively. A linear, $1/x^2$ weighted algorithm was used for analysis of unknown plasma samples, with an assay range of 10-5000 ng/mL for dordaviprone and 3-1500 ng/mL for ONC207. The inter-run accuracy (%RE) and inter-run precision (%CV) for the dordaviprone method validation were −3.67% to 5.00% and 1.99% to 8.31%, respectively. The %RE and %CV for the ONC207 method validation were -3.33 to 2.17% and 2.86 to 8.47%, respectively. Dordaviprone and ONC207 plasma stability were evaluated during the method validation; both were stable on the bench for 25 hours at ambient temperature, stable for at least 5 cycles at −20 °C and −70 °C, and for at least 1044 days at −20 °C and −70 °C.

Plasma samples with dordaviprone concentrations <10 ng/mL were re-extracted and analyzed by a second method with a quantitation range of 1-500 ng/mL. Chromatographic separation for dordaviprone was performed using an ACE C18 HPLC column (50 × 2.1 mm, 3 um) using the same mobile phases at a flow rate of 0.70 mL/min. The %RE and %CV for the low range dordaviprone method validation were −0.30% to 8.00% and 2.54% to 5.22%, respectively. Additional information on dordaviprone and ONC207 method performance can be found in Table S4.

Standard noncompartmental methods were used to calculate PK parameters for dordaviprone and ONC207 (Phoenix WinNonlin®, ver 8.3) in each part of the study.

Safety

The safety and tolerability of dordaviprone were evaluated in each part of the study. Endpoints included

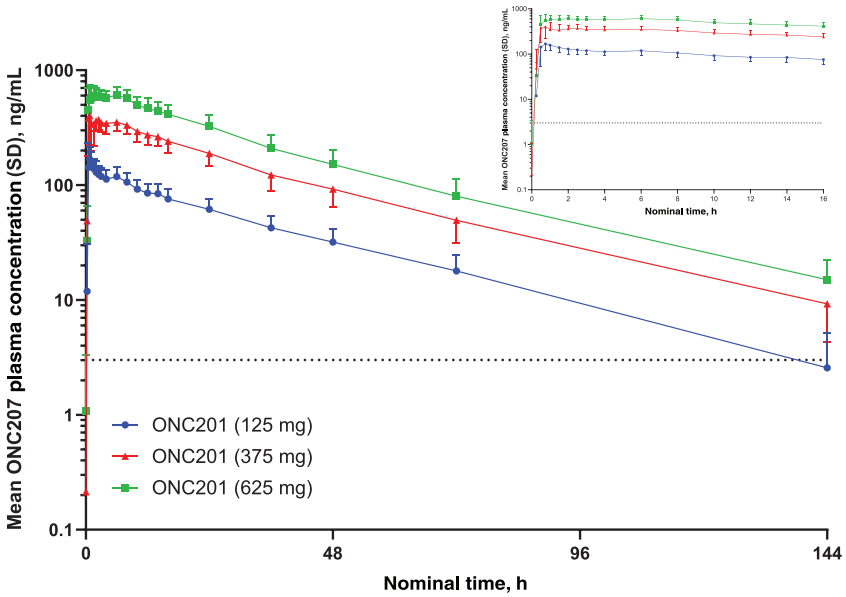

Figure 3. Mean (± standard deviation) ONC207 plasma concentration–time profile after a single dose of dordaviprone to healthy adults (Part A).

AEs and absolute and changes over time of clinical and laboratory parameters, vital signs, neurological assessments, and ECG intervals.

Statistical Analysis

Fifteen and 18 participants were enrolled in Parts A and B1, respectively. Intrasubject variability observed in Part A was used to inform the final sample size used in Part B2 (N = 30).

The dose proportionality of dordaviprone systemic exposure parameters in Part A was assessed on AUC_{inf}, AUC_{last}, and C_{max} using the power model (PK parameter = β_0.$Dose^{\beta}{}_1$). In parts B1 and B2, the effect of administering dordaviprone capsule contents sprinkled on applesauce and dissolved in sports drink compared to intact capsules and the effect of a high-fat meal on dordaviprone PK parameters, respectively, was evaluated using a mixed-effects model appropriate for a crossover design.

Safety data were analyzed by frequency (incidence) of events and descriptive statistical summaries by treatment. Selected laboratory values, ECG parameters, vital sign measurements, neurological findings, and corresponding changes from baseline were summarized by timepoint.

Results

PK

Part A: Single Ascending Dose. Dordaviprone was rapidly absorbed into the circulation following single oral administration and was eliminated in a multiphasic manner (Figure 2). Median T_{max} occurred at 0.75 hours postdose across doses. Mean $t_{\frac{1}{2}}$ was ~10 hours (Table 1). Dordaviprone systemic exposure (C_{max} and AUC) increased dose proportionally across the range of 125-625 mg, as indicated by slope estimates from the power model near 1.00 (the slope estimates ranged from 0.96 to 1.12) and 95% confidence interval (CI) for the slope including 1.00 for C_{max}, AUC_{last}, and AUC_{inf}.

Metabolite ONC207 appeared rapidly after oral administration of dordaviprone (Figure 3), with a median T_{max} of 0.75-1.5 hours postdose across doses, although T_{max} in some subjects occurred as late as 8 hours postdose. The ONC207 mean $t_{\frac{1}{2}}$ was greater than that observed for dordaviprone and consistent across dose levels (27-28 hours; Table 1). Mean metabolite to parent ratios (not corrected for molecular weight differences) were 0.246, 0.198, and 0.201 for C_{max} and 1.59, 1.27, and 1.28 for AUC_{inf}, following the 125, 375, and 625 mg doses of dordaviprone, respectively.

Part B1: Treatment Condition (Intact Capsule, Sports Drink, or Applesauce). Following single-dose administration of dordaviprone 125 mg, dordaviprone was rapidly absorbed into the circulation and eliminated in a multiphasic manner following all 3 treatment conditions. Median T_{max} ranged from 0.75 hour (intact capsule and sports drink) to 1.0 hour (applesauce) postdose. Dordaviprone C_{max} from capsule contents sprinkled on applesauce was decreased relative to the intact capsule, but all other PK parameters were consistent across the 3 treatment conditions (Table 2). Geometric mean ratios and 90% CIs of dordaviprone PK parameters for each dosing condition versus intact capsules fell within

Table 2. Single-dose Plasma PK Parameters for Dordaviprone and Metabolite ONC207 After Oral Administration of a Single 125-mg Capsule of Under Different Treatment Conditions

	Dordaviprone			ONC207		
Administered dordaviprone formulation	Intact	Applesauce	Sports drink	Intact	Applesauce	Sports drink
N	18	18	18	18	18	18
C_{max} (ng/mL)						
Mean (SD)	1015 (261)	839 (404)	953 (325)	226 (64.7)	188 (43.7)	205 (63.4)
GM (%CV)	980 (28.8)	766 (44.4)	906 (33.2)	218 (27.8)	183 (25.0)	197 (28.5)
AUC_{last} (h•ng/mL)						
Mean (SD)	3460 (1098)	3621 (1491)	3854 (1609)	5011 (824)	5227 (856)	5136 (1004)
GM (%CV)	3307 (31.5)	3392 (37.5)	3610 (37.1)	4947 (16.7)	5158 (17.2)	5048 (19.2)
AUC_{inf} (h•ng/mL)						
Mean (SD)	3490 (1102)	3656 (1499)	3888 (1618)	5285 (845)	5488 (881)	5456 (1056)
GM (%CV)	3338 (31.3)	3425 (37.4)	3642 (37.2)	5221 (16.3)	5418 (16.9)	5364 (19.1)
$t_{1/2}$ (hours)						
Mean (SD)	10.2 (2.60)	10.1 (2.35)	9.98 (2.69)	31.1 (6.30)	31.3 (5.83)	32.0 (6.26)
GM (%CV)	9.85 (27.5)	9.79 (24.6)	9.63 (28.3)	30.4 (24.0)	30.7 (20.7)	31.3 (23.1)
T_{max} (hours)	0.750 (0.500,	1.00 (0.500,	0.750 (0.500,	0.750 (0.500,	1.50 (0.500,	0.750 (0.250,
Median (range)	1.50)	2.50)	2.00)	1.50)	6.00)	3.00)
Cl/F (L/h)						
Mean (SD)	39.1 (11.8)	38.8 (14.1)	36.4 (12.4)	NC	NC	NC
GM (%CV)	37.4 (31.3)	36.5 (37.4)	34.3 (37.2)			
M/P ratio C_{max}						
Mean (SD)	NA	NA	NA	0.237 (0.0902)	0.252 (0.0763)	0.232 (0.0867)
GM (%CV)				0.223 (35.5)	0.239 (35.7)	0.217 (38.6)
M/P ratio AUC_{inf}						
Mean (SD)	NA	NA	NA	1.64 (0.584)	1.68 (0.628)	1.58 (0.567)
GM (%CV)				1.56 (31.6)	1.58 (37.4)	1.49 (36.1)

AUC_{inf}, area under the plasma concentration versus time curve from time zero to infinity; AUC_{last}, area under the plasma concentration–time curve from time zero to time of last measurable plasma concentration; Cl/F, apparent clearance of drug from plasma after extravascular administration; C_{max}, peak (maximum) plasma concentration of the drug; GM (%CV), geometric mean (percentage coefficient of variation); NA, not applicable; NC, not calculated; M/P, metabolite to parent ratio (not corrected for molecular weight differences); $t_{1/2}$, half-life; SD, standard deviation; T_{max}, time to peak (maximum) plasma concentration.

the BE limits of 80.00% to 125.00% for all PK parameters and dosing conditions except for C_{max} following dordaviprone administered as capsule contents sprinkled on applesauce. Following dordaviprone sprinkled on applesauce, the geometric mean ratio and lower bound of the 90% CI for C_{max} were below BE limits, 0.78 (0.70-0.87), indicating dordaviprone maximal absorption was marginally decreased when sprinkled on applesauce. The geometric mean ratio and 90% CIs for AUC_{last} and AUC_{inf} following capsule contents sprinkled on applesauce versus intact capsule were 1.03 (0.94-1.12). Geometric mean ratios and 90% CIs were 0.92 (0.83-1.03) for C_{max} and 1.09 (1.00-1.19) for AUC_{last} and AUC_{inf} when comparing dordaviprone dissolved in sports drink to the intact capsule.

For metabolite ONC207, the median T_{max} following dordaviprone capsule contents sprinkled on applesauce was delayed relative to the other treatment conditions (1.50 hours vs. 0.75 hours) and geometric mean C_{max} was decreased (183 ng/mL vs. 197 and 218 ng/mL), but the other PK parameters were consistent across all treatment conditions (Table 2).

Part B2: Food Effect. Following single oral administration of 625 mg of dordaviprone, geometric mean total exposure (AUC) was similar following administration under fed (high-fat meal [50%], 800-1000 calories) and fasted conditions; geometric mean C_{max} was lower under fed conditions and median T_{max} was delayed to 2.25 hours, indicating the rate of dordaviprone absorption decreased in the presence of food (Table 3).

Geometric mean ratios and 90% CIs of dordaviprone administered under fed compared to fasted conditions fell within BE limits of 80.00%-125.00% for AUC_{last} and AUC_{inf}, indicating no effect of food on dordaviprone total exposure. Ratios and 90% CIs were 1.00 (0.95-1.06) for AUC_{last} and AUC_{inf}. For C_{max}

Table 3. Single-dose Plasma PK Parameters for Dordaviprone and Metabolite ONC207 After Oral Administration of a Single 625 mg Dordaviprone Dose Under Fed and Fasted Conditions

	Dordaviprone		ONC207	
	Fasted	Fed	Fasted	Fed
N	30	30	30	30
C_{max} (ng/mL)				
Mean (SD)	4588 (2069)	2654 (885)	829 (174)	721 (133)
GM (%CV)	4148 (51.2)	2522 (33.3)	810 (22.9)	708 (19.4)
AUC_{last} (h•ng/mL)				
Mean (SD)	20252 (8242)	20057 (7281)	22769 (4794)	23191 (4358)
GM (%CV)	18656 (44.5)	18722 (40.7)	22286 (21.4)	22810 (18.6)
AUC_{inf} (h•ng/mL)				
Mean (SD)	20317 (8263)	20133 (7298)	23337 (5020)	23816 (4608)
GM (%CV)	18715 (44.5)	18794 (40.7)	22820 (21.9)	23402 (19.1)
$t_{1/2}$ (hours)				
Mean (SD)	10.3 (4.53)	10.2 (3.96)	27.1 (3.51)	26.9 (4.29)
GM (%CV)	9.59 (39.7)	9.61 (35.3)	26.9 (13.1)	26.6 (16.5)
T_{max} (hours)				
Median (range)	0.750 (0.500, 4.00)	2.25 (0.500, 4.00)	1.25 (0.500, 8.03)	3.00 (0.500, 8.00)
Cl/F (L/h)				
Mean (SD)	36.7 (18.2)	36.0 (16.0)	NC	NC
GM (%CV)	33.4 (44.5)	33.3 (40.7)		
M/P ratio C_{max}				
Mean (SD)	NA	NA	0.212 (0.100)	0.297 (0.102)
GM (%CV)			0.195 (40.5)	0.281 (35.2)
M/P Ratio AUCinf				
Mean (SD)	NA	NA	1.28 (0.451)	1.31 (0.431)
GM (%CV)			1.22 (32.3)	1.25 (31.5)

AUC_{inf}, area under the plasma concentration versus time curve from time zero to infinity; AUC_{last}, area under the plasma concentration–time curve from time zero to time of last measurable plasma concentration; Cl/F, apparent clearance of drug from plasma after extravascular administration; C_{max}, peak (maximum) plasma concentration of the drug; GM (%CV), geometric mean (percent coefficient of variation); M/P, metabolite to parent ratio (not corrected for molecular weight differences); NA, not applicable; NC, not calculated; $t_{1/2}$, half-life; SD, standard deviation; T_{max}, time to peak (maximum) plasma concentration.

following fed conditions, the geometric mean ratio and lower bound of the 90% CI fell below BE limits to 0.61 (0.55-0.67). ONC207 behaved in the same manner, displaying lower geometric mean C_{max} with delayed median T_{max} and no impact on AUC.

Safety

All treatment-emergent adverse events (TEAEs) and dordaviprone-related TEAEs reported during this study are summarized by dose in Tables S5–S10. All TEAEs reported during the study were assessed as mild (Grade 1) in severity for all dose levels and dosing conditions. There were no deaths, serious adverse events (SAEs), or AEs leading to discontinuations of dordaviprone or withdrawals from the study.

The system organ class (SOC) with the highest number of participants reporting TEAEs was nervous system disorders (Tables S5-S10). To better understand the incidence of other less common potentially treatment-related neurologic events, treatment-related TEAEs with a neurologic component (in any SOC) that were observed within 24 hours of dordaviprone administration were pooled (dizziness, depressed level of consciousness, disturbance in attention, sensory disturbance, imperception, dissociation, and dissociative disorder) for each study part. At least 1 of these events was reported for 4 of 15 participants (26.7%) in Part A, 6 of 18 participants (33.3%) in Part B1, and 15 of 30 patients (50.0%) in Part B2 (Tables S11-S13). All events were Grade 1 in severity, and all but 1 resolved within 9 hours.

There were no clinically meaningful trends in mean change from baseline for any chemistry, hematology, or vital signs (systolic and diastolic blood pressure, respiratory rate, pulse rate, and temperature), nor were there any clinically meaningful findings in ECGs or neurological assessments (evaluating gait, strength, ataxia in the

upper extremity, sensation, visual field, facial strength, language, level of consciousness, and behavior).

Discussion

This study established the safety profile of dordaviprone in healthy adult participants and characterized its PK profile at multiple dose levels and under different dosing conditions. Dosing in healthy adults permitted a clean safety assessment, as well as an enhanced evaluation of the pharmacokinetics of dordaviprone.

Dordaviprone plasma exposures increased in a dose proportional manner following administration of 125, 375, and 625 mg, supporting linearity of exposure, and allowing for future extrapolation of pharmacokinetic changes observed in organ impairment and drug interaction studies following subtherapeutic (ie, <625 mg) dose administration. Dordaviprone was rapidly absorbed into the circulation on administration and rapidly eliminated in a multiphasic manner.

The data generated demonstrated the relative bioavailability of dordaviprone administered as capsule contents sprinkled on applesauce and as capsule contents dissolved in extemporaneous compounding liquid (ie, sports drink) as compared to intact capsules, and increases the flexibility of dosing of dordaviprone in pediatric patients and adults unable to swallow capsules whole.

Exposure results following a high-fat (50%), 800-1000 calorie meal demonstrated lower peak concentrations under fed versus fasted conditions, with AUC exposures remaining similar following administration under the 2 conditions. Dordaviprone was well tolerated under both fed and fasted conditions.

The safety data collected in the study demonstrate that dordaviprone was safe at dose levels ranging from 125 to 625 mg in healthy participants administered a single oral dose under different dosing conditions (intact capsules, dissolved in sports drink, sprinkled on applesauce, and with or without food). TEAEs were all mild in severity and there were no SAEs or AEs leading to discontinuation of study intervention or early withdrawal from the study.

Conclusions

The results from this study demonstrate that dordaviprone is safe and well tolerated at dose levels of 125, 375, and 625 mg, and display dose-proportional PKs. Assessments of the effect of dosing conditions as well as administration with a high-fat meal revealed that while dordaviprone C_{max} is decreased when sprinkled on applesauce and following a high-fat meal, the total exposure (AUC) was similar to that of the intact capsule or when administered fasted, respectively.

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Conflicts of Interest

Shamia L. Faison, Joelle Batonga, and Thangam Arumugham are paid consultants for Chimerix, Inc. Angela Bartkus, Marion Morrison, Mark J. Mullin, Tim Tippin, and Odin Naderer are employees of and have stock ownership in Chimerix, Inc.

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Supplemental Information

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