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ORIGINAL RESEARCH ARTICLE

Effect of Severe Renal Impairment on Dordaviprone (ONC201) Pharmacokinetics

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Abstract

Background and Objective Dordaviprone (ONC201) is a novel small molecule with antitumor effects in patients with glioma. The major elimination pathway of dordaviprone is metabolism via cytochrome P450 (CYP) 3A4. This study was designed to assess the effect of severe renal impairment (RI) on dordaviprone pharmacokinetics.

Methods Eight participants with severe RI and eight participants matched for age, body mass index, and sex, with normal renal function, received a single oral 375-mg dose of dordaviprone. Plasma and urine samples were analyzed for dordaviprone using validated liquid chromatography tandem mass spectrometry methods. Plasma and urine pharmacokinetics, plasma protein binding, and safety profiles were evaluated.

Results Dordaviprone exposure was increased in participants with severe RI. Geometric mean ratios (90% confidence intervals) of the severe RI cohort compared with the healthy matched cohort were 1.13 (0.92–1.39), 1.48 (0.98–2.23), and 1.47 (0.97–2.21), for maximum concentration (C_{max}), area under the plasma concentration-time curve from time zero to time of last measurable plasma concentration (AUC_{last}), and AUC from time zero to infinity (AUC_{inf}), respectively. Renal clearance of dordaviprone was negligible and similar in both cohorts. Plasma protein binding was similar in both cohorts, leading to similar increases in unbound dordaviprone C_{max} and AUC in severe RI versus healthy participants. All dordaviprone-related adverse events were mild, occurring in 50% of participants with severe RI and 37.5% of healthy matched participants.

Conclusions Despite its minimal renal clearance, dordaviprone geometric mean AUC was increased by ~50% in severe RI participants, suggesting CYP3A4 activity may have been suppressed in these participants. The results of this study will be used to inform dordaviprone dosing in patients with RI.

Trial Registration Number ACTRN12622000405718; Registered on March 9, 2022.

Key Points

Dordaviprone is a small molecule drug candidate for the treatment of glioma and is eliminated by non-renal mechanisms.

In this clinical trial performed in severely renal-impaired participants, dordaviprone plasma concentrations were increased relative to those observed in healthy participants.

This result suggests that the metabolic enzyme activity of CYP3A4 was reduced in severely renal-impaired participants.

1 Introduction

Dordaviprone is a brain penetrant, small molecule imipridone which targets mitochondrial caseinolytic protease P (ClpP) and G protein-coupled dopamine receptor D2 (DRD2). Dordaviprone-mediated agonism of the mitochondrial protease ClpP and DRD2 antagonism in H3 K27M-mutant glioma cells results in impaired tumor cell metabolism, mitochondrial damage, reactive oxygen species production, activation of integrated stress response, and apoptosis in vitro and in vivo [1–3]. Dordaviprone has demonstrated antitumor activity in patients with glioma [4] and is currently enrolling a phase III clinical trial (ClinicalTrials.gov identifier: NCT05580562) [5].

In vitro, cytochrome P450 (CYP) 3A4 was the primary enzyme involved in dordaviprone elimination (fraction metabolized 0.55–0.87), with minor involvement of other

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CYP enzymes, including CYP2D6, 2C8, 2C9, 2B6 and 3A5 [6]. In healthy participants, the geometric mean area under the concentration–time curve (AUC) and maximum concentration (C_{max}) of dordaviprone increased by 4.4- and 1.9-fold after coadministration with the strong CYP3A4 inhibitor itraconazole compared with dordaviprone alone, confirming the importance of CYP3A4 in the oxidative elimination of dordaviprone [6]. After oral administration of [^{14}C]-dordaviprone 625 mg, radioactivity was eliminated in urine (~70% of the dose) and feces (~20% of the dose) as oxidative metabolites [7]. The major circulating metabolite was the inactive N-dealkylated product ONC207 [7]. Negligible renal excretion of parent drug was observed (0.2% of the dose). Dordaviprone was not a substrate for efflux transporters P-glycoprotein (P-gp) or Breast Cancer Resistance Protein (BCRP) (AACR poster), nor anionic uptake transporters, Organic Anion Transporting Polypeptide (OATP) 1B1, 1B3, Organic Anion Transporter (OAT) 1, and OAT3 (data on file).

It has been reported that an increase in plasma concentrations in patients with kidney disease can occur for some drugs despite their clearance pathway being primarily non-renal, due to metabolism and/or transporter-mediated elimination [8–10], though for drugs that are cleared primarily by CYP3A4, a change in plasma clearance due to renal impairment was not always evident [11].

The purpose of this study was to evaluate the impact of severe renal impairment on the pharmacokinetics and safety of dordaviprone, following single oral administration.

2 Methods

2.1 Clinical Trial Design

The 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 (CIOMS) International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and other applicable laws and regulations (Ethics [HDEC] Project ID = 12158). The protocol, protocol amendments, informed consent forms, Investigator Brochure, and other relevant documents (e.g., 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.

This trial was an open-label, parallel-group, single-period, single-dose study conducted with eight participants (Cohort 1) with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min) and eight healthy matched participants (Cohort 2) with normal renal function (see electronic supplementary material [ESM], Fig. S1); eGFR was calculated using the Cockcroft-Gault formula. All participants received a single dose of dordaviprone 375 mg (3 × 125-mg capsules) with 240 mL of room temperature water following a 10-hour fast. Screening evaluations were performed no more than 28 days prior to dosing (Day 1) to identify participants eligible to participate in the study. Inclusion criteria included females of non-childbearing potential or males who were surgically sterilized or agreed to use acceptable method(s) of contraception, age 18–75 years (inclusive), BMI 18–40 kg/m^2 (inclusive), and blood pressure within the specified range. Cohort 1: eGFR < 30 mL/min and stable disease. Cohort 2: normal renal function, generally healthy, and matched with Cohort 1 participants based on age (±1 0 years), BMI (± 20%), and sex (match). Eligible participants were admitted to the clinic facility on Day − 1, the day prior to dosing, and remained in the clinic until discharge on the morning of Day 3 following completion of all scheduled study procedures and assessments. Cohort 1 participants were allowed to continue their prior medications for the management of renal impairment during the trial period, except during the 10-h fasting period prior to dosing and for 4 hours following dose administration when all food and medications were withheld. Participants returned for outpatient visits on Days 4 and 8. A follow-up visit for all participants was performed on Day 14 (±2 days).

2.2 Bioanalysis

Blood samples for quantification of dordaviprone and ONC207 concentrations in plasma were collected at predose 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 168 h post-dose. Urine samples for quantification of dordaviprone and ONC207 concentrations were collected predose and during 0–4, 4–8, 8–12, and 12–24 h post-dose. Plasma and urine were analyzed for dordaviprone and ONC207 using validated liquid chromatography tandem mass spectrometry as described previously [6, 7]. The inter-run accuracy (%RE) and inter-run precision (%CV) for dordaviprone in plasma and urine quality control samples were − 2.4 to 5.3% and ≤7.6%, and − 0.7 to 5.3% and ≤ 4.7%, respectively. The inter-run accuracy (%RE) and inter-run precision (%CV) for ONC207 in plasma and urine quality control samples were − 4.4 to 4.3% and ≤ 4.3%, and 0.0 to 3.3% and ≤ 3.9%, respectively.

2.3 Plasma Protein Binding

Separate blood samples for determination of dordaviprone plasma protein binding were collected at 0.5, 1, and 24 hours post-dose. The plasma samples were dialyzed in triplicate

Table 1 Summary of participant demographics and screening characteristics

Parameter	Severe renal impairment ($N = 8$)	Healthy matched participants ($N = 8$)	Overall ($N = 16$)
Age at screening (years)			
Mean (SD)	62.9 (8.4)	57.6 (8.1)	60.3 (8.4)
Median (minimum, maximum)	62.5 (52, 74)	57.5 (47, 72)	59.0 (47, 74)
Sex, *n* (%)			
Female	1 (12.5)	1 (12.5)	2 (12.5)
Male	7 (87.5)	7 (87.5)	14 (87.5)
Race, *n* (%)			
White	7 (87.5)	8 (100)	15 (93.8)
Native Hawaiian or other Pacific Islander	1 (12.5)	0	1 (6.3)
Weight (kg)			
Mean (SD)	84.4 (15.8)	83.5 (7.4)	83.9 (11.9)
Median (minimum, maximum)	82.1 (66.4, 108.5)	82.6 (72.0, 91.7)	82.6 (66.4, 108.5)
Body mass index (kg/m^2)			
Mean (SD)	29.1 (4.2)	28.3 (2.9)	28.7 (3.5)
Median (minimum, maximum)	28.3 (24.2, 36.0)	27.9 (25.2, 34.3)	28.0 (24.2, 36.0)
eGFR (mL/min)[a]			
Mean (SD)	22.1 (4.5)	107.4 (15.3)	64.770 (45.4)
Median (minimum, maximum)	23.840 (14.9, 26.2)	102.630 (93.2, 140.6)	59.695 (14.9, 140.6)

eGFR estimated glomerular filtration rate, *SD* standard deviation

against phosphate buffered saline using a Rapid Equilibrium Dialysis device (RED; ThermoFisher Scientific Pierce Biotechnology, Rockford, IL, USA) equipped with an 8000 Dalton molecular weight cutoff membrane for a period of 4 hours at 37 °C. At the end of the dialysis period, aliquots of the respective plasma (donor) and buffer (receiver) compartments were diluted 1:1 with blank buffer or plasma, respectively. The resulting 1:1 plasma : buffer samples were treated with acetonitrile containing dordaviprone-d7 internal standard and the extracts were analyzed by high-performance liquid chromatography tandem mass spectrometry using positive ion TurboIonSpray ionization and multiple reaction monitoring transitions (for dordaviprone and its internal standard, 387.2/268.2 and 394.2/268.2). Due to the large range of concentrations in the donor/receiver samples, a low curve with an assay range of 0.20–100 ng/mL and a high curve of 10.0–2000 ng/mL were employed to quantify dordaviprone. The inter-run accuracy (%RE) and inter-run precision (%CV) for the dordaviprone low and high curve quality control samples were 0.5–10.9% and ≤9.7%, and −1.3 to 0.1% and ≤ 1.9%, respectively.

2.4 Pharmacokinetics

Standard noncompartmental methods were used to calculate pharmacokinetic parameters for dordaviprone (Phoenix WinNonlin® ver 8.3). Unbound parameters for each participant were calculated using the participant's mean % fraction unbound (%fu) values (average of %fu values determined at 0.5, 1, and 24 hours post-dose).

2.5 Safety

Safety was assessed through the reporting of adverse events (AEs), vital signs measurements, electrocardiograms (ECGs), neurological assessments, and clinical laboratory results.

2.6 Statistical Analyses

To determine the effect of severe renal impairment on the pharmacokinetics of dordaviprone, AUC from time zero to infinity (AUC_{inf}), AUC from time zero to time of last measurable plasma concentration (AUC_{last}), and C_{max} were log_e-transformed and compared between cohorts using an analysis of variance model with a fixed-effect term for cohort (participants with severe renal impairment and healthy matched participants) in the model. For each pharmacokinetic parameter, point estimates and corresponding 90% confidence intervals (CIs) were calculated for the ratio of geometric means between the severe renal impairment cohort and the healthy matched participant cohort.

Safety data were analyzed descriptively using frequencies of events or continuous statistical summaries by cohort.

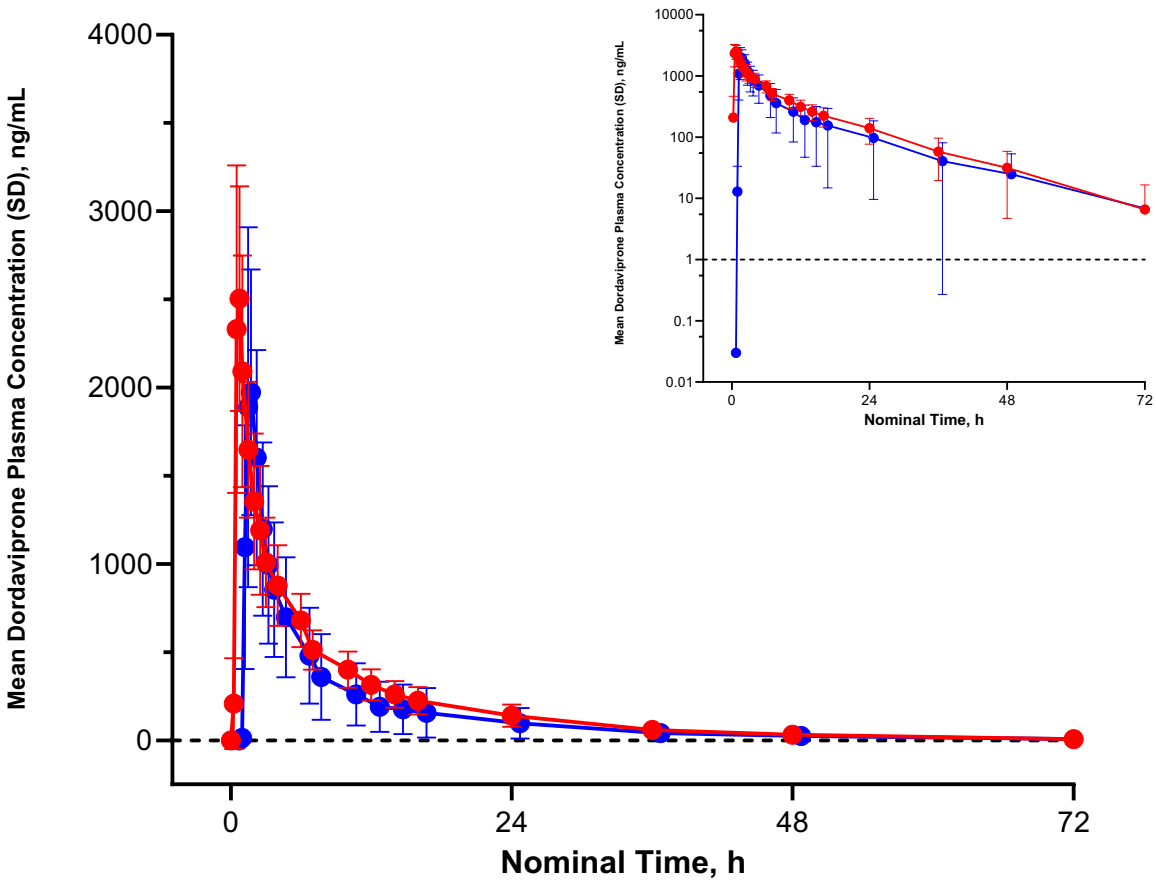

Fig. 1 Mean dordaviprone plasma concentration–time profiles in severe renally impaired participants and healthy matched participants after a single oral dose of dordaviprone 375 mg. Values are mean ± SD; individual values below the limit of quantification are imputed as 0 and included in the calculation of mean concentration for a given timepoint. *Red circles* represent data from renal impaired subjects; *blue circles* represent data from healthy matched subjects. *h* hour, *SD* standard deviation

3 Results

3.1 Demographics

Demographic and screening characteristics were similar between the two cohorts (indicating appropriate matching criteria), except for a reduced eGFR, which was a required inclusion criteria in the severe renal impairment cohort (Table 1). The mean eGFR of the severe renal impairment cohort was 22.10 mL/min (range: 14.9–26.2 mL/min) as compared with 107.4 mL/min (range: 93.2–140.6 mL/min) in the healthy matched cohort. Overall, the mean age of the 16 participants was 60.3 years (range 47–74 years), with most participants being male (87.5%). Fifteen (15) of the 16 participants were White (93.8%), with the remaining participant being a Native Hawaiian or other Pacific Islander (Table 1).

3.2 Dordaviprone Pharmacokinetics

3.2.1 Plasma

Dordaviprone was rapidly absorbed into the circulation and eliminated in an apparent multiphasic manner in both cohorts (Figure 1). Plasma concentrations were quantifiable in most participants at 0.25 hours post-dose, with median time to maximum concentration (T_{max}) occurring at 0.75 hours post-dose in both cohorts. Mean dordaviprone exposure parameters (C_{max} and AUC) in the severe renal impairment cohort trended higher (up to ~50%) and mean apparent clearance of drug from plasma (CL/F) was lower (~30%) compared with mean dordaviprone exposure parameters in the healthy matched cohort (Table 2). The effect was greater and more variable for AUC parameters compared with C_{max}. For dordaviprone, respective least squares mean

Table 2 Dordaviprone plasma pharmacokinetic parameters after a single oral dose of dordaviprone 375 mg in severe renally impaired and healthy matched participants

	T_{max} (h)		C_{max} (ng/mL)		AUC_{last} (h.ng/mL)		AUC_{inf} (h.ng/mL)		$t_{½}$ (h)		CL/F (L/h)		Vz/F (L)	
	Severe RI	Healthy	Severe RI	Healthy	Severe RI	Healthy	Severe RI	Healthy	Severe RI	Healthy	Severe RI	Healthy	Severe RI	Healthy
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean (SD)	NC	NC	2683 (601)	2380 (572)	14,103 (4096)	10,518 (5985)	14,342 (4239)	10,789 (6192)	10.3 (3.0)	11.5 (3.9)	28.7 (10.6)	46.2 (27.1)	399 (90.1)	648 (166)
CV%	NC	NC	22.4	24.0	29	56.9	29.6	57.4	28.9	34.2	37.1	58.7	22.6	25.6
Geometric mean	NC	NC	2621	2321	13,522	9147	13,733	9373	9.9	10.9	27.3	40	391	629
Geometric mean (95% CI)	NC	NC	(2158–3185)	(1901–2834)	(10,324–17,711)	(5659–14,784)	(10,442–18,061)	(5794–15,163)	(7.9–12.4)	(8.1–14.8)	(20.8–35.9)	(24.7–64.7)	(325–469)	(−505–784)
Geometric mean, CV%	NC	NC	23.6	24.2	33.1	62.5	33.7	62.6	27.7	37.5	33.7	62.6	22.2	26.7
Median	0.75	0.75	2695	2250	13,530	9723	13,728	9983	8.7	10.6	27.3	38.3	379	661
Range (min, max)	(0.50, 2.00)	(0.75, 1.50)	(1850, 3600)	(1760, 3180)	(7129, 20,147)	(3761, 22,843)	(7188, 20,706)	(3858, 23,640)	(7.6, 15.5)	(5.6, 17.7)	(18.1, 52.2)	(15.9, 97.2)	(273, 573)	(404, 933)

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, *CV%* percentage coefficient of variation (geometric), *RI* renal impairment, *$t_{½}$* half-life associated with the terminal slope of the semi-logarithmic drug concentration–time curve; *T_{max}* time to peak (maximum) plasma concentration, *Vz/F* apparent volume of distribution during the terminal (λz) phase after extravascular administration

Table 3 Dordaviprone urine pharmacokinetic parameters after a single oral dose of dordaviprone 375 mg to severe renally impaired and healthy matched participants

	Ae (mg)		Ae% (%)		CLr (L/h)	
	Severe RI	Healthy	Severe RI	Healthy	Severe RI	Healthy
n	8	8	8	8	8	8
Mean (SD)	0.875 (0.823)	0.704 (0.310)	0.233 (0.220)	0.188 (0.0826)	0.0641 (0.0687)	0.0723 (0.0223)
CV%	94.1	44.0	94.1	44.0	107.2	30.8
Geometric mean	0.591	0.651	0.158	0.173	0.0430	0.0694
Geometric mean (95% CI)	(0.265–1.32)	(0.460–0.921)	(0.0706–0.352)	(0.123–0.246)	(0.0198–0.0935)	(0.0537–0.0897)
Geometric mean CV%	123.0	43.4	123.0	43.4	117.0	31.4
Median	0.603	0.633	0.161	0.169	0.0427	0.0694
Range (min, max)	(0.216, 2.55)	(0.403, 1.18)	(0.0576, 0.680)	(0.107, 0.315)	(0.0133, 0.223)	(0.0498, 0.108)

Ae cumulative amount of drug excreted unchanged in urine from time 0–24 h post-dose, *CLr* renal clearance, *CV%* percentage coefficient of variation (geometric), *RI* renal impairment, *SD* standard deviation

ratios and 90% CIs for C_{max}, AUC_{last}, and AUC_{inf} were 1.13 (0.92–1.39), 1.48 (0.98–2.23), and 1.47 (0.97–2.21).

3.2.2 Urine

Dordaviprone was minimally recovered in urine in both cohorts (amount excreted [Ae] < 0.2% of the dose; Table 3).

3.2.3 Plasma Protein Binding

Overall, there was no difference between the %fu dordaviprone in participants with severe RI and those with normal renal function. Respective arithmetic means (%CV) for the eight participants with severe RI and the eight with normal renal function were 3.24% (21.7%) and 3.20% (15.8%). When comparing mean %fu at each timepoint, similar mean %fu was also observed across cohorts (ESM Figure S2). No difference between cohorts was observed in a plot of unbound dordaviprone versus dordaviprone concentration, further supporting the lack of impact of renal impairment on %fu (ESM Figure S3).

Using the mean %fu across the three timepoints, individual unbound pharmacokinetic parameters were calculated for each participant. The mean unbound dordaviprone C_{max} and AUC for the severe RI and healthy cohorts followed the trend observed for total (bound and unbound) dordaviprone C_{max} and AUC; unbound dordaviprone AUC_{last} and AUC_{inf} were appreciably higher in the severe RI cohort compared with the normal renal function cohort, while increases in unbound dordaviprone C_{max} were marginal (Table 4).

3.3 ONC207 Pharmacokinetics

3.3.1 Plasma

The ONC207 exposure parameters (C_{max} and AUC) were increased in RI participants compared with healthy participants (ESM Table S1).

3.3.2 Urine

Elimination of ONC207 in the urine was reduced in participants with severe renal impairment as compared with matched participants with normal renal function (ESM Table S2).

3.4 Safety

Treatment-emergent adverse events (TEAEs) were reported in 6/8 (75%) severe RI participants and 5/8 (62.5%) healthy matched participants (Table 5); all TEAEs were mild. The most common treatment-related AE was headache, occurring in two (25%) participants from each cohort; no other treatment-related AEs occurred in more than one participant. Treatment-related AEs occurred in 50% of severe RI participants compared with 37.5% of healthy matched participants.

4 Discussion

Dordaviprone is predominantly eliminated by non-renal mechanisms [7]. The lack of renal involvement in dordaviprone elimination was reproduced in the present study, as

Table 4 Unbound plasma pharmacokinetic parameters of dordaviprone after a single oral dose of ONC201 375 mg in participants with severe renal impairment and in healthy matched participants

	C_{max_unb} (ng/mL)		AUC_{last_unb} (h.ng/mL)		AUC_{inf_unb} (h.ng/mL)		CL/F unbound (L/h)		Mean % fraction unbound	
	Severe RI	Healthy	Severe RI	Healthy	Severe RI	Healthy	Severe RI	Healthy	Severe RI	Healthy
n	8	8	8	8	8	8	8	8	8	8
Mean (SD)	87.0 (28.6)	75.3 (19.5)	451 (168)	324 (166)	459 (174)	332 (171)	894 (242)	1413 (716)	3.24 (0.703)	3.20 (0.506)
CV%	32.9	25.9	37.3	51.3	38.0	51.4	27.0	50.6	21.7	15.8
Geometric mean	83.3	73.5	430	290	437	297	859	1263	3.18	3.17
Geometric mean (95% CI)	(64.2–108)	(60.8–88.9)	(331–559)	(189–444)	(334–570)	(194–455)	(658–1121)	(824–1938)	(2.66–3.80)	(2.76–3.64)
Geometric mean CV%	31.9	23.1	32.2	54.7	32.7	54.7	32.7	54.7	21.6	16.7
Median	82.0	67.3	405	288	411	297	915	1264	3.17	3.29
Range (min, max)	(48.0, 149)	(61.9, 116)	(309, 834)	(139, 636)	(312, 857)	(143, 658)	(437, 1202)	(570, 2628)	(2.36, 4.34)	(2.32, 3.90)

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, *CV%* percentage coefficient of variation (geometric), *RI* renal impairment, *unb* unbound

dordaviprone was minimally recovered in urine in both cohorts, indicating negligible renal clearance in both severe RI and healthy matched populations. Despite this, the current study shows elevated mean C_{max} and AUC, with lower mean clearance for dordaviprone in severe RI participants relative to matched healthy controls. While the change in geometric mean C_{max} was not appreciable (13% increase), the change in geometric mean AUC_{last} and AUC_{inf} were notable (48% and 47% increases, respectively). The increase in total AUC was not attributable to a change in plasma protein binding, as the %fu was comparable in severe RI and healthy participants, which led to similar trends in unbound dordaviprone C_{max} and AUC parameters.

The primary elimination pathway for dordaviprone is via CYP3A4 [6]. Chronic kidney disease has been noted to increase plasma concentrations for some drugs that are primarily eliminated via CYP3A4 [12–14], but not all [11, 15]. This variable effect of renal impairment on CYP3A4 eliminated drugs has been attributed to multiple potential reasons, including 1) additional unknown elimination pathways [11], or 2) changes (decrease) in protein binding due to renal impairment that would increase drug clearance, thereby obscuring any decrease in clearance due to decreased CYP3A4 activity [11]. The effect on CYP3A4 and other non-renal elimination pathways has been hypothesized to result from suppression of enzymatic activity by high concentrations of uremic toxins that are not eliminated as effectively due to renal impairment or due to the high circulating concentrations of inflammatory cytokines [10, 16–18]. On average, a decrease in dordaviprone CL/F and an increase in dordaviprone AUC were observed. Though participants were matched for factors such as age, weight, and sex, the renal impaired cohort were allowed to continue their prior medications for management of existing conditions (i.e., renal impairment). Three participants were taking atorvastatin, a weak CYP3A4 inhibitor. On average, these three participants had comparable C_{max} and slightly lower AUC compared with the average C_{max} and AUC of the five renally impaired participants who were not taking atorvastatin, suggesting that overall, atorvastatin was not a factor influencing dordaviprone concentrations in these participants. Some inter-subject variability was observed within and across cohorts with notable AUC_{inf} variability within the healthy cohort. While the healthy cohort AUC_{inf} observed in this study was comparable to previous results [19], additional factors such as pharmacogenomics, which may have influenced exposure variability, were not controlled.

Despite the higher dordaviprone exposure in the severe RI cohort after a single dose of dordaviprone 375 mg, the incidence of AEs (overall and treatment-related) were similar in the severe RI cohort and the healthy matched cohort, and all reported AEs were consistent with the known AE profile of dordaviprone.

Table 5 Treatment-emergent adverse events after a single oral dose of ONC201 375 mg in participants with severe renal impairment and in healthy matched participants

Category, *n* (%)	Severe renal impairment (*N*= 8)	Healthy matched participants (*N* = 8)	Overall (*N* = 16)
Any TEAE	6 (75.0)	5 (62.5)	11 (68.8)
Headache	2 (25.0)	2 (25.0)	4 (25.0)
COVID-19	1 (12.5)	1 (12.5)	2 (12.5)
Dizziness	0	1 (12.5)	1 (6.3)
Muscle contractions involuntary	0	1 (12.5)	1 (6.3)
Nausea	1 (12.5)	0	1 (6.3)
Dry mouth	0	1 (12.5)	1 (6.3)
Back pain	1 (12.5)	0	1 (6.3)
Neck pain	1 (12.5)	0	1 (6.3)
Nasal congestion	0	1 (12.5)	1 (6.3)
Oropharyngeal discomfort	0	1 (12.5)	1 (6.3)
Erythema	0	1 (12.5)	1 (6.3)
Pruritus	1 (12.5)	0	1 (6.3)
Eye irritation	0	1 (12.5)	1 (6.3)
Feeling abnormal	1 (12.5)	0	1 (6.3)
Dysuria	0	1 (12.5)	1 (6.3)

AEs were coded using MedDRA Version 24.0

MedDRA Medical Dictionary for Regulatory Activities, *TEAE* treatment-emergent adverse event

5 Conclusions

Despite its minimal renal clearance, dordaviprone AUC increased on average by ~50% in severe RI participants, suggesting CYP3A4 activity may have been suppressed in these participants as has been reported for other drugs primarily eliminated by CYP3A4. The results of this study, namely the fold increase observed in dordaviprone exposure, will be used with patient exposure data in safety exposure response analyses to inform dosing paradigms in patients with RI, including any necessary dose adjustments.

Data Sharing Statement Participant-level data collected as part of this analysis are not available for analysis by independent researchers.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40268-025-00520-x.

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Declarations

Conflicts of Interest Angela Bartkus, Marion E. Morrison, Mark J. Mullin, Tim Tippin, and Odin Naderer are employees of Chimerix, Inc. and hold stock in Chimerix, Inc.; Shamia L. Faison and Joelle Batonga are paid consultants of Chimerix, Inc. Thangam Arumugham is a paid consultant of and holds stock in Chimerix, Inc.

Availability of Data and Material Subject-level data collected as part of this study are not available for analysis by independent researchers.

Code Availability Code used for this analysis is not available to independent researchers.

Ethics Approval This study was conducted 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 (CIOMS) International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and other applicable laws and regulations. The protocol, protocol amendments, informed consent forms, Investigator Brochure, and other relevant documents (e.g., 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. Trial Registration Number, ACTRN12622000405718.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication Not applicable.

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