NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	219876
Priority or Standard	Priority
Submit Date(s)	December 18, 2024
Received Date(s)	December 18, 2024
PDUFA Goal Date	August 18, 2025
Division/Office	Division of Oncology 2 / Office of Oncologic Diseases
Review Completion Date	Electronic stamp date
Established Name	dordaviprone
(Proposed) Trade Name	MODEYSO
Pharmacologic Class	protease activator
Code name	ONC201
Applicant	Chimerix, Inc.
Formulation(s)	Capsules: 125 mg
Dosing Regimen	Recommended dosage in adults: 625 mg orally once weekly Recommended dosage in pediatric patients aged 1 to <17 years who weigh at least 10 kg: • 10 kg to <12.5 kg: 125 mg orally once weekly • 12.5 kg to <27.5 kg: 250 mg orally once weekly • 27.5 kg to <42.5 kg: 375 mg orally once weekly • 42.5 kg to <52.5 kg: 500 mg orally once weekly • ≥52.5 kg: 625 mg orally once weekly
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Accelerated Approval

Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRM=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEOSI	adverse event of special interest
ALT	alanine aminotransferase
AUC	area under the concentration-time curve
AUCinf	AUC from time zero to infinity
AUClast	AUC from time zero to the last measurable concentration
BICR	blinded independent central review
BOR	best overall response
CI	confidence interval
CFR	Code of Federal Regulations
ClpP	caseinolytic protease P
C_{max}	maximum concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CR	complete response
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DIPG	diffuse intrinsic pontine glioma
DOR	duration of response
DRD2	dopamine receptor D2
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
eCTD	electronic common technical document
EFD	embryo-fetal development
eGFR	estimated Glomerular Filtration Rate
E-R	exposure-response
FDA	Food and Drug Administration
FOB	functional observation batteries

GCP	good clinical practice
geoCV	geometric coefficient of variation
GLP	good laboratory practice
H3 K27me3	H3 K27 trimethylation
HGG	high-grade glioma
IACUC	Institutional Animal Care and Use Committee
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonization
IIT	investigator-initiated trial
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISR	integrated stress response
ISS	integrated summary of safety
ITT	intent-to-treat
LGG	low-grade glioma
LOAEL	lowest-observed-adverse-effect level
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NOAEL	no-observed-adverse effect level
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	physiologically based pharmacokinetics
PD	progressive disease
PFS	progression-free survival

PK	pharmacokinetics
POPPK or PPK	population pharmacokinetics
PR	partial response
PRO	patient reported outcome
PT	preferred term
ΔΔQTcF	change from baseline in QTcF
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RANO	Response Assessment in Neuro-Oncology
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standardized MedDRA queries
SOC	system organ class
TEAE	treatment emergent adverse event
T_{max}	time to reach C_{max}
WHO	World Health Organization
US	United States

1 Executive Summary

1.1. Product Introduction

Dordaviprone is a protease activator of the mitochondrial caseinolytic protease P (ClpP). Dordaviprone also inhibits the dopamine D2 receptor. Diffuse midline gliomas harboring an H3 K27M mutation are associated with the loss of H3 K27 trimethylation. In-vitro, dordaviprone activated the integrated stress response, induced apoptosis, and altered mitochondrial metabolism leading to restored histone H3 K27 trimethylation in H3 K27M-mutant diffuse glioma models. At the time of application submission, dordaviprone was not approved for any indication.

The recommended dosage regimen for the proposed indication is 625 mg orally once weekly in adults, with body weight-based dosing in pediatric patients aged 1 to < 17 years who weigh at least 10 kg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support the accelerated approval of dordaviprone under 21 CFR part 314 subpart H, for the treatment of adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy.

The efficacy of dordaviprone was evaluated in adult and pediatric patients with glioma across five open label, non-randomized clinical studies conducted in the U.S. (ONC006 [NCT02525692], ONC013 [NCT03295396], ONC014 [NCT03416530], ONC016 [NCT05392374], and ONC018 [NCT03134131]). Due to the rarity of the disease and poor prognosis, and in order to evaluate a sufficiently homogenous patient population to assess the effect of the drug, FDA determined it was reasonable to consider safety and efficacy data from a pooled population of patients derived from single arm trials of dordaviprone monotherapy at the recommended dosage in adult and pediatric patients with recurrent H3 K27M-mutant diffuse midline glioma (DMG) who met pre-specified criteria. Specifically, eligible patients were required to have progressive and measurable disease per Response Assessment in Neuro-Oncology-High Grade Glioma (RANO-HGG) criteria, be ≥ 90 days post-radiation therapy, have adequate washout from prior anticancer therapies, have a Karnofsky Performance Status/Lansky Performance Status (KPS/LPS) score ≥ 60, and have stable or decreasing corticosteroid use. Patients received a weight-based dose of dordaviprone until disease progression or unacceptable toxicity.

The integrated efficacy population included 50 patients who met the pre-defined criteria. The major efficacy outcome measure was overall response rate (ORR) assessed by blinded independent central review (BICR) according to Response Assessment in Neuro-Oncology (RANO) 2.0 criteria. Additional efficacy outcome measures were BICR-assessed ORR according to RANO-High Grade Glioma (RANO-HGG) criteria and RANO-Low Grade Glioma (RANO-LGG) criteria, duration of response (DOR), and time to response.

The ORR assessed by BICR according to RANO 2.0 criteria was 22% (95% CI: 12, 36), with 16% partial responses and 6% minor responses. The median DOR was 10.3 months (95% CI: 7.3, 15.2), with an observed DOR of ≥ 6 months in 73% of responders and ≥ 12 months in 27%. In this population with a high unmet medical need, and for which there are no available therapies in any setting, a durable ORR is considered a clinically meaningful intermediate endpoint given that spontaneous responses are not observed in this disease setting and median overall survival after progression is typically 4 to 6 months (Baugh et al, 2024; Coleman et al, 2023).

Drug approval requires demonstration of substantial evidence of effectiveness (SEE) through adequate and well-controlled studies, which are described in 21 CFR 314.126. Given that the integrated efficacy population was derived from patients enrolled on five completed non-randomized clinical trials, FDA considered the following elements in the determination of whether the requirement for an adequate and well-controlled study was met:

- There was a clear statement of objectives with a pre-specified statistical analysis plan which was reviewed by FDA, including pre-defined eligibility and response criteria.
- The study design incorporated data from single arm studies with standardized eligibility criteria and this design was considered appropriate for this rare disease with no available therapy and adequate understanding of the natural history of disease, characterized by tumor progression and no evidence of spontaneous tumor regression.
- All patients had progressive measurable disease after up-front standard of care treatment including radiotherapy and all patients received dordaviprone monotherapy on study. Bias was minimized by pre-specification of inclusion criteria for the integrated efficacy population based on relevant clinical characteristics, in addition to supportive analyses which characterized the results in the context of the broader population enrolled across the single arm studies.
- The response assessments were reliable and adequate to assess the effect of the drug using appropriate statistical methods.

Potential limitations to the evaluation of objective responses in brain tumor imaging are described herein; however, these limitations were mitigated by the study design (i.e., requiring at least 3 months from the time of last receipt of radiation prior to study entry), systematic collection of imaging at pre-defined time periods, with retrospective collection of additional relevant data as available (e.g., pre-baseline MRI scans, data confirming true progression at baseline), and the granularity of data submitted in the application (e.g., narratives describing clinical improvements associated with responses).

The submitted evidence meets the statutory evidentiary standard for accelerated approval. An ORR of sufficient magnitude and duration is an intermediate endpoint reasonably likely to predict clinical benefit in patients with H3 K27M-mutant DMG, and this endpoint has supported the accelerated approvals of other therapies for patients with solid tumors harboring oncogenic driver alterations.

The Applicant intends to verify and describe the clinical benefit of dordaviprone based on the results of an ongoing randomized trial in patients with newly diagnosed H3 K27M-mutant DMG (Study ONC201-108) designed to evaluated overall survival (OS) and progression-free survival

(PFS) endpoints, which is >50% enrolled as of July 2025. As this randomized trial does not include pediatric patients with diffuse intrinsic pontine glioma (DIPG), which is the most common subset of H3 K27M-mutant DMG among pediatric patients, additional clinical trial data will be required to support verification of benefit in this group of patients.

In this application, SEE was established with one adequate and well-controlled clinical investigation and confirmatory evidence. Confirmatory evidence included BICR-assessed objective responses observed in patients with H3 K27M-mutant non-midline gliomas (i.e., hemispheric location), investigator-assessed objective responses in patients with recurrent H3 K27M-mutant DMG from other cohorts in Studies ONC013 and ONC014 (including patients with DIPG), investigator-assessed objective responses in patients with newly diagnosed H3 K27M-mutant DMG (i.e., an earlier line setting), and the lack of objective responses in patients with H3 K27M-wildtype disease. These clinical data are further supported by the biologically relevant mechanism of action of dordaviprone and evidence of restoration of histone H3 K27M trimethylation in tumor samples from patients treated with dordaviprone (Venneti et al, 2023).

This is the first FDA approval of a systemic therapy for patients with diffuse midline glioma harboring an H3 K27M mutation.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

In 2025, it is estimated that there will be 24,820 new cases of brain and other nervous system cancers and approximately 18,330 people will die of this disease (NCI SEER, 2025). While rare, these tumors cause significant morbidity and mortality across all ages.

Diffuse midline glioma (DMG) harboring an H3 K27M mutation is a rare brain tumor subtype, defined by somatic mutations in genes encoding the histone H3 protein. These mutations result in a loss of trimethylation at the H3K27 residue, disrupting normal epigenetic regulation and resulting in upregulation of downstream oncogenic pathways (Saratsis et al, 2023). The 2021 WHO Classification of CNS Tumors (Louis et al, 2021) defines these tumors as a pediatric-type diffuse high grade glioma (WHO Grade 4). According to the most recent Central Brain Tumor Registry of the United States (CBTRUS; Price et al, 2024), 0.06 per 100,000 patients are diagnosed per year (approximately 200 patients per year), however this may be an underestimate as this tumor was molecularly defined for the first time in 2016. H3 K27M-mutant DMGs are diagnosed in both adult and pediatric patients. Negative prognostic factors include infratentorial location, younger age, H3.3 mutations, and higher Ki-67 index (Gong et al, 2023; Zheng et al, 2022; Vuong et al, 2022).

Standard of care therapy for H3 K27M-mutant DMG includes surgery and radiation. Gross total resections are typically infeasible due to the midline location. Prior to the approval of dordaviprone, there were no systemic therapies approved for this disease. Furthermore, studies of chemotherapeutic agents such as temozolomide have not demonstrated a benefit in this population. After radiation, most patients are enrolled on clinical trials or elect to pursue palliative/best supportive care. The median overall survival is 10-15 months from diagnosis, with 2-year OS ranging from 5-20% depending on the cohort analyzed (van den Bent et al, 2023; Mackay et al, 2017). Some studies suggest that pediatric patients have shorter overall survival compared to adult patients, however the data are mixed (Gong et al, 2023; Kleinschmidt-DeMasters et al, 2018; Ebrahimi et al, 2019).

Dordaviprone is a protease activator of the mitochondrial caseinolytic protease P (ClpP). Dordaviprone also inhibits the dopamine D2 receptor. Diffuse midline gliomas harboring an H3 K27M mutation are associated with the loss of H3 K27 trimethylation. In-vitro, dordaviprone activated the integrated stress response, induced apoptosis, and altered mitochondrial metabolism leading to restored histone H3 K27 trimethylation in H3 K27M-mutant diffuse glioma models.

The primary evidence of efficacy in this application was based on an integrated efficacy population comprising a subset of adult and pediatric patients with glioma enrolled in five open label, non-randomized clinical studies conducted in the U.S. (ONC006 [NCT02525692], ONC013 [NCT03295396], ONC014 [NCT03416530], ONC016 [NCT05392374], and ONC018 [NCT03134131]). Pre-specified criteria were defined to

establish an integrated efficacy population; eligible patients were required to have received single-agent dordaviprone, have diffuse midline glioma harboring an H3 K27M mutation with progressive and measurable disease per Response Assessment in Neuro-Oncology-High Grade Glioma (RANO-HGG) criteria, be ≥ 90 days post-radiation therapy, have adequate washout from prior anticancer therapies, have a Karnofsky Performance Status/Lansky Performance Status (KPS/LPS) score ≥ 60, and have stable or decreasing corticosteroid use. Patients received a weight-based dose of dordaviprone until disease progression or unacceptable toxicity. The expanded access protocols (ONC016 and ONC018) each included specific eligibility criteria, required imaging assessments at pre-defined intervals (8 weeks), had specific instructions to ensure safety and consistency of treatment such as dose modifications in the event of toxicities, and employed systematic data collection. These characteristics, in conjunction with pre-defined eligibility criteria for the pooled efficacy population, enabled FDA to consider data from these expanded access protocols in addition to that from prospective clinical trials in the setting of a rare disease with a high unmet medical need.

In the integrated efficacy population of 50 patients who met these pre-defined criteria, the confirmed overall response rate (ORR) assessed by blinded independent central review (BICR) according to RANO 2.0 criteria was 22% (95% CI: 12, 36), with 16% partial responses and 6% minor responses. The median duration of response (DOR) was 10.3 months (95% CI: 7.3, 15.2), with an observed DOR of ≥ 6 months in 73% of responders and ≥ 12 months in 27%. In this population, a durable ORR is considered a clinically meaningful intermediate endpoint given that spontaneous responses are not observed in this disease setting and median overall survival after progression is typically 4 to 6 months (Baugh et al, 2024; Coleman et al, 2023).

Dordaviprone has an acceptable safety profile when assessed in the context of a life-threatening disease. The overall safety population included 376 patients with glioma who received dordaviprone monotherapy at the recommended dose or the equivalent body weight adjusted dose for patients weighing < 52.5 kg. Among these patients, the most common adverse reactions (≥ 20%) were fatigue, headache, vomiting, nausea, and musculoskeletal pain. Other clinically important adverse reactions observed in less than 10% of patients treated with dordaviprone were peripheral neuropathy, seizure, diarrhea, tremor, and venous thromboembolic events. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased calcium, and increased alanine aminotransferase. Permanent discontinuation of dordaviprone due to an adverse reaction occurred in 2.1% of patients. Fatal adverse reactions, excluding those definitively attributable to progressive disease or extraneous cause, occurred in 1% of patients, including cardiac arrest (0.5%), intracranial hemorrhage (0.3%), and encephalopathy (0.3%). The product label will include Warnings for hypersensitivity, QTc prolongation, and embryofetal toxicity.

Although safety data was not available for patients less than 3 years of age, the FDA determined that the inclusion of patients 1 year of age and older was appropriate based on the totality of the data, including the ability to extrapolate pharmacokinetic data from older pediatric patients. However, given immature CYP3A levels in pediatric patients less than 1 year with resulting difficulty in determining a safe dose of dordaviprone in this age group, as well as extreme rarity of patients less than 1 year of age with recurrent H3 K27M diffuse middle glioma, patients less than 1

year of age are not included in the indication statement.

The risks of dordaviprone are considered acceptable in the indicated population. The safe use of dordaviprone can be adequately implemented in the post-market setting through instructions for surveillance and actions to mitigate risk as described in product labeling. No additional risk management strategies are recommended.

The submitted evidence meets the statutory evidentiary standard for accelerated approval. An ORR of sufficient magnitude and duration is an endpoint reasonably likely to predict clinical benefit in patients with solid tumors, and this endpoint has supported the accelerated approvals of other therapies for patients with solid tumors harboring oncogenic driver alterations. The reliability of the observed durable responses was supported by the efficacy population requirement for completion of radiotherapy at least 3 months prior to enrollment, pre-treatment imaging and supportive data confirming true disease progression at baseline, and the granularity of available data including narratives describing clinical improvements associated with radiographic responses.

Confirmatory evidence included BICR-assessed objective responses observed in patients with H3 K27M-mutant non-midline gliomas (i.e., hemispheric location), investigator-assessed objective responses in patients with recurrent H3 K27M-mutant DMG from other cohorts in Studies ONC013 and ONC014 (including patients with DIPG), investigator-assessed objective responses in patients with newly diagnosed H3 K27M-mutant DMG (i.e., an earlier line setting), and the lack of objective responses in patients with H3 K27M-wildtype disease. These clinical data are further supported by the biologically relevant mechanism of action of dordaviprone and evidence of restoration of histone H3 K27M trimethylation in tumor samples from patients treated with dordaviprone (Venneti et al, 2023).

This is the first approval of a systemic therapy for patients with H3 K27M-mutant diffuse midline glioma. An ongoing randomized trial evaluating OS and PFS in patients with newly diagnosed H3 K27M-mutant DMG (Study ONC201-108), which is >50% enrolled as of July 2025, is intended to verify the clinical benefit of dordaviprone. As this trial does not include pediatric patients with diffuse intrinsic pontine glioma (DIPG), which is the most common subset of H3 K27M-mutant DMG among pediatric patients, additional clinical trial data will also be required to support verification of benefit in this group of patients.

Therefore, the review teams recommend accelerated approval of dordaviprone for the following indication:

> *Adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diffuse midline glioma (DMG) harboring an H3 K27M mutation is a rare brain tumor subtype, defined by somatic mutations in genes encoding the histone H3 protein. These mutations result in a loss of trimethylation at the H3K27 residue, disrupting normal epigenetic regulation and resulting in upregulation of downstream oncogenic pathways (Saratsis et al, 2023). • Approximately 200 patients per year are diagnosed with H3 K27M-mutant DMG (Price et al, 2024), however this may be an underestimate as this tumor was molecularly defined for the first time in 2016. • Median overall survival is 10-15 months from diagnosis, with 2-year OS ranging from 5-20% depending on the cohort analyzed (van den Bent et al, 2023; Mackay et al, 2017). • Some studies suggest that pediatric patients have shorter overall survival compared to adult patients, however the data are mixed (Gong et al, 2023; Kleinschmidt-DeMasters et al, 2018; Ebrahimi et al, 2019).	Diffuse midline glioma (DMG) harboring an H3 K27M mutation is a rare life-threatening cancer with a high unmet medical need.
Current Treatment Options	• Standard of care therapy for H3 K27M-mutant DMG includes surgery and radiation. Gross total resection is not feasible for most tumors due to their midline location. • Prior to the approval of dordaviprone, there were no systemic therapies approved for this disease. Studies of chemotherapeutic agents such as temozolomide have not demonstrated a benefit in this population. • After radiation, most patients are enrolled on clinical trials or elect to pursue palliative/best supportive care.	There are no available systemic therapies for patients with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The primary evidence of efficacy in this application was based on an integrated efficacy population comprising 50 patients (9 to 70 years of age) with progressive H3 K27M-mutant DMG who received dordaviprone monotherapy in one of five open label, non-randomized clinical studies conducted in the U.S. • Eligible patients were required to be ≥ 90 days post radiation therapy, have adequate washout from prior anticancer therapies, have a Karnofsky Performance Status/Lansky Performance Status (KPS/LPS) score ≥ 60, and have stable or decreasing corticosteroid use. • The confirmed ORR in the integrated efficacy population assessed by BICR according to RANO 2.0 criteria was 22% (95% CI: 12, 36), with 16% partial responses and 6% minor responses. The median duration of response (DOR) was 10.3 months (95% CI: 7.3, 15.2), with an observed DOR of ≥ 6 months in 73% of responders and ≥ 12 months in 27%. • Additional supportive evidence includes BICR-assessed objective responses observed in patients with H3 K27M-mutant non-midline gliomas (i.e., hemispheric location), investigator-assessed objective responses in patients with recurrent H3 K27M-mutant DMG from other cohorts in Studies ONC013 and ONC014 (including patients with DIPG), investigator-assessed objective responses in patients with newly diagnosed H3 K27M-mutant DMG (i.e., an earlier line setting), and the lack of objective responses in patients with H3 K27M-wildtype disease. • The clinical efficacy data are supported by the biologically relevant mechanism of action of dordaviprone and evidence of restoration of histone H3 K27M trimethylation in tumor samples from patients	The submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed ORR, along with the observed duration of responses, is clinically meaningful in the setting of a genetically based biologic rationale and the lack of available systemic therapies in this disease with poor prognosis. The review team considers the observed durable responses reliable given that eligible patients were at least 3 months from completion of prior radiotherapy, pre-treatment imaging and supportive data confirmed true progression at baseline, and the available data included narratives describing clinical improvements associated with responses. Confirmatory evidence includes clinical data in related disease settings as well as nonclinical data as described in the review. This is the first approval of a systemic therapy for patients with H3 K27M-mutant diffuse midline glioma. The Applicant intends to verify and describe the clinical benefit of dordaviprone based on the results of an ongoing randomized trial in patients with newly diagnosed H3 K27M-mutant glioma (Study ONC201-108) designed to evaluated OS and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treated with dordaviprone (Venneti et al, 2023)	PFS, which is >50% enrolled as of July 2025.
Risk and Risk Management	• The overall safety population included 376 patients with glioma who received dordaviprone monotherapy at the recommended dose or the equivalent body weight adjusted dose for patients weighing < 52.5 kg. • The most common adverse reactions (≥ 20%) were fatigue, headache, vomiting, nausea, and musculoskeletal pain. • The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased calcium, and increased alanine aminotransferase. • Warnings included hypersensitivity, QTc prolongation and embryofetal toxicity.	The observed safety profile is acceptable in the context of the treatment of a life-threatening disease. Although dordaviprone can cause serious toxicities, these safety concerns are adequately addressed by information in the product labeling. Dordaviprone will be prescribed by oncologists who know how to monitor, identify, and manage the toxicities described in the USPI. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). The clinical review team determined that it is in the best interest of US patients to approve dordaviprone before a companion diagnostic assay is available. Since an application for an in vitro companion diagnostic was not submitted for contemporaneous approval with this NDA, the approved labeling will state that there is no

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		FDA-approved test for selecting patients for treatment with dordaviprone. The Applicant has committed to a PMC to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect H3 K27M mutations for identifying patients with H3 K27M mutations who may benefit from dordaviprone.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:			N/A
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		

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	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Diana Bradford, MD

Cross-Disciplinary Team Leader

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

The 4th edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) for the first time defined some gliomas by specific molecular alterations, including diffuse midline glioma, H3 K27M-mutant (Louis 2016) as a distinct form of Grade 4 glioma. The H3 K27M mutation is predominantly found among gliomas that occur in midline locations of the CNS: 75% of thalamic tumors, ~54% of brainstem tumors, and 55% of spinal cord tumors; 24% of pediatric gliomas and 8% of adults. H3 K27M is a founder mutation that causes a global reduction in histone H3 K27 trimethylation (H3 K27me3), which is a histone modification generally associated with epigenetic repression.

A meta-analysis of H3 K27M-mutant glioma reported a median age at initial diagnosis of 11 years (range: 1 to 82) and median overall survival (OS) from initial diagnosis of 11.3 months (Vuong 2022). Although rare overall, gliomas constitute around half of brain tumors in patients under 14 years of age and are the leading cause of death due to a brain tumor.

The epidemiology of H3 K27M-mutant glioma shows an estimated annual incidence in the United States (US) is ~2000 patients and it is recognized as a rare disease that predominantly affects children and young adults. In pediatric patients, diffuse midline gliomas have a prevalence of only 0.54 cases per 1 million person-years, with the H3 K27M mutation present in 80% of pediatric high-grade glioma patients. In adult patients (>20 years), diffuse midline gliomas have a prevalence of 2.32 cases per 1 million person-years and represent only 3% to 5% of primary brain tumors (Broggi 2024).

The FDA's Assessment:

FDA agrees with the Applicant's summary of H3 K27M-mutant diffuse midline glioma (DMG). The H3.3 mutation was first described in the literature in 2012 (Schwatzentruber et al, 2012), and since that time, multiple publications have described the epidemiology and clinical relevance of somatic mutations in genes encoding the histone H3 protein. These mutations result in a loss of trimethylation at the H3K27 residue, disrupting normal epigenetic regulation and resulting in upregulation of downstream oncogenic pathways (Saratsis et al, 2023).

H3 K27M-mutant DMGs are diagnosed in both adult and pediatric patients. Negative prognostic factors include infratentorial location, younger age, H3.3 mutations, and higher Ki-67 index (Gong et al, 2023; Zheng et al, 2022; Vuong et al, 2022). Some studies suggest that pediatric patients have shorter overall survival compared to adult patients, however the data are mixed (Gong et al, 2023; Kleinschmidt-DeMasters et al, 2018; Ebrahimi et al, 2019). Co-occurring

genetic variants may also impact prognosis, although these data are still evolving (Mateos et al, 2025).

DMGs include the historically radiographically diagnosed entity, diffuse intrinsic pontine glioma (DIPG), characterized by rapid onset of neurologic symptoms (e.g., cranial nerve deficits, long tract signs, cerebellar signs), tumor centered in and involving >50% of the pons with ill-defined borders, heterogeneous contrast enhancement and no significant exophytic component (Hoffman et al, 2018). Although brainstem biopsies were often avoided in the past due to risk of neurologic injury, more recently stereotactic biopsy has been shown to have a minimal effect on mortality with a high diagnostic yield (Weisbrod et al, 2024). DIPG remains a clinically relevant term, though diagnostically approximately 80% of DIPG cases harbor the H3 K27M mutation and have been reclassified as diffuse midline glioma, H3 K27M-mutant (Vitanza et al, 2019).

2.2. Analysis of Current Treatment Options

There are currently no pharmacologic agents approved specifically for the treatment of H3 K27M-mutant diffuse glioma. H3 K27M generally does not co-occur in gliomas with targetable genomic alterations such as IDH and BRAF.

Standard frontline treatment typically consists of surgical resection (if feasible) followed by radiotherapy, which only provides transient benefit and remains the sole established therapy for this disease. Despite these measures, disease progression following radiotherapy remains inevitable, with a median progression-free survival (PFS) from initial diagnosis of 7 to 9 months (Vuong 2022). A meta-analysis employing multivariate techniques to assess demographics, disease characteristics, and treatment regimens found that radiation and age were the only prognostic factors for OS that achieved statistical significance (Vuong 2022).

In the recurrent setting, available therapy is palliative. Objective responses to systemic therapies with standardized criteria and adequate washout have not been reported for recurrent H3 K27M-mutant diffuse glioma. For adult and pediatric patients with recurrent high-grade gliomas, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommend enrollment in a clinical study as the preferred option. Other treatment options for these patients include surgery, chemotherapy, targeted therapy based on molecular composition, re-irradiation, and/or palliative/best supportive care (NCCN 2024).

The Applicant's Position:

H3 K27M-mutant diffuse glioma is a rare, serious, life-limiting condition. There are currently no pharmacologic agents approved specifically for the treatment of H3 K27M-mutant diffuse glioma. Due to the high morbidity and mortality of this high-grade glioma that lacks effective therapy in the recurrent setting, there is a substantial unmet medical need for novel pharmacologic agents that provide clinical benefit with a favorable safety profile.

The FDA's Assessment:

FDA agrees with the Applicant's summary of current treatment options for recurrent H3 K27M-mutant diffuse midline glioma. Standard of care therapy includes surgery and radiation. Most tumors are unable to be gross totally resected due to their midline nature. There are no systemic therapies approved for this disease. Studies of chemotherapeutic agents, such as temozolomide, have not shown a benefit in this population. After radiation, most patients are enrolled on clinical trials or elect to pursue palliative/best supportive care. The median overall survival is 10-15 months from diagnosis, with 2-year OS ranging from 5-20% depending on the cohort analyzed (van den Bent et al, 2023; Mackay et al, 2017). FDA agrees there is an unmet need for safe and effective therapies for this serious and life-threatening condition.

3 Regulatory Background

The Applicant's Position:

Chimerix, Inc. (Chimerix, the Sponsor) acquired Oncoceutics, Inc. and its investigational molecule dordaviprone in 2021, assuming sponsorship and regulatory responsibilities for several key studies previously initiated by Oncoceutics. Studies ONC006 (NCT02525692), ONC013 (NCT03295396), ONC014 (NCT03416530), ONC016 (NCT05391724), and ONC018 (NCT03134131) were designed to evaluate dordaviprone for treating glioma.

Post-acquisition, Chimerix completed these studies and continued advancing the clinical development of dordaviprone. As of 31 July 2024, over 1600 adult and pediatric participants have received dordaviprone across completed and ongoing company-sponsored clinical studies, expanded access programs, investigator-initiated studies, and clinical pharmacology studies. A global blinded, randomized, placebo-controlled Phase 3 study enrolling patients with H3 K27M-mutant glioma to evaluate 2 dose frequencies of dordaviprone versus placebo following completion of frontline radiation is being conducted, and enrollment is well underway.

Dordaviprone has been granted Fast Track Designation for the treatment of adult recurrent H3 K27M-mutant high-grade glioma, Rare Pediatric Disease Designation for the treatment of H3 K27M-mutant glioma, and Orphan Drug Designations for the treatment of glioblastoma and for the treatment of malignant glioma.

The FDA's Assessment:

FDA agrees with the Applicant's position. Study ONC006 was conducted under IND (b) (4) and determined safe to proceed on February 28, 2014. Studies ONC013, ONC014, ONC016, and ONC018 were conducted under IND 136090.

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

This is the first time a New Drug Application (NDA) or marketing application has been submitted for dordaviprone. Dordaviprone is not currently registered, approved, or marketed in the US.

The FDA's Assessment:

FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary table of regulatory interactions is provided below.

Date of Meeting/ Date of Minutes	Topic / Purpose of the Meeting or Interaction
2017-Aug-31/ Not applicable	Study May Proceed letter received for IND 136090.
2019-Jul-08/ 2019-Jul-15	Clinical and general development – Type C – Guidance Purpose: To discuss high level, general development feedback in advance of an end of phase 2 (EOP2) meeting for the development of dordaviprone as a single agent in adults with recurrent H3 K27M-mutant high-grade glioma.
2020-May-12/ 2020-May-29	Clinical – Type C Purpose: To obtain feedback on the ongoing development program for dordaviprone in recurrent diffuse midline glioma, H3 K27M-mutant.
2020-Sep-11/ 2020-Sep-29	Nonclinical – Type B – Other Purpose: To discuss the proposed nonclinical development program, for dordaviprone, for the treatment of previously treated H3 K27M-mutant glioma, in support of a new drug application.
2021-Jan-11/ 2021-Feb-01	CMC – Type C – pre-NDA Purpose: To seek feedback on the proposed CMC development plan in order to ensure fulfillment of FDA expectations and to provide an acceptable CMC package for marketing authorization.
2021-Mar-11/ Not applicable	IND transferred from Oncoceutics to Chimerix
2021-Jun-08/ 2021-Jun-17	Clinical – Type C – Guidance Purpose: To discuss the proposed clinical pharmacology program to support a planned NDA for dordaviprone for the treatment of H3 K27M-mutant glioma.
2021-Jun-29/ 2021-Jun-22 (WRO)	Clinical – Type C – Guidance Purpose: to discuss the safety and efficacy integrated analysis strategy and administrative aspects of the planned NDA for dordaviprone for treatment of H3 K27M-mutant glioma.

Date of Meeting/ Date of Minutes	Topic / Purpose of the Meeting or Interaction
2022-Mar-31/ 2022-Apr-19	Clinical – Type C – Guidance Purpose: To discuss the ongoing natural history study (ONC019), the design of a planned Phase 3 study for the treatment of newly diagnosed H3 K27M-mutant glioma, and the use of currently available diagnostics for detection of the H3 K27M mutation.
2022-Nov-28 (cancelled)/ 2022-Nov-23 (WRO)	Clinical – Type C – Guidance Purpose: To discuss acceptability of filing a potential NDA for accelerated approval of dordaviprone for the treatment of recurrent, H3 K27M-mutant diffuse midline glioma.
2023-Jun-26/ 2023-Aug-10	Q-Submission Purpose: To confirm the mutation testing plan with the FDA's Center for Devices and Radiological Health (CDRH).
2024-Jul-17/ 2024-Jul-30/ 2024-Aug-01	Clinical – Type C – Guidance Purpose: To discuss the current status of dordaviprone development and, based on recent program interactions, gain alignment on the issues raised and best steps for moving forward. The sponsor requested clarifications on pages 11 and 19 of the meeting minutes.
2024-Oct-15 (WRO)	CMC – Type D – Guidance Purpose: To seek agreement on the dissolution method for quality control testing of dordaviprone capsules, and to seek guidance regarding the use of data generated with 2 different dissolution methods to support the quality control specifications and shelf life of the proposed drug product in the NDA.
2024-Oct-30/ 2024-Oct-29 (WRO)	CMC – Type B – pre-NDA Purpose: To discuss the supporting data and details of the planned NDA and to reach agreement that the content and format of the submission will be acceptable for filing.
2024-Nov-01/ 2024-Oct-30 (WRO)/ 2024-Nov-12 2024-Nov-21	Clinical – Type B – pre-NDA Purpose: To discuss details of the proposed NDA for dordaviprone capsules and to reach agreement that the content and format of the NDA will be acceptable for filing. The sponsor provided responses to the pre-NDA preliminary meeting comments. The FDA provided the following response: *We generally agree with your plan for NDA submission; however, determination regarding whether substantial evidence of effectiveness of dordaviprone in the intended population has been demonstrated will be a matter of review.*

Abbreviations: CMC=Chemistry, Manufacturing, and Controls; FDA=Food and Drug Administration; IND=Investigational New Drug; NDA=New Drug Application; WRO=Written Request Only

The FDA's Assessment:

FDA agrees with the Applicant's summary of regulatory interactions. The NDA was submitted on December 18, 2024.

On July 8, 2025, a Late Cycle Meeting was held via videoconference with the Applicant. During the meeting, the Applicant stated that 292 patients had been enrolled to the ACTION trial (ONC201-108), including 46 pediatric patients. Refer to the Late Cycle Meeting minutes for full details.

APPEARS THIS WAY ON ORIGINAL

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

FDA performed clinical inspections of three U.S. clinical investigators, Drs. Isabel Arrillaga-Romany (Site MGH), Nazanin Majd (Site MDACC), and Marissa Barbaro (Site NYU), as well as the Sponsor, Chimerix Inc. A remote regulatory assessment (RRA) of the imaging Contract Research Organization (CRO), (b) (4) was also conducted. The inspections did not find significant concerns regarding the study conduct, data discrepancies or integrity, Good Clinical Practice (GCP), or regulatory compliance. Based on these inspections and the RRA, Studies ONC006, ONC013, ONC014, ONC016, and ONC018, appear to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

For additional details, refer to the Clinical Inspection Summary by Lee Pai-Scherf, MD, dated July 1, 2025.

4.2. Product Quality

Refer to the Office of Pharmaceutical Quality (OPQ) Integrated Quality Assessment Template in DARRTs, dated June 25, 2025. Briefly, OPQ determined that applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable based on prior inspection history. The Agency agrees with the Applicant's proposal to continue performing (b) (4) testing on all three process validation batches on stability and at batch release for future commercial batches to establish an appropriate (b) (4) specification. A post-marketing commitment (PMC) will be issued. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommended approval of NDA 219876 for dordaviprone capsules, for oral use.

4.3. Clinical Microbiology

Refer to Section 4.2.

4.4. Devices and Companion Diagnostic Issues

No device or companion diagnostic (CDx) data were submitted in the original application. Tumor samples are limited in this disease setting and challenging to obtain primarily due to their anatomic location in the midline of the brain and brainstem. The Applicant plans to collect local laboratory data and validation information for the diagnostic H3 K27M tests which are being used to qualify patients for enrollment on the randomized clinical trial Study ONC201-108, from which the results are intended to verify and confirm the clinical benefit of dordaviprone. As FDA

does not intend to delay the approval of dordaviprone to permit contemporaneous approval with the CDx, and H3 K27M testing is standard of care and integral to the diagnosis of this disease, a PMC will be issued with the accelerated approval letter as follows:

> Conduct an appropriate analytical and clinical validation study to support the development of an in vitro diagnostic device using clinical trial data that demonstrates that the device is essential to the effective and safe use of dordaviprone for the treatment of adult and pediatric patients with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Dordaviprone is a small molecule protease activator of the mitochondrial caseinolytic protease P (ClpP). The established pharmacological class for dordaviprone is protease activator. Dordaviprone also inhibits the dopamine D2 receptor (D2R). Downstream activation of ClpP in H3K27M-mutant glioma cells includes impaired tumor cell metabolism, mitochondrial damage, activation of the integrated stress response (ISR) pathway, disruption of metabolic and epigenetic pathways, and apoptosis (Venneti et al, 2023).

Dordaviprone bound to ClpP and D2R in several binding studies. Increased ClpP protein and mRNA expression correlated to increased tumor grade across patient-derived pediatric brain tumors with upregulation in patient-derived high-grade glioma (HGG) and medulloblastoma compared to low grade glioma (LGG). D2R was also overexpressed in patient-derived HGG compared to normal brain tissue and was significantly higher in H3K27M-positive tumors compared to H3K27-wild type (wt) tumors. Dordaviprone increased activation of ClpP in enzymatic assays with EC_{50} values ranging from 1.1 to 2.3 μM. The Applicant evaluated the antiproliferative activity of dordaviprone in several diffuse midline glioma (DMG) cancer cell lines including diffuse intrinsic pontine glioma (DIPG) cells, a specific subset of DMGs, and in glioblastoma (GBM) cells. Dordaviprone dose-dependently decreased cell viability up to 91% in DIPG H3K27M-positive cells and up to 60% in glioblastoma (GBM) H3K27-wt cells. Knockout (KO) of ClpP in these same DIPG and GBM cells led to dordaviprone resistance. KO of D2R had no effect on sensitivity to dordaviprone in the DIPG cells with dordaviprone decreasing cell viability up to 86% in cells with and without D2R. The Applicant states that this is potentially due to lack of microenvironment in an in vitro model but did not provide additional evidence. Dordaviprone dose-dependently decreased mitochondrial membrane potential and increased reactive oxygen species (ROS) in DMG cells (H3K27 status unknown). In several DMG cell lines, dordaviprone upregulated markers of the integrated stress response (ISR) and apoptosis. In H3K27M-positive DIPG and DMG cells, dordaviprone downregulated the TCA cycle, glycolysis, and pyruvate metabolism compared to vehicle control, which additionally led to increased H3K27 methylation in a dose-dependent manner. In mice bearing orthotopic intracranial (brainstem inoculated) tumors, the in vivo antitumor activity of dordaviprone was assessed by evaluating survival and pharmacodynamic endpoints. Dordaviprone treatment of DIPG/DMG tumor-bearing mice in several studies increased lifespan compared to vehicle controls, under the conditions tested. Immunohistochemistry analysis of tumor tissue showed decreased markers of cellular proliferation in dordaviprone treated mice. Dordaviprone decreased D2R and ClpP downstream effectors indicative of D2R inhibition and ClpP activation and increased the apoptotic markers in tumor tissue from treated mice compared to vehicle treated mice.

Secondary pharmacology analysis indicated that dordaviprone (10 μM) inhibited the sodium

channel, site 2 (rat) and the L-type calcium channel (rat) by 82 and 61%, respectively, but IC_{50} values were not provided because studies with lower dordaviprone doses were not conducted. There were no additional human secondary targets noted.

Dordaviprone inhibited hERG potassium channel current with an IC_{50} of 2.4 μM in an in vitro safety pharmacology assessment. No changes were noted in ECG parameters in dogs; however, because of the on-target activity of dordaviprone on mitochondrial enzyme ClpP, cardiotoxicity was anticipated due to the heart's high metabolic demands and reliance on normal mitochondrial function. In line with this, QT prolongation was an adverse event observed in clinical studies. The major human metabolite, ONC207, also had no effect in the in vitro hERG channel assay and in dogs was noted at levels sufficient to cover exposure in the clinic. Dordaviprone led to minimal to moderate transient decreased respiratory rate and minute volume following a single oral administration at 225 mg/kg in rats both of which recovered by 2 hours post dose. CNS toxicity due to on-target activity of dordaviprone inhibition of the D2R was observed in the 4-week repeat-dose GLP toxicity study in rats and the 13-week repeat-dose GLP toxicity study in dogs based on clinical signs. CNS toxicity in rats included piloerection, abnormal gait and stance, circling, wobbling, crawling, whole body twitching, decreased muscle tone, and decreased activity occurring at ≥125 mg/kg once weekly. CNS toxicity in dogs included whole body tremors, cranial tremors, seizure, excessive salivation, lateral recumbency, rigidity, paddling of limbs, overall rigid body, salivation, abnormal gait/stance, and twitching at ≤60 mg/kg, and dogs required treatment with diazepam to alleviate seizures and seizure-like activity. Findings occurred post dose in both rats and dogs and generally recovered between dosing. Gait disturbances, hemiparesis, dysarthria, muscle weakness, and dysphagia were observed in the clinic and are likely due to on target D2R inhibition by dordaviprone.

Dordaviprone was 70-90% protein bound in rat, mouse, and dog plasma, and 95-97% protein bound in human plasma. Dordaviprone distributed to the uveal tract, eye, endocrine system, GI tract, and meninges in rats. Brain exposure was minimal for radiolabeled-dordaviprone in rats. Dordaviprone was excreted in feces due to biliary secretion (70%) and urine (25%) in rats. Dordaviprone accumulated to a greater extent in tumor tissue compared to surrounding normal brain tissue in intracranial tumor-bearing mice and accumulated to a greater extent in the pons and thalamus compared to plasma in both tumor-bearing and non-tumor bearing mice. Oral administration of the proton-pump inhibitor omeprazole did not affect the bioavailability of orally administered dordaviprone in the plasma or brain tissues including the brainstem, thalamus, and prefrontal cortex.

The Applicant evaluated the safety of dordaviprone administered orally once or twice weekly in 28-day and 13-week GLP-compliant general toxicology studies using Sprague Dawley rats and Beagle dogs. The weekly oral administration is consistent with the intended clinical route of administration. There were no deaths in either rat study or the 28-day dog study. One death occurred in the 13-week dog study at 60 mg/kg with significant dordaviprone-induced CNS toxicity and a gross brain lesion thought to be congenital and not drug-related. Dogs dosed with 90 mg/kg were dose reduced to 75 mg/kg and then further to 45 mg/kg due to CNS toxicities.

Dordaviprone dose-dependently increased glucose, cholesterol, AST, ALT, and ALP in rats starting at doses ≥31.25 mg/kg for cholesterol and ≥62.5 mg/kg for all others; these findings were considered on-target effects for D2R inhibition by dordaviprone and were also observed in patients. Dordaviprone led to dose-dependent GI toxicity in dogs starting at doses ≥30 mg/kg; vomiting, nausea, and constipation were noted as adverse events in patients. Dogs had significant CNS toxicity that required intervention as discussed in the safety pharmacology paragraph above. Target organs in the rat included stomach (inflammation), liver (hepatocyte vacuolation), thyroid (hypertrophy), and mammary gland (hyperplasia). Histopathology findings in the dog were limited one animal per finding for mononuclear cell infiltration in the brain, epididymis, lacrimal gland, prostate, and lungs.

ONC207 is considered a major human metabolite and accounted for ~11-20% in patients. ONC207 had no effect in the in vitro hERG channel safety pharmacology assay and had no pharmacological activity in the pharmacology studies thus is considered an inactive metabolite. ONC207 was found at significant levels in dogs and rats treated with dordaviprone once weekly in the 13-week toxicology studies with sufficient coverage of clinical exposure observed in the animal studies.

Dordaviprone was negative for mutagenicity in the Ames test and negative for clastogenicity in both the in vitro and in vivo micronucleus tests. Dordaviprone did not meet the criteria for phototoxicity in a 3T3 phototoxicity assay.

Carcinogenicity studies have not been conducted with dordaviprone and are not warranted for the proposed indication. Inhibition of D2R may cause hyperprolactinemia (Al-Chalabi M, 2023; Fitzgerald P, 2008); mammary gland hyperplasia was reported in animals in the13-week study in rats and will be included in section 13.2 of the product label.

Dedicated fertility studies were not conducted and are not warranted for the proposed indication. Dordaviprone did not target reproductive organs in repeat-dose toxicology studies at doses ≥125 mg/kg once weekly; however, given the mechanism of action of inhibiting D2R and alterations to mitochondrial function, dordaviprone may adversely impact fertility in humans. Non-GLP-compliant dose-range finding (DRF) embryo-fetal development studies were conducted in pregnant rats and rabbits to assess the effect of dordaviprone on fetal development. The FDA agreed that additional GLP-compliant studies were not warranted due to significant findings in the DRF studies. Once daily oral dordaviprone given to rats from gestation day (GD) 7 to GD17 resulted in maternal mortality at 125 mg/kg (≥2-times the highest recommended dose based on body surface area) with animals showing adverse clinical signs (labored breathing, abnormal respiratory rate, CNS toxicities) and decreased body weight prior to death. Deaths were considered dordaviprone-related. Dose-dependent increased pre-implantation loss occurred starting at the 25 mg/kg dose and ranged from 12 to 18.5% in the rats (≥0.01-times the highest recommended dose based on body surface area). The 125 mg/kg dose led to decreased mean fetal body weight (7% compared to controls) and fetal abnormalities of absent eye and small renal papillae in kidney. Exposure multiples for rats compared to humans were calculated based on

body surface area due to lack of PK/TK data in the embryo-fetal development study. Once daily oral dordaviprone given to rabbits from GD7 to GD19 resulted in early termination of all the animals at doses ≥62.5 mg/kg (0.2 times the exposure in patients at the highest recommended dose based on AUC) due to dordaviprone-related maternal toxicities including adverse clinical signs (labored breathing, dehydration, CNS toxicities) and maternal body weight loss, as such, no evaluation of embryofetal affects was conducted at these doses. Dordaviprone at 10 and 25 mg/kg (≥0.4 times the highest recommended dose-based on Cmax) led to incidences of fetal external and visceral abnormalities including short snout, absent teeth, and misshapen brain. Exposure multiples for rabbits compared to humans were calculated based on Cmax data, which was evaluated in the rabbit embryo-fetal development study, and it is pertinent as it reflects the drug concentration on a specific gestational day. FDA recommend a warning for embryo-fetal toxicity.

Based on FDA guidance, "Oncology Pharmaceutical: Reproductive Toxicity Testing and Labeling Recommendations," and considering a half-life of 11.4 hours, the duration of contraception after the last dose of the drug may be set at 1 week. However, as stated in the guidance, deviations from the labeling recommendation are acceptable when justified. FDA accepts the duration of 1 month proposed by the Applicant to allow the pharmacodynamic effects (and associated toxicities) to reverse.

FDA recommends that women do not breastfeed during treatment with dordaviprone and for 1 week after the last dose based on 5 times the plasma half-life (5 * 11.4 hours = 57 hours/24 hours = 2.4 days rounded up to 1 week).

There are no approvability issues from a pharmacology/toxicology perspective. The Pharmacology/Toxicology team recommends approval of dordaviprone (b) (4)

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, Biologics License Applications, or Drug Master Files related to nonclinical pharmacology or toxicology for dordaviprone.

The FDA's Assessment:

FDA agrees.

5.3. Pharmacology

5.3.1. Primary Pharmacology

The Applicant's Position:

Dordaviprone (also known as ONC201), is a brain-penetrant, small-molecule imipridone that acts as both a mitochondrial caseinolytic protease P (ClpP) agonist and a dopamine receptor D2 (DRD2) antagonist. Dordaviprone treatment in H3 K27M-mutant glioma cells leads to impaired tumor cell metabolism and mitochondrial damage, triggering activation of the integrated stress response (ISR) pathway, and resulting in apoptosis both in vitro and in vivo. The alteration in mitochondrial metabolism also impacts histone demethylases, which in turn increases H3 K27me3 levels, thereby reversing the central hallmark of H3 K27M-mutant diffuse glioma. These effects are observed in nonclinical models and tumor samples from patients treated with dordaviprone.

Binding Targets

ClpP

Dordaviprone acts as an allosteric agonist of ClpP, a mitochondrial protease that is highly expressed in H3 K27M-mutant gliomas (Ishizawa 2019; Graves 2019). Hyperactivation of ClpP by dordaviprone results in increased degradation of specific mitochondrial proteins with low micromolar potencies (1.1 to 2.3 µM) (Study O_hClpP_210121). ONC207, the major metabolite of dordaviprone, did not activate ClpP up to a concentration of 100 µM (Study O_hClpP_210121).

ClpP expression is essential for dordaviprone anti-cancer efficacy (Przystal 2022; Jackson 2023). In vitro studies demonstrated that dordaviprone sensitivity in H3 K27M-mutant glioma cells correlates with ClpP expression. Cells with ClpP knockout or knockdown exhibited resistance to dordaviprone (Study ONC201-BIO-101), showing diminished effects on cellular markers like CLPX, NDUFA12, OGDH, and impaired PARP cleavage. Furthermore, whole genome sequencing identified ClpP mutations in both H3 wild-type and K27M-mutant cells that had developed acquired resistance to dordaviprone. Introducing ClpP mutants into parental glioma cells conferred resistance, whereas expressing wild-type ClpP in resistant cells partially restored dordaviprone sensitivity (Lee 2023) (Study ONC201-BIO-100).

DRD2/3

Radioligand and multiple functional assays have demonstrated that dordaviprone is a full antagonist of DRD2 and DRD3 with low micromolar potencies (~2 to 3 µM) that exhibits mixed competitive and non-competitive antagonism (Madhukar 2019; Free 2021; Studies GPCRD04537D, GPCRD04403D). Compared to dordaviprone, ONC207 showed minimal inhibition of DRD2 in these assays (Study ONC207-BIO-101). DRD2 is highly expressed in H3 K27M-mutant gliomas and DRD2 expression correlates with dordaviprone in vitro anticancer efficacy (Chi 2017; Jackson 2023). In the presence of the other binding target ClpP, DRD2

expression may not be essential for efficacy (Study ONC201-BIO-101). DRD3 is functionally redundant with DRD2, and its expression is not detectable in most cancer cell lines (Kline 2018).

Downstream effects of target interaction

H3 K27M-mutant tumors, characterized by a global reduction in H3 K27me3 levels, show a reversal of this pathognomonic loss upon treatment with dordaviprone in glioma cells (Venneti 2023). Treatment also leads to significant upregulation of proteins involved in the ISR, including phospho-eIF2α, ATF4, DR5, and CHOP (Przystal 2022). Western blot analyses indicate that dordaviprone exposure decreases phosphorylation of Akt at Thr308 and Ser473 and reduces ERK phosphorylation in DIPG cells in vivo (Sharma 2019; Jackson 2023). Furthermore, dordaviprone's mechanism as a ClpP agonist impairs tumor cell metabolism, degrades mitochondrial respiratory chain proteins like NDUFA12 and SDHB, alters mitochondrial morphology with cristae disintegration and cristae membrane whirl formation, and diminishes mitochondrial membrane potential, culminating in increased mitochondrial reactive oxygen species production and apoptosis (Przystal 2022; Jackson 2023).

In vitro anti-cancer activity

Dordaviprone has shown efficacy in vitro in cell lines, patient-derived cells and 3D neurosphere cultures of H3 K27M-mutant glioma. Dordaviprone reduces cell viability across various H3 K27M-mutant glioma cell lines, with IC_{50} values ranging from 0.75 to 5.3 µM (Chi 2017; Przystal 2022; Jackson 2023; Venneti 2023; Study ONC201-BIO-102). These concentrations align with those required to engage its direct molecular targets, DRD2 and ClpP, underscoring its targeted mechanism of action. In contrast, the major human metabolite of dordaviprone, ONC207, did not exert significant effects on the viability of cancer cells, even at concentrations up to 80 µM (Study ONC207-BIO-101).

In vivo anti-cancer activity and pharmacodynamic effects

Once weekly administration of single agent dordaviprone (125 mg/kg once weekly or twice weekly or every 5 days, human equivalent dose of approximately 625 mg) significantly extended survival in multiple in vivo preclinical mouse models of H3 K27M-mutant glioma, including intra-cranial, PDXs, immune-competent and genetic mouse models (Jackson 2023; Venneti 2023; de la Nava 2023; Duchatel 2021). Dordaviprone treatment in mice was associated with decreased SDHA, Ki67, p-ERK staining, ISR activation (ATF4 and DR5 upregulation) and mitochondrial damage (ClpX and NDUFA12 downregulation) in H3 K27M-mutant glioma tumor tissue (Przystal 2022; Sharma 2019; Duchatel 2021; Jackson 2023).

The FDA's Assessment:

The Applicant submitted study results from conducted pharmacology studies and cited research data from scientific literature to support the primary pharmacology of dordaviprone. The

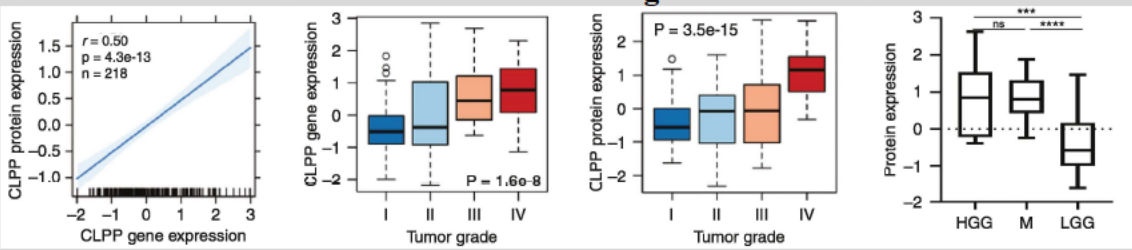
information presented from literature and cited by the Applicant is descriptive and is not relied upon for approval of NDA 219876 or for labeling recommendations.

In general, FDA agrees with the Applicant's assessment of the primary pharmacology data with additional pertinent details below. The Applicant refers to the dopamine 2 receptor as DRD2, the which is also known as D2R. In the following sections it will be referred to as DRD2.

ClpP and DRD2 expression in H3K27M diffuse midline tumors

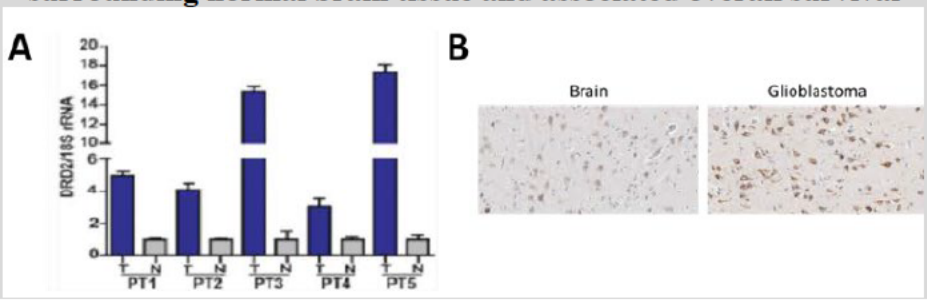
For context of the relevance of the primary pharmacology data and the purposes of scientific discussion, the following information was included in the review. ClpP protein expression correlated with mRNA expression across pediatric brain tumors and their abundance was associated with increased tumor grade with upregulation in both in high grade glioma (HGG) and medulloblastoma (M) compared to low grade glioma (LGG) (Figure 2; Przystal et al., 2022). Additionally, DRD2 was overexpressed in patient-derived HGG compared to normal brain tissue and associated with poor clinical outcome (Figure 3; Li et al., 2014 [A], Prabhu et al., 2019 [B, C]). DRD2 expression was significantly higher in H3K27M+ tumors vs. H3K27 wild type (wt) tumors (data not shown in review).

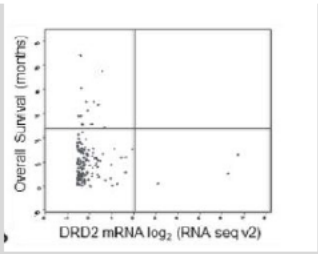
Figure 5.1: ClpP protein and mRNA expression in pediatric brain tumors is associated with increased tumor grade



(Excerpted from Przystal et al., 2022)
HGG – high grade glioma. M – medulloblastoma. LGG – low grade glioma.

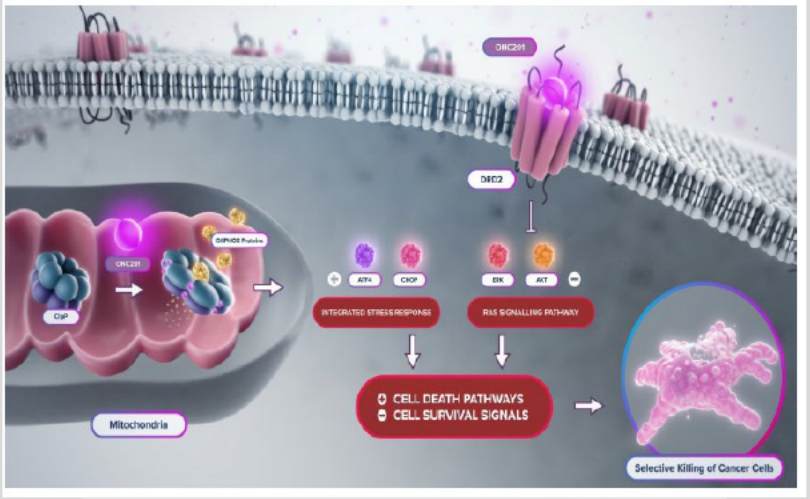
Figure 5.2: Increased DRD2 expression in patient derived gliomas compared to surrounding normal brain tissue and associated overall survival

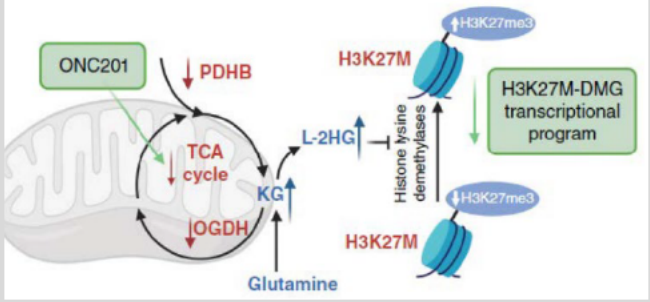




(Excerpted from Li et al., 2014 [A], Prabhu et al., 2019 [B, C])
T = tumor tissue. N = normal brain tissue. PT = patient.

Figure 5.3: Dordaviprone is a ClpP agonist and a DRD2 antagonist leading to increased stress response, increased cell death, and modification of histone methylation





(Excerpted from Venneti et al., 2023)

In vitro primary pharmacology

Dordaviprone (ONC201) bound to the caseinolytic protease proteolytic subunit (ClpP) and led to a conformational change associated with activation of ClpP (Ishizawa et al., 2019).
Dordaviprone bound to the dopamine receptor D2 (DRD2) (Studies gpcrd04537d and gpcrd04403d).

FDA agrees that dordaviprone but not the metabolite, ONC207, had agonistic activity towards ClpP.

In Study ONC201-bio-101, knockout (KO) of ClpP in the H3K27M-positive diffuse intrinsic pontine glioma (DIPG) cell line SF8628 led to dordaviprone resistance (no effect on cell viability). In SF8628 cells with a non-targeted control (NTC) vector, treatment with dordaviprone decreased cell viability 82 to 91% after 3 or 5 days of treatment, suggesting that ClpP expression in cancer cells with H3K27M mutations is necessary for dordaviprone activity (Figure 4; top). KO of ClpP was confirmed by Western blot analysis (data not shown in review). A similar study was conducted in the glioblastoma multiforme (GBM) cell line T98G harboring H3K27 wt; KO of ClpP led to increased dordaviprone resistance compared to NTC cells (Figure 4; bottom).

Figure 5.4: KO of ClpP in DIPG-H3K27M-positive (top) and GBM-H3K27 wt (bottom) cells led to dordaviprone resistance

Cell line	ONC201 % of Response at 100 µM	
	3 Days	5 Days
SF8628-NTC	81.8	90.7
ClpP KO	30.6	30.5

Cell line	ONC201 % of Response at 100 µM
T98G	59.5
ClpP KO	39.8

(Excerpted from Study ONC201-bio-101)
NTC = non-targeting control. KO = knockout. ONC201 = dordaviprone.

KO of DRD2 in SF8628 cells did not affect the sensitivity to dordaviprone with similar sensitivity observed compared to NTC cells (Figure 5). The Applicant states that these results may be due to the lack of dopamine dependency in in vitro tumor cultures and lack of microenvironment in an in vitro model but did not provide additional data to support this statement. DRD2 KO was verified using immunohistochemistry (data not shown in review).

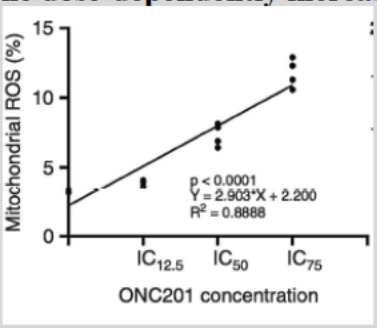
Figure 5.5: KO of DRD2 did not affect dordaviprone sensitivity in DIPG H3K27M+ cells

Cell line	ONC201 % of Response at 100 µM	
	3 days	5 days
SF8628-NTC	83.7	85.9
DRD2 KO	70.7	83.2

(Excerpted from Study ONC201-bio-101)
NTC = non-targeting control. KO = knockout. ONC201 = dordaviprone.

Dordaviprone led to dose-dependent decreased mitochondrial membrane potential as measured by decreased tetramethylrhodamine methyl ester (TMRM) staining and increased mitochondrial reactive oxygen species (ROS) as measured by increased MitoSox staining in treated diffuse midline glioma (DMG) cells (Figure 7; Przystal et al., 2022).

Figure 5.6: Dordaviprone dose-dependently increased mitochondrial ROS

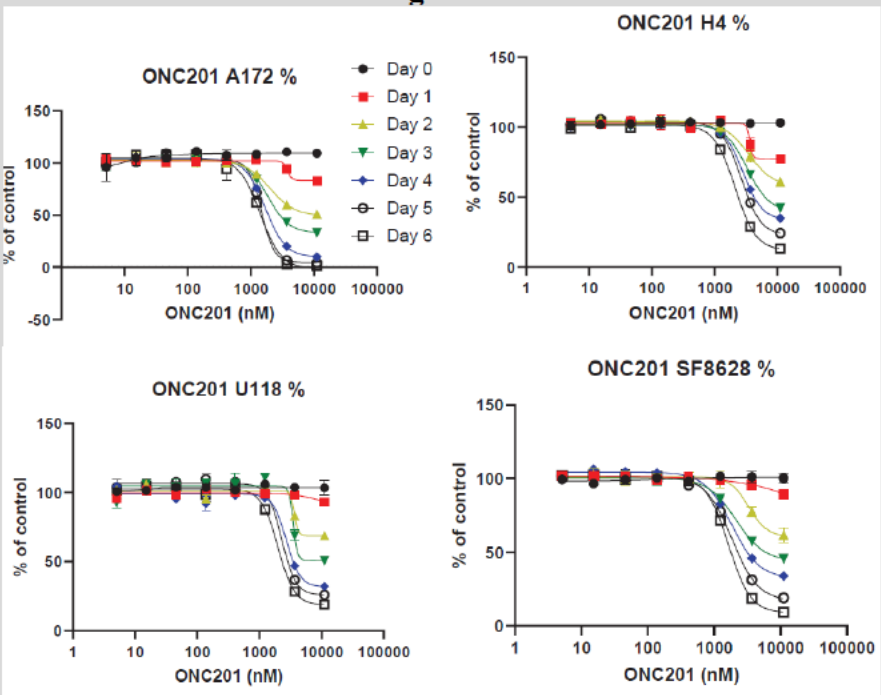


(Excerpted from Przystal et al., 2022)
ROS = reactive oxygen species. ONC201 = dordaviprone.

Treatment of 3 different DMG cells with dordaviprone at the antiproliferative activity IC_{50} or at 5x the IC_{50} led to upregulation of the integrated stress response (ISR) markers phospho-elF2a, ATF4, DR5, and CHOP. In addition, dordaviprone increased the expression of apoptotic markers cleaved caspase-7 and -3, PARP, and XIAP (Przystal et al., 2022).

In Study ONC201-bio-102, dordaviprone decreased cell survival in glioma cell lines despite H3K27 status with effects on survival starting 2 days after treatment initiation and maximum cell death at Day 6, the last day measured (Figure 9; Table 2).

Figure 5.7: Dordaviprone decreased cell survival in a time- and concentration-dependent manner in glioma cell lines



(Excerpted from ONC201-bio-102)
ONC201 = dordaviprone.

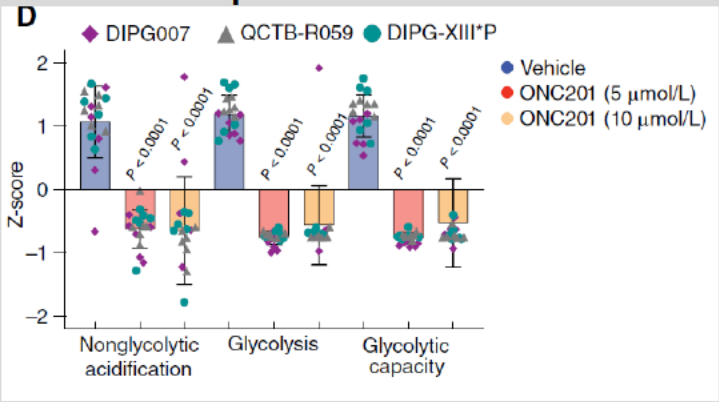
Table 5.1: EC_{50} values for dordaviprone inhibition of glioma cell survival over a 6 day treatment course

Cell line	EC50 (µM) Day 1	EC50 (µM) Day 2	EC50 (µM) Day 3	EC50 (µM) Day 4	EC50 (µM) Day 5	EC50 (µM) Day 6
A172 (Glioblastoma)	7.448	2.132	2.020	1.746	1.505	1.382
H4 (Neuroglioma)	19.039	7.910	3.801	3.595	2.710	2.019
U-118 MG (Astrocytoma)	43.128	8.563	3.625	2.930	2.408	2.086
SF8628 (H3.3 K27M-mutant DIPG)	22.647	4.303	2.499	2.381	1.854	1.625

(Excerpted from ONC201-bio-102)
A172, H4, and U118-MG cells are H3K27wt.

Dordaviprone treatment in DIPG007 H3K27M positive cells downregulated the TCA cycle, glycolysis, and pyruvate metabolism (data not shown in review). Additionally, H3K27M positive DMG cell lines treated with dordaviprone showed reductions in glycolysis and glycolytic capacity compared to vehicle treated cells (Figure 11; Venneti et al., 2023).

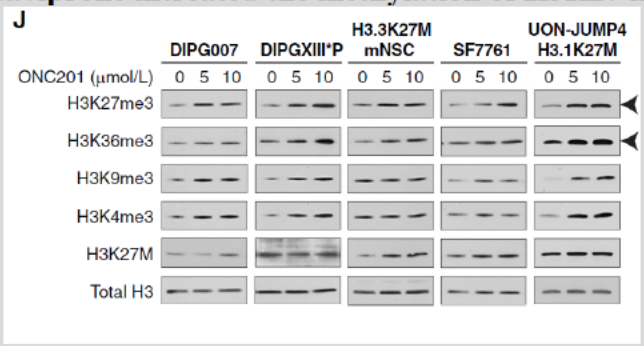
Figure 5.8: Dordaviprone decreased glycolysis and glycolytic pathways in H3K27M positive DMG cells



(Excerpted from Venneti et al., 2023)

In H3K27M positive DMG cell lines (DIPG007, DIPGXIII*P, H3.3K27M mNSC, SF7761, and UON-JUMP4), dordaviprone increased H3K27me3 across cell lines. Dordaviprone did not increase methylation levels in cell lines with H3K27 wt (data not shown in review).

Figure 5.9: Dordaviprone intreated the methylation of H3K27 in DMG cell lines



(Excerpted from Venneti et al., 2023)
The arrowhead indicates increased H3K27me3 and H3K36me3 across all cell lines

In vivo pharmacology

FDA agrees with the Applicant's assessment of the in vivo pharmacology data.

5.3.2. Secondary Pharmacology

Data:

The off-target pharmacology of dordaviprone and the major human metabolite, ONC207, were assessed using in vitro radioligand binding assays to determine the potentiation or inhibition of a variety of G protein coupled receptors, enzymes, and transporters relevant to human safety

(Studies TW04-0011367-1259539 and TW04-0011367-1259541). The assays did not incorporate protein in the assay medium to model the physiological availability of free circulating dordaviprone or ONC207 for target binding. Dordaviprone is highly (>95%) protein bound in vivo.

The Applicant's Position:

The minimal off-target binding of dordaviprone identified under these most conservative conditions does not demonstrate a risk of adverse off-target pharmacology that would not be sufficiently characterized in nonclinical safety pharmacology or toxicology studies or in clinical studies.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment of the secondary pharmacology data with the following additional pertinent details. Dordaviprone tested at 10 µM inhibited the sodium channel, site 2 (rat) and the L-type calcium channel (rat) by 82 and 61%, respectively. IC_{50} values were not provided and studies with lower dordaviprone doses were not conducted. ONC207 evaluation confirmed that it is an inactive metabolite.

5.3.3. Safety Pharmacology

The Applicant's Position:

This section provides a detailed overview of the key findings from standalone studies assessing the safety profile of dordaviprone across various biological systems, including cardiovascular, central nervous, and respiratory systems, with a focus on identifying any potential adverse effects relevant to human safety.

Cardiovascular System

Several studies have been performed to assess the effect of dordaviprone and the major metabolite, ONC207, on cardiovascular function. The effects of dordaviprone and ONC207 on ionic currents in voltage-clamped cells that stably express hERG were determined in vitro (Studies 190924.POC and ONC207-TX-100; m4.2.1.3). While the IC_{50} for the inhibitory effect of dordaviprone on hERG potassium current was 2.4 µM, dordaviprone is approximately 95% protein bound in human plasma which yields a free C_{max} of approximately 0.5 µM after a 625 mg dose. No exposure-relevant inhibition of the hERG current was observed with ONC207. The in vivo cardiovascular assessment was conducted via electrocardiogram (ECG) analysis incorporated into single dose and 13-week Good Laboratory Practice (GLP) repeat-dose studies in Beagle dog (Studies 0406DO27.003 and ONC201-TX-101). No changes in ECG parameters or traces were noted after a single oral dose ≤ 120 mg/kg or after 13 weeks of once weekly oral dosing with ≤60 mg/kg dordaviprone.

Central Nervous System

Clinical observations related to the effects of on-target pharmacology of DRD2 inhibition in the CNS were observed in rats and dogs in single- and repeat-dose studies with dordaviprone. The extrapyramidal symptoms, which limited dose levels in rats and dogs, generally occurred at T_{max} and resolved with decreasing plasma concentrations. In addition to the clinical observations observed in general toxicology studies, functional observation batteries (FOB) were performed in rats and dogs in single oral dose GLP studies (Studies 0406RO27.002 and 0406DO27.003). The FOB findings mirrored the clinical observations described in Section 5.5.1 and were related to the on-target pharmacology of DRD2 inhibition. No other symptoms in addition to the DRD2-related extrapyramidal symptoms of abnormal gait, circling, wobbling, decreased activity, tremors, salivation and vomiting were observed after a single dose of 225 mg/kg or 120 mg/kg dordaviprone in rats or dogs, respectively.

Respiratory System

The effects of oral administration of dordaviprone on the pulmonary function of rats were assessed in a single dose GLP study in rats (Study 1275RO27.001). Oral administration of dordaviprone at 12.5 and 125 mg/kg did not induce any biologically relevant effects on any respiratory parameters. A marginal to moderate transient decrease in respiratory rate and minute volume was observed following 225 mg/kg dordaviprone; these effects recovered by 1- and 2-hours post-dose for respiratory rate and minute volume, respectively.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment of the safety pharmacology studies with the following additional pertinent details. CNS toxicity was observed in the 4-week repeat-dose GLP toxicity study in rats and the 13-week repeat-dose GLP toxicity study in dogs. Clinical signs in the rats included piloerection, abnormal gait and stance, circling, wobbling, crawling, whole body twitching, decreased muscle tone, and decreased activity with most observations occurring at the highest dose of 225 mg/kg once weekly with findings in one or 2 animals at the mid dose of 125 mg/kg once weekly. Findings occurred post dose and recovered between dosing. Clinical signs in the dogs included whole body tremors, cranial tremors, seizure, excessive salivation, lateral recumbency, rigidity, paddling of limbs, overall rigid body, salivation, abnormal gait/stance, and twitching at doses of 60, 75, and 90 mg/kg; animals required treatment with diazepam. Clinical signs occurred post dosing and mostly recovered between dosing. There were no findings in the 4-week repeat-dose GLP dog study up to a dose of 60 mg/kg once weekly and no findings in the 13-week repeat-dose GLP rat study up to doses of 125 mg/kg once weekly and 62.5 mg/kg for 2 consecutive days once weekly. The FDA agrees that these clinical signs are due to on-target activity of dordaviprone inhibition of the D2R and gait disturbances, hemiparesis, dysarthria, muscle weakness, and dysphagia were observed in the clinic.

5.4. ADME/PK

Data / The Applicant's Position:

Absorption
Dordaviprone displayed high permeability across cell monolayers (Study C19208). Absorption of dordaviprone-related radioactivity in rats and humans was high at 81% and 71%, respectively (Studies C19178 and ONC201-106). The bioavailability of dordaviprone was comparably high at the same high dose but was low to moderate at lower doses in rats (11% to 53%) and dogs (10% to 25%) (Studies 0406RO27.002, 0406D027.003, 0832DO27.001). In general, following single and repeat oral administration in rats and dogs, the increase in systemic exposures of dordaviprone were more than dose proportional going from the lowest to mid-range doses but approximately proportional to dose going from mid-range to high doses (Studies 0406RO27.002, 0436RO27.008, ONC201-TX-100, 0406D027.003, 0436DO27.007, ONC201-TX-101). There were differences in systemic exposure between the sexes in rodents (female > male), but no sex difference was observed in dogs. There was no accumulation observed after repeated once-weekly dosing in either species.
Distribution
In vitro protein binding was higher in human plasma (95% to 97%) (Study ONC201-NCA-106) compared to animals (79% to 90%) (Study 16625), and the primary binding protein in human plasma was AAG (Study ONC201-NCA-101). Association with blood cellular components generally was low in humans (blood to plasma ratio 0.67) and rats (blood to plasma ratio 0.91) (Studies C19178, ONC201-106). In transfected cell lines or membrane vesicles, dordaviprone was not a substrate of uptake and efflux transporters (Study C19207). Dordaviprone inhibited transporter proteins (Study 15679), but based on basic and mechanistic models, the risk for dordaviprone to inhibit these transporters was low. Dordaviprone was distributed widely in tissues from rats (Study C19179). The CNS:plasma ratio was ~1, with tissue:plasma ratios for endocrine, metabolic/excretory, and ocular tissues, as well as the tissues of the gastrointestinal tract exceeding 1. Overall, [^{14}C]-dordaviprone-derived radioactivity was steadily cleared from most tissues in rats, with concentrations that were below the lower limit of quantification in most tissues 72 hours post-dose, except for melanin containing tissues. The binding to melanin appeared to be reversible, as the dordaviprone-derived radioactivity decreased with time.
Metabolism
Dordaviprone undergoes extensive biotransformation to many products. Dordaviprone was primarily eliminated by metabolism via CYP3A4 (fraction metabolized 0.55 to 0.87), and to a lesser extent by CYP2D6, CYP2B6, CYP2C8, CYP2C9, and CYP3A5 (Study ONC201-NCA-100). The qualitative in vitro metabolic profile in human, rat, dog, and rabbit hepatocytes was similar across species (Study 17717). Dordaviprone undergoes extensive oxidative metabolism including oxygenation, N-dealkylation, desaturation, and a combination thereof. The major metabolic pathway observed in humans and animals was N-dealkylation (Studies C20018, C22145, C20087). The inactive N-dealkylated metabolite, ONC207, was a major circulating metabolite in plasma following oral administration of [^{14}C]-dordaviprone to healthy subjects. ONC207 accounted for >31% of TRA AUC in plasma; no other metabolite had exposure greater than 10% of TRA AUC. All notable metabolites in human plasma were observed in at least one nonclinical species. Dordaviprone was a direct inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 in vitro (Study 15678). Assessment of risk using basic and mechanistic models indicated little to no risk of dordaviprone causing drug-drug interactions with CYP enzymes. Dordaviprone did not induce CYP1A2, CYP2B6, or CYP3A4/5 (Study 15676).

Excretion
Unchanged dordaviprone was not appreciably excreted in urine or feces after oral administration to rats and humans. In rats 70% of the dose was excreted in feces (due to biliary secretion) while 25% of the dose was eliminated via urine after oral administration of [^{14}C]-dordaviprone (Study C19178). In humans 71% of the dose was excreted in urine while 20% of the dose was eliminated through feces and (Study ONC201-106).

Abbreviations: AAG=alpha-1-acid glycoprotein; AUC=area under the concentration-time curve; CNS=central nervous system; CYP=cytochrome P450; TRA=total radioactivity.

Integrative Summary Table of C_{max} and AUC Parameters Across Toxicology Studies

Species/Strain (Duration; Study Number)	Route (Dose Frequency)	Dose (mg/kg)	Sex	C_{max} (ng/mL)		AUC_{last} (ng·hr/mL)		AUCN	$C_{max}N$
				Day 1	EOD	Day 1	EOD	Day 1	
Rat/SD (Single dose; 0406RO27.002)	Oral gavage (single dose)	12.5	M	86.8	NA	164	NA	13.1	6.9
			F	301	NA	507	NA	40.6	24.1
		125	M	1035	NA	8795	NA	70.4	8.3
			F	1847	NA	16319	NA	130.6	14.8
		225	M	1680	NA	16876	NA	75	7.5
			F	3927	NA	19075	NA	84.8	17.5
Rat/SD (28 days; 0436RO27.008)	Oral gavage (once weekly)	75	F	2753	1830	9096	4851	121.2	36.7
		125	F	4377	3807	12358	8383	98.9	35
		225	F	8437	5940	26164	13503	116.3	37.5
Rat/SD (13 weeks; ONC201-TX-100)	Oral gavage (once weekly)	31.25	M	346	692	729	1030	23.3	11.1
			F	1330	1430	2730	2530	87.4	42.6
		62.5	M	906	1470	3080	2380	49.3	14.5
			F	2410	5360	7720	7700	123.5	38.6
		125	M	2860	3190	11700	9980	93.6	22.8
			F	5980	5480	12800	16600	102.4	47.8
	Oral gavage (twice weekly*)	62.5	M	1320	2120	3500	5400	56	21.1
			F	2770	2660	7570	10100	121.1	44.3
Dog/Beagle (Single dose; 0406D027.003)	Oral gavage (single dose)	4.2	M	91.6	NA	183	NA	43.6	21.8
			F	86.4	NA	153	NA	36.4	20.6
		42	M	3267	NA	6798	NA	161.9	77.8
			F	2525	NA	5410	NA	128.8	60.1
		120	M	5792	NA	13751	NA	114.6	48.3
			F	3700	NA	12905	NA	107.5	30.8

Dog/Beagle (4 weeks; 0436DO27.007)	Oral gavage (once weekly)	15	C	1395	2005	2593	4054	173	93
		30	C	6720	8080	14146	15363	471.5	224
		60	C	5983	9945	17737	19297	296	99.7
Dog/Beagle (13 weeks; ONC201-TX-101)	Oral gavage (once weekly)	15	C	2790	2350	2730	2800	182	186
		30	C	5090	5650	6920	8020	231	170
		45	C	NA	6380	NA	10600	NC	NC
		60	C	11000	11200	14200	15400	237	183
		90	C	9050	NA	12500	NA	139	101

Abbreviations: AUC_{last}=area under the concentration-time curve from time 0 to time of last measurable concentration; AUCN=dose-normalized AUC_{last} value (units of ng.hr/mL/[mg/kg]); C=values reported for males and females combined; C_{max}=maximum concentration; C_{max}N=dose normalized C_{max} (units of ng/mL/[mg/kg]); EOD=End of Dosing; F=female; M=male; NA=not applicable; NC=not calculated due to insufficient data; SD=Sprague-Dawley.
* = Dosed twice weekly on consecutive days

Tabulation of ADME Parameters

Study Number/Study Title /eCTD Location	Study Type	Doses (mg/kg)/Formulation	Noteworthy Findings
C19208/ONC201 permeability/4.2.2.2	Dordaviprone permeability measured in Caco-2 monolayers	Dordaviprone at 7, 70 μM, and 700 μM in Caco-2 monolayers	Dordaviprone highly permeable (similar to the positive control)
C19178/ Rat Pharmacokinetics and Mass Balance, Single Oral Administration/ 4.2.2.5	Mass Balance and Excretion: 5 groups of 3 male SD rats dosed with [^{14}C]-dordaviprone: Group 1 oral; excretion mass balance; Group 2 oral; biliary excretion; Group 3 oral; metabolism and PK; Group 4 and 5 IV; excretion mass balance and metabolism/PK.	Oral dose 225 mg/kg (200 μCi/kg), IV dosed 12.5 mg/kg (200 μC/kg) /PBS formulation	Oral mass balance 70% excreted via feces and 25% via urine; Oral BDC, 61% excreted via bile and 20% via urine, absorption 81%; IV excretion balance 71% excreted via feces and 29% via urine; bioavailability of radiolabeled material 77%; low blood to plasma ratio (median 0.91).
ONC201-106 (8480317)/ Human mass balance/ 5.3.3.1	Human AME study: 6 male healthy subjects dosed orally with [^{14}C] -dordaviprone	625 mg (100 μCi)/Gatorade® formulation	Oral mass balance 71% excreted via urine and 20% via feces; low blood to plasma ratio (median 0.67).
0406R027.002/ Single oral/IV TK in rats/4.2.3.1	Single dose rat TK: Rats (SD) single oral dose (3 groups) and single IV (1 group, 3M/3F per timepoint)	Oral dose 12.5 mg/kg, 125 mg/kg, and 225 mg/kg and IV 12.5 mg/kg dordaviprone/PBS formulation	Bioavailability 11% to 27% at 12.5 mg kg and 53% to 84% at 125 mg kg and 225 mg/kg, respectively. Exposure in females more than males.
0406D027.003, 0832D027.001/ TK in Dogs Single Oral and IV/4.2.3.1	Single dose dog TK: 3 groups of beagle dogs administered a single oral dose and 1 group IV; 2 dogs per group 1M/1F	Oral dose 4.2 mg/kg, 42 mg/kg, and 120 mg/kg and IV 4.2 mg/kg dordaviprone/PBS formulation	Bioavailability 7% at 4.2 mg kg and 20% to 25% at 42 mg kg and 120 mg/kg, respectively. No [redacted] difference in exposure.
0436RO27.008/ 4-Week TK in Rats, Once Weekly/4.2.3.2	4-week TK: Rats (SD) oral dose (3 groups) once a week for 4 weeks.	Oral dose 75 mg/kg, 125 mg/kg, and 225 mg/kg /Phosphate Buffered Saline formulation	No accumulation observed. Females had higher exposure than males.
ONC201-TX-100/ 13-Week TK in Rats, Once or Twice weekly/4.2.3.2	13-week TK: Rats (SD) oral dose once a week (3 groups) and twice a week (one group) for 13 weeks	Once a week 31.25 mg/kg, 62.5 mg/kg, and 125 mg/kg or twice a week 62.5 mg/kg /PBS formulation	No Accumulation observed. Females had higher exposure than males. Dordaviprone half-lives ranged from 2 to 5 hours.

0436DO27.007/4-Week TK in Beagle Dogs, Once Weekly/4.2.3.2	4-week TK: Beagle dogs oral dose (3 groups) once a week for 4 weeks.	Oral dose 15 mg/kg, 30 mg/kg, and 60 mg/kg /PBS formulation	No Accumulation observed. No [redacted] difference in exposure.
ONC201-TX-101/ 13-Week TK in Beagle Dogs, Once Weekly/4.2.3.2	13-week TK: Beagle dogs oral dose (4 groups) once a week for 13 weeks.	Once a week 15 mg/kg, 30 mg/kg, 60 mg/kg, and 90 mg/kg (45 mg/kg) /PBS formulation	No Accumulation observed. No [redacted] difference in exposure. Dordaviprone half-lives ranged from 1 to 3 hours.
ONC201-NCA-106 ([redacted]C23038)/ In vitro binding to plasma protein/4.2.2.3	In vitro binding of dordaviprone to human plasma protein	Plasma Equilibrium Dialysis of dordaviprone in Human Plasma	Dordaviprone human plasma protein binding ranged from 95% to 97%.
ONC201-NCA-101([redacted]C21217)/ Binding to HSA and AAG/4.2.2.3	In vitro binding of dordaviprone to HSA and AAG	Equilibrium Dialysis of dordaviprone with HSA or AAG	Dordaviprone binds primarily to AAG.
16625/ Protein Binding in Nonclinical Species /4.2.2.3	In vitro mouse (C57/BL), rat (SD), and dog (beagle) plasma protein binding	Plasma Equilibrium Dialysis of dordaviprone in mouse, rat, and dog plasma	Dordaviprone mouse, rat, and beagle plasma protein binding ranged from 79% to 90%.
C19207/ Transporter Substrate Evaluation/4.2.2.3	In vitro assessment of dordaviprone as substrate of human MDR1, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K	Incubation of dordaviprone with cells stably expressing the respective SLC transporters and the corresponding control cell lines.	Dordaviprone was not a substrate of transporters.
15679/ Transporter Inhibitor Evaluation/4.2.2.3	In vitro assessment of dordaviprone as inhibitor of MDR1, BCRP, and BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2.	Incubation of dordaviprone with either transporter-expressing vesicles or transporter-expressing cells.	Dordaviprone inhibited transporter proteins, but based on basic and mechanistic models, the risk for dordaviprone to inhibit these transporters was low.
C19179/ QWBA in Long-Evans Rats/4.2.2.3	Quantitative assessment of distribution of [^{14}C]-dordaviprone in rat tissue	Oral dose of [^{14}C]-dordaviprone to male rats (Long Evans)/PBS	[^{14}C]-Dordaviprone widely distributed in tissues with tissue to plasma ratio of ≥1.
C20018/ Metabolite identification in rats/4.2.2.4	Plasma, urine, bile, and feces metabolite identification in rats (from Study C19178)	Rats dosed orally and IV with [^{14}C]-dordaviprone/PBS formulation	Major metabolites were oxidative and their conjugates (glucuronides and sulfates).

C22145 / Metabolite identification in humans/ 5.3.3.1	Plasma, urine, and feces metabolite identification in humans (from Study ONC201-106).	Healthy subjects dosed orally with [^{14}C]-Dordaviprone/Gatorade® formulation	The majority of metabolites were oxidative with no conjugated metabolites observed. Major circulating products were dordaviprone and ONC207.
C20087/ Dog Plasma Metabolite Identification/ 4.2.2.4	Metabolite searching in dogs (samples from dog 28-day TK).	Dogs dosed orally with dordaviprone/PBS formulation	Circulating metabolites were oxidative with dordaviprone and ONC207 as major.
C20086/ Relative Exposure of Metabolites in Rat, Dog, and Human Plasma/4.2.2.4	Relative exposure of metabolites in rat, dog, and human plasma (metabolites in safety testing)	Rats, dogs, and humans (patients) dosed orally with dordaviprone/PBS formulation (animals) and capsules (patients)	All notable metabolites observed in humans were present in rats and/or dogs.
17717/ Metabolism in Animal and Human Hepatocytes /4.2.2.4	In vitro metabolite identification in rat, rabbit, dog, and human hepatocytes	Incubation of dordaviprone with rat, rabbit, dog, or human hepatocytes	Major metabolites were oxidative. All notable metabolites in human hepatocytes were observed either in rats or dogs.
ONC201-NCA-100 ([(b) (4)]C21157)/ CYP Enzymology with *f*m,CYP/4.2.2.4	In vitro identification of CYP responsible for metabolism of dordaviprone	Incubation of dordaviprone with recombinant CYP enzymes or co-incubated with a specific CYP inhibitor in human liver microsomes	CYP3A4 identified as the major enzyme of dordaviprone metabolism. fraction metabolized; (*f*m) ranged from 0.55 (HLM) to 0.87 (rCYP).
15678/ CYP Inhibition Potential/4.2.2.4	In vitro CYP inhibition potential of dordaviprone in human liver microsomes	Incubation of specific substrates of various CYPs and dordaviprone in human liver microsomes	Dordaviprone was a direct inhibitor of CYP enzymes (Ki $\geq$ 20 μM), but based on basic and mechanistic models, the risk for dordaviprone to inhibit these enzymes was low.
15676/ CYP Induction Potential/4.2.2.4	In vitro identification of CYP induction potential of dordaviprone in human hepatocytes	Incubation of dordaviprone in human hepatocytes	Dordaviprone was not an inducer of CYP1A2, CYP2B6, or CYP3A4.

Abbreviations: AAG=alpha acid glycoprotein; BDC=bile duct cannulation; BCRP=Breast Cancer Resistance Protein; BSEP=Bile Salt Export Pump; CYP=cytochrome P450; F=female; HLM=human liver microsomes; HSA=human serum albumin; IV=intravenous; Ki=inhibition constant; M=male; MATE1/2-K=Multidrug and Toxin Extrusion Protein 1/2-Kidney; MDRI=Multidrug Resistance Protein 1; PBS=phosphate-buffered saline; OAT= Organic Anion Transporter; OATP1B1=Organic Anion Transporting Polypeptide 1B; OCT=Organic Cation Transporter; PK=pharmacokinetics; rCYP=recombinant CYP; SD=Sprague-Dawley; SLC=solute carrier; TK=toxicokinetic.

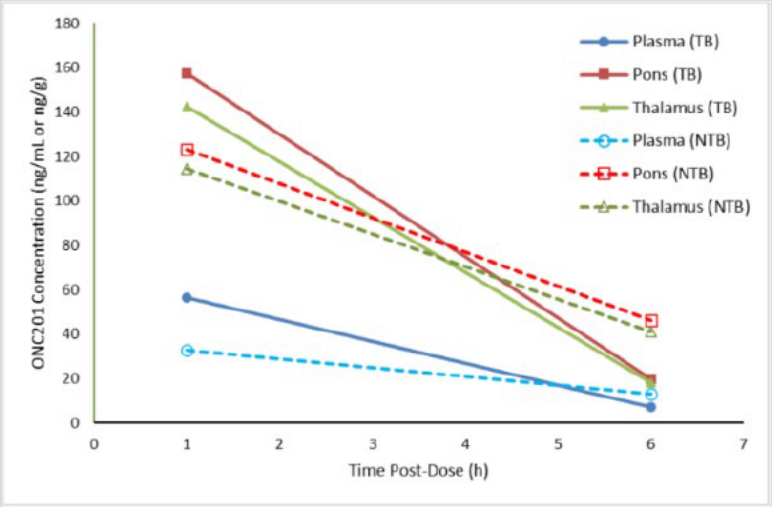
The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment of the ADME studies with the following additional pertinent details. In the rat distribution study (Study #c19179), oral administration of [^{14}C]-ONC201 (225 mg/kg, 200µCi/kg) distributed readily to the uveal tract (420 to 4154 nmol equiv/g) and eye (84 to 846 nmol equiv/g) and was still measurable after 2016 hours post dose. Levels in the lens were minimal (3 to 23 nmol equiv/g) up to 72 hours and below quantification levels (BQL) by 168 hours post dose. [^{14}C]-ONC201 was also found at high levels in the endocrine system (adrenal gland, pineal gland, pituitary gland, thyroid gland) and the organs of the GI tract, with most tissue measuring BQL by 72 hours post dose. High levels were measured in the contents of the GI tract and in bile which is consistent with route of excretion of oral dordaviprone. Levels in CNS tissues, including brain, ranged from 20 to 80 nmol equiv/g in most tissues except the meninges which had peak exposure at 1 hour post dose of 922 nmol equiv/g and still had measurable radioactivity 2016 hours post dose.

The major circulating metabolite identified in patients, ONC207, was found at significant levels in dogs treated with dordaviprone once weekly in the 13-week toxicology study with Cmax values ranging from 20 to 49% of the Cmax values of dordaviprone on Day 85. In a rat 13-week toxicology study, ONC207 was found at Cmax values ranging from 3 to 13% of the dordaviprone Cmax on Day 85. Full review of toxicokinetic data from the rat and dog 13-week repeat-dose studies can be found under section 5.5.1 General Toxicology. The ONC207 metabolite accounted for ~11-20% in humans, thus the levels of exposure observed in the animal studies covers the clinical exposures of the major metabolite. Additionally, evaluation of metabolic profiles in human, rat, and dog plasma (Study c20086) indicated that all detected human metabolites were also present in rats and/or dogs at levels sufficient to cover human exposure and no unique human metabolites were identified when evaluating in vitro metabolism in rat, rabbit, dog, and human hepatocytes (Study 17717). ONC207 is considered an inactive metabolite (see Section 5.3.1 Primary Pharmacology).

Oral administration of dordaviprone once weekly in tumor bearing and non-tumor bearing mice showed measurable dordaviprone in the pons and thalamus at levels higher than measured in the plasma. Values were negligibly higher in tumor bearing mice vs. non-tumor bearing mice (Figure 14; top). Treatment schedules of once weekly for 2 weeks or twice weekly on consecutive days for 2 weeks did not result in differences in exposure in the measured tissues (Figure 14, bottom).

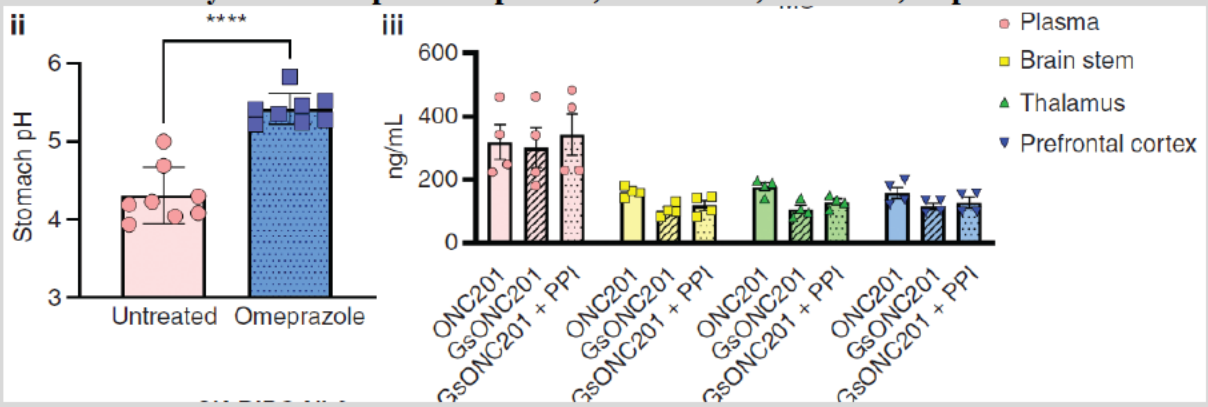
Figure 5.10: Exposure in the plasma, pons, and thalamus in tumor bearing and non-tumor bearing mice (left) or tumor bearing mice treated with dordaviprone on two different schedules (right)



(Excerpted from ONC207-bio-102)
TB = tumor bearing. NTB = non-tumor bearing. Q1W = once weekly. Q2W = twice weekly on consecutive days.

Assessment of the bioavailability of dordaviprone in mice given omeprazole (1.5 mg/kg/day) for 7 days prior to dordaviprone treatment showed that omeprazole significantly increased stomach pH levels (data not shown in review); however, the change in gastric pH did not decrease bioavailability of dordaviprone in plasma and brain tissues including the brainstem, thalamus, and prefrontal cortex evaluate 1 hour post treatment (Figure 15; Dutchatel 2021).

Figure 5.11: Omeprazole significantly changed stomach pH without affecting oral bioavailability of dordaviprone in plasma, brain stem, thalamus, or prefrontal cortex



(Excerpted from Duchatel 2021)

ONC201- dordaviprone. GsONC201-German manufactured dordaviprone. PPI – proton pump inhibitor.

5.5. Toxicology

5.5.1. General Toxicology

The toxicity profile of orally administered dordaviprone was defined in GLP-regulated studies with once or twice (on 2 consecutive days) weekly administration for up to 13 weeks in both rodents (Sprague-Dawley rats) and nonrodents (Beagle dogs) (Studies ONC201-TX-100, ONC201-TX-101; m4.2.3.2). This program was consistent with ICH S9, the guideline for nonclinical evaluation for anticancer pharmaceuticals (ICH 2010).

The nonclinical safety profile of dordaviprone reflects the on-target pharmacology and downstream effects of DRD2 antagonism. While CNS-related extrapyramidal symptoms limited dose levels in rats and dogs, the maximum tolerated dose allowed for an assessment of target organ toxicity with 3 months of dosing that achieved clinically relevant C_{max} and/or AUC plasma exposures. The adverse clinical signs occurred at T_{max} and generally resolved with decreasing plasma concentrations. The C_{max} plasma concentrations measured in rats (NOAEL; 125 mg/kg once weekly as the highest dose administered) and dogs (LOAEL; 60 mg/kg once weekly exhibiting adverse but reversible clinical signs) exceeded plasma concentrations observed in humans administered 625 mg dordaviprone by 1.9 and 3.9-fold, respectively. Shorter half-lives in nonclinical species compared to humans resulted in AUC plasma concentrations at these doses that were 75% and 70% clinical AUCs in rat and dogs, respectively. Aside from the dose-limiting CNS-related symptoms, no additional adverse toxicity was identified in any organ system after 3 months of once- (dog) or twice-weekly (rat) dosing.

Importantly, no extended adverse clinical observations were noted from once- (dogs) or twice-weekly (rats) dordaviprone administration for 3 months. This includes no observations related to inhibition of dopamine pathways, significant clinical chemistry changes, or macroscopic or microscopic tissue effects, even in the brains of animals exhibiting extrapyramidal symptoms. Additionally, no effects on cardiac rhythm or ECG morphology were noted after 13 weeks of weekly administration in both male and female dogs, and no ophthalmologic findings were observed in either rats or dogs.

The C_{max} plasma concentrations in both species at tolerated doses exceeded concentrations measured in humans administered 625 mg dordaviprone (see Section 5.4 and Section 5.5). While adverse histopathology was not identified in any organ with 3 months of dosing in rat or dog, administration of higher doses was not possible due to the CNS-associated clinical observations and limitations imposed by IACUC guidelines protecting animal welfare.

The metabolite profile of dordaviprone, characterized in rats, dogs, and humans, showed the inactive, N-dealkylated metabolite, ONC207 as a major metabolite in dogs and humans. Following 13 weeks of oral administration, the nonclinical safety assessment of this metabolite,

with a dog:human exposure ratio of 0.98 for ONC207, was considered to have a clinically relevant exposure. No identified impurities or degradants requiring safety qualification have been identified in manufactured dordaviprone batches to-date.

In conclusion, nonclinical safety data from rodents, rabbits, and dogs enabled the hazard identification and risk characterization relevant for the clinical use of dordaviprone in treating H3 K27M-mutant diffuse glioma in adult and pediatric patients. The nonclinical adverse effects, linked to species with higher plasma concentrations than those in humans, are associated with monitorable endpoints that are included in the assessment of clinical safety throughout clinical development.

The FDA's Assessment:

Study title/ number: A Three-Month Weekly and Twice Weekly Oral Dosing Toxicity Study of ONC201 in Sprague Dawley Rats Followed by a Four-Week Recovery Period (GLP) / 0470RC78.001

- No deaths and no clinical signs in dordaviprone treated rats.
- The target organs of toxicity were stomach (inflammation), liver (hepatocyte vacuolation), thyroid (hypertrophy), and mammary gland (hyperplasia).
- Dordaviprone dose-dependently increased glucose, cholesterol, AST, ALT, and ALP.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	<table><tr><th>Group/Treatment</th><th>Dose Level (mg/kg)</th></tr><tr><td>1/Control (vehicle)[1]</td><td>0</td></tr><tr><td>2/Control (vehicle)[2]</td><td>0</td></tr><tr><td>3. ONC201 Low Dose[1]</td><td>31.25</td></tr><tr><td>4. ONC201 Mid-Dose[1]</td><td>62.5</td></tr><tr><td>5. ONC201 High dose[1]</td><td>125</td></tr><tr><td>6. ONC201 High dose[2]</td><td>62.5</td></tr></table> [1]once weekly. [2]twice weekly on consecutive days.
Route of administration:	oral gavage
Formulation/Vehicle:	Phosphate buffered saline (PBS)
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	15/sex/group for main toxicity group
Age:	8 weeks

Satellite groups/ unique design:	12/sex/group for once daily administration TK group and twice daily high dose group
Deviation from study protocol affecting interpretation of results:	None that affected interpretation of results

Observations and Results: changes from control

Parameters	Major findings
Mortality	No ONC201-related deaths. Several gavage error and retro-orbital venipuncture error related deaths.
Clinical Signs	No ONC201-related clinical signs.
Body Weights	Unremarkable.
Ophthalmoscopy	Unremarkable.
Hematology	**%-Change in Hematology Parameters on Day 86 from Vehicle-Treated Control Group in Rats Treated with Dordaviprone Once Weekly**

Dose mg/kg	31.25		62.5		125	
sex	M	F	M	F	M	F
#Lymphocytes	-	+33%	-	+44%	-	-
LUC	-	-	-	-61%	-	-65%
Platelets	-	-	-	-	-	+14%

'-' = no findings. Findings recovered by the end of the recovery period. Findings in high dose animals dosed twice weekly were unremarkable. LUC: large unstained cells

Clinical Chemistry

% Change in Clinical Chemistry on Day 86 from Vehicle-Treated Control Group in Rats Treated with Dordaviprone Once Weekly (QW) or Twice Weekly (QWx2)

Dose mg/kg	31.25 (QW)		62.5 (QW)		125 (QW)		62.5 (QWx2)	
sex	M	F	M	F	M	F	M	F
Glucose	-	-	-	-	+17%	+24%	-	+19%
Cholesterol	+12%	-	+23%	-	+29%	+14%	+26%	+19%
AST	-	-	-	-	+30%	-	-	-
ALT	-	-	-	-	+62%	-	-	-
ALP	-	-	-	-	+28%	-	-	+26%

Glucose, AST, and ALT in male rats treated at the high dose (QW) were still significantly elevated at the end of the recovery period. Cholesterol in male rats treated QWx2 was still significantly elevated at the end of the recovery period. Findings in all female rats recovered by the end of the recovery period.

Urinalysis

Unremarkable.

Toxicokinetics

- Female to male exposure ratios for dordaviprone were greater than 2-fold.
- Exposure increased with an increase in dose.

Toxicokinetic Data in Rats treated with Dordaviprone Once Weekly (QW) or Twice Weekly (QWx2)

Dose (mg/kg)	31.25 (QW)		62.5 (QW)		125 (QW)		62.5 (QWx2)	
Sex	M	F	M	F	M	F	M	F
Day 1/2								
Cmax (ng/mL)	346	1330	906	2410	2860	5980	1320	2770
AUC_{last} (h*ng/mL)	729	2730	3080	7720	11700	12800	3500	7570
Day 85								
Cmax (ng/mL)	692	1430	1470	5360	3190	5480	2120	2660
AUC_{last} (h*ng/mL)	1030	2530	2380	7700	9980	16600	5400	10100

- Female to male exposure ratios for metabolite ONC207 were less than 2-fold, thus males and females were reported as combined values.
- Exposure increased with an increase in dose.

Toxicokinetic Data for the Major Metabolite ONC207 in Rats treated with Dordaviprone Once Weekly (QW) or Twice Weekly on Consecutive Days (QWx2)

Dose (mg/kg)	31.25 (QW)	62.5 (QW)	125 (QW)	62.5 (QWx2)
Day 1/2				
Cmax (ng/mL)	47.5	93.7	227	171
AUC_{last} (h*ng/mL)	186	591	2000	760
Day 85				
Cmax (ng/mL)	68.3	185	261	183
AUC_{last} (h*ng/mL)	251	636	1930	1240

Gross Pathology

Unremarkable.

Organ Weights

% Change in absolute organ weights from controls in rats treated with Dordaviprone Once Weekly (QW) or Twice Weekly on Consecutive Days (QWx2)

Dose mg/kg	31.25 (QW)		62.5 (QW)		125 (QW)		62.5 (QWx2)	
sex	M	F	M	F	M	F	M	F
Liver	-	-	-	-	-	+20%	+29%	+17%
Adrenal glands	-	-	-	-	-	-	+16%	+16%
Kidney	-	-	-	-	-	-	+33%	-
Spleen	-	-	-	-	-	-	+11%	-
Thyroid/parathyroid	-	-	-	-	-	-	+33%	-

Findings recovered.

Histopathology

Adequate battery: Yes

Dose (mg/kg)		0 (QW)		0 (QWx2)		31.25 (QW)		62.5 (QW)		125 (QW)		62.5 (QWx2)	
Sex		M	F	M	F	M	F	M	F	M	F	M	F
# animals main /recovery		10/5	10/5	10	10	9	10	8	10	10/5	10/5	9/5	10/5
Stomach, nonglandular													
Inflammation, mixed cell	Minimal	-	-	-	-	1	-	2	3	6	5	4	3
	Mild	-	-	-	-	-	-	-	-	-	-	1	2
Pustule	Minimal	-	-	-	-	-	-	-	1	2	1	1	2
Liver													
Vacuolation, hepatocellular	Minimal	-	-	-	-	5	3	8	8	8	7	7	8
	Mild	-	-	-	-	-	-	-	-	2	3	2	2
Thyroid													
Hypertrophy, follicular cell	Minimal	1	1	4	-	2	-	2	-	3	5	1	3
	Mild	-	-	-	-	1	-	2	-	2	-	2	-
	Moderate	-	-	-	-	-	-	-	-	1	-	-	-
Mammary gland													
Hyperplasia, lobuloalveolar	Minimal	-	2	-	3	NE	2	NE	5	-	5	-	4
	Mild	-	-	-	-	NE	2	NE	1	-	2	-	3
Brain													
Mineralization	Minimal	-		-		-		-		1		-	
Artery, aorta													
Degeneration, elastic lamina	Minimal	1	1	-		-		-		-	2	-	1
	Mild	-		-		-		-		1		-	

NE = not examined. Histopathology findings recovered by the end of the recovery period.
QW = once weekly. QWx2 = twice weekly on consecutive days.

Study title/ number: A Three-Month Weekly Oral Dosing Toxicity Study of ONC201 in Beagle Dogs with a Four-Week Recovery Period / 0470DC78

- Dordaviprone treatment in dogs led to CNS toxicities including seizures, tremors, recumbency, salivation, abnormal gait and stance, rigid body, twitching, paddling of limbs, increased vocalization, and decreased activity and was considered related to the on-target mechanism of action as a D2R antagonist.
  - Animals dosed at 60, 75, and 90 mg/kg required diazepam.
- Dordaviprone led to dose-dependent GI toxicity in the form of emesis and loose/soft stool.

GLP compliance: Yes

Methods

Dose and frequency of dosing: Once weekly

Group	Test Material	Dose Level (mg/kg)
1	Control (vehicle)	0
2	ONC201	15
3	ONC201	30
4	ONC201@	60
5	ONC201@	90/75/60/45

@Group 5 dose level was lowered from 90 to 75 mg/kg after receiving two doses (Days 1 and 8), due to the severity of the clinical signs. Group 5 animals received 75 mg/kg for the third dose (Day 15). On Day 22 (the fourth dose), Group 5 animals received the same dose level as Group 4 animals (60 mg/kg), at the request of the Sponsor. Starting on Day 29 (the fifth dose onwards), Group 5 animals received a lower dose than 45 mg/kg and became the Mid-High dose group. Group 4 animals received the highest tolerated dose level and became the High dose group. Two males and two females assigned to Group 5 were transferred to Group 4 on Day 29 and served as recovery (drug-free) animals for a 4-week recovery period.

Route of administration: oral gavage

Formulation/Vehicle: Phosphate buffered saline (PBS)

Species/Strain:	Beagle dogs
Number/Sex/Group:	4/sex/main toxicity group
Age:	5-7 months
Satellite groups/ unique design:	2/sex/recovery group for controls and Groups 4 and 5
Deviation from study protocol affecting interpretation of results:	None that affected interpretation of results

Observations and Results: changes from control

Parameters	Major findings
Mortality	*60 mg/kg* • One male euthanized on Day 75 (Week 11) (dosed Day 71) • Emesis and salivation (most days of treatment period) • Mild to severe body tremors and/or cranial tremors starting Day 15 and occurring on each weekly dosing administration day • Abnormal stance/gait starting Day 15 • Day 15 seizure with lateral recumbency excessive salivation, rigidity and paddling limbs, overall rigid body tone. Diazepam administered on Day 15 and Day 71 for head tremors and limb rigidity • Day 74/75 decreased activity, abnormal gait/stance, whole body twitching, crawling, hind limb rigidity, difficulty standing, moderate ataxia, tremors, dilated pupils • Cause of moribundity due to gross brain lesions with increased volume of fluid and dilated lateral ventricles though to be congenital and not drug-related with minimal mononuclear cell infiltration of the meninges and minimal focal perivascular mononuclear cell infiltration in the parenchyma (caudate nucleus) thought to be drug related

Clinical Signs	*30 mg/kg* • Emesis and soft or loose feces, salivation on dosing days *60 mg/kg* • Emesis and soft or loose feces, salivation on most days • Increased vocalization, decreased activity, abnormal gait/stance, tremors (whole body, the head, or limbs), twitching, hunched posture, rigid body tone occurring shortly after administration • Diazepam administered on Day 15 and when deemed necessary *90/75/45 mg/kg* • 90 mg/kg - Emesis, soft/loose stool, vocalization, whole body tremors, abnormal gait/stance, hunched posture, twitching and increased activity post dose Days 1 and 8. Once male received diazepam on Day 8. • 75 mg/kg – emesis, salivation, decreased activity, whole body/head tremors, abnormal gait/stance, twitching post dose Day 15. One male received diazepam Day 15. • 45 mg/kg – emesis, salivation, soft/loos stool, whole body tremors, abnormal gait/stance post dose.
Body Weights	Unremarkable.
Ophthalmoscopy	Unremarkable.
Body Temp/ ECG	Unremarkable.
Hematology	Unremarkable.
Clinical Chemistry	Unremarkable.
Urinalysis	Unremarkable.

Toxicokinetics

Because the exposures between males and females were less than 2-fold different, male and females were combined. *Day 1 values are from dogs treated with 90 mg/kg and Day 85 values are from dogs treated with 45 mg/kg.

Toxicokinetic Data in Dogs Treated with Dordaviprone Orally Once Weekly

Dose (mg/kg)	15	30	60	90/45*
Day 1				
Cmax (ng/mL)	2790	5090	11000	9050
AUC_{∞} (h*ng/mL)	2770	6240	14300	13100
Day 85				
Cmax (ng/mL)	2350	5650	11200	6380
AUC_{tau} (h*ng/mL)	2860	8090	15500	10800

Toxicokinetic Data for the Major Metabolite ONC207 in Dogs Treated with Dordaviprone Orally Once Weekly

Dose (mg/kg)	15	30	60	90/45*
Day 1				
Cmax (ng/mL)	883	1580	2420	2010
AUC_{∞} (h*ng/mL)	13000	26400	42800	42500
Day 85				
Cmax (ng/mL)	1140	1480	2150	2070
AUC_{tau} (h*ng/mL)	15100	25500	42400	39700

Gross Pathology

Unremarkable.

Organ Weights

Unremarkable.

Histopathology Adequate battery: Yes	**Dose (mg/kg)**		**0**		**15**		**30**		**45**		**60**	
	Sex		**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
	# animals main tox group		**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**3**	**4**
	Brain											
	Infiltration, mononuclear cell, parenchyma (caudate nucleus)	Minimal	-	-	-	-	-	-	1	-	1	-
		Mild	-	-	-	-	-	-	1	-	1	-
	Infiltration, mononuclear cell, parenchyma (multiple locations)	Minimal	2	-	-	-	1	-	1	-	-	1
	Epididymis											
	Infiltration, mononuclear cell	Mild									1	
	Lacrimal gland											
	Infiltration, mononuclear cell	Minimal	-	-	-	1	-	-	-	-	1	
	Prostate											
	Infiltration, mononuclear cell	Minimal	-		-		1					
	Lungs											
	Fibrosis/epithelial hyperplasia	Minimal		3		3		3		3	1	2
		Mild		1						1		
	Infiltration, mononuclear cell, perivascular	Minimal			1							
	Inflammation, mixed cell, alveolar	Minimal		-		-		1		-		-
		Mild								1		
	All findings recovered.											

Twenty-eight day GLP-compliant oral once weekly toxicology studies were performed in rats and dogs. In rats, dordaviprone administration caused CNS-related clinical signs including mild changes in gait and stance, decreased muscle tone, wobbling, and circling, as well as mild hypoactivity. Clinical chemistry changes included increased ALT, ALP, and glucose similar to that observed in the 13-week toxicology study in rats. No additional significant changes were noted in rats from the 28-day study up to a dose of 225 mg/kg. In dogs, dordaviprone led to decreased activity, emesis, salivation, and/or soft or mucoid feces. In addition, dogs in all treatment groups gained less weight compared to controls during the study. No additional significant changes were noted in dogs from the 28-day study up to a dose of 60 mg/kg.

5.5.2. Genetic Toxicology

The Applicant's Position:

The bacterial reverse mutation (Ames) test, the in vitro micronucleus test, and the in vivo rat micronucleus test were conducted to define the potential mutagenicity and clastogenicity of dordaviprone (Studies AF87PY.502ICH.(b) (4), AF87PY.361ICH.(b) (4) and

AF87PY.125M021FLPBICH.(b) (4)). Dordaviprone was negative for mutagenicity in the Ames test and negative for clastogenicity in both the in vitro and in vivo micronucleus tests.

Study type: In vitro Ames assay **Study title / study number / eCTD location:** Bacterial Reverse Mutation Assay of dordaviprone / AF87PY.502ICH.(b) (4) / m4.2.3.3.1. **Key drug-related adverse findings:** • Cytotoxicity of dordaviprone was observed at 3333 or 5000 µg/plate. • No mutagenic potential of dordaviprone observed with or without metabolic activation. **GLP compliance:** Yes	
Test System:	Test for induction of reverse mutation in bacterial cells (Salmonella typhimurium and Escherichia coli TA98, TA100, TA1535, TA1537, WP2 uvrA) using the plate incorporation method with or without metabolizing system (MolTox liver S9). Dordaviprone tested at 33.3, 100, 333, 1000, 3333, and 5000 µg/plate.
Study Valid:	Yes

Study type: In Vitro Mammalian Cell Micronucleus Assay **Study title / study number / eCTD location:** In Vitro Mammalian Cell Micronucleus Assay in TK6 Cells / AF87PY.361ICH.(b) (4) / m4.2.3.3.1. **Key drug-related adverse findings:** • Cytotoxicity was observed at ≥105 µg/mL in the non-activated 4-hour exposure group and at ≥89.3 µg/mL in the S9-activated 4-hour and non-activated 27-hour exposure groups. • No statistically significant or dose-dependent increases in micronuclei induction were observed at any dose with or without S9 activation. **GLP compliance:** Yes	
Test System:	Test for induction of micronuclei performed on human TK6 cells with or without metabolizing system (Aroclor-induced rat liver S9). Dordaviprone tested at concentrations of 30.3, 75.9, 89.3, 105, and 145 µg/ml without S9 activation and at 30.3, 60.7 and 89.3 µg/ml with S9 activation.
Study Valid:	Yes

Study type: In Vivo Mammalian Micronucleus Assay in Rats **Study title / study number / eCTD location:** In Vivo Mammalian Micronucleus Assay in Rats with Flow Cytometric Analysis of Peripheral Blood Reticulocytes / AF87PY.125M021FLPBICH.(b) (4) / m4.2.3.3.2 **Key drug-related adverse findings:**

• Hunched posture, piloerection, ataxia, decreased motor activity, prostrate posture, labored breathing and/or squinty eyes. • Statistically significant reductions in the proportion of reticulocytes per total number of cells scored (%RETs) in the dordaviprone 200 ang 400 mg/kg/day groups compared to vehicle control, suggesting adequate exposure. • There was no significant increase in the incidence of micronuclei in the dordaviprone-dosed animals compared to concurrent vehicle control. **GLP compliance:** Yes	
Test System:	Test for induction of micronuclei in polychromatic and monochromatic reticulocytes of Sprague Dawley rats by oral gavage at 100, 200, and 400 mg/kg/day for 2 days.
Study Valid:	Yes

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

5.5.3. Carcinogenicity

The Applicant's Position:

Carcinogenicity studies with dordaviprone were not conducted based on the life expectancy of the indicated population as well as the ICH S9 guidance, which states that studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICH 2010).

The FDA's Assessment:

The FDA agrees that carcinogenicity studies are not warranted for the current indication of pediatric and adult patients with H3 K27M-mutant diffuse glioma. Based on its mechanism of action of D2R inhibition, dordaviprone may cause hyperprolactinemia (Al-Chalabi M, 2023; Fitzgerald P, 2008). Mammary gland hyperplasia was reported in animals in the13-week study in rats.

5.5.4. Reproductive and Developmental Toxicology

Data / The Applicant's Position:

Fertility and Early Embryonic Development

No fertility and early embryonic development to implantation studies or effects on postnatal development were conducted, consistent with ICH S9 guidance (ICH 2010). Effects on reproductive organs were assessed during GLP-compliant repeat-dose toxicology studies with dordaviprone in rats and dogs. No effects on reproductive organs were seen in rats or dogs during 28-day or 13-week studies (Studies 0436RO27.008, ONC201-TX-100, 0436DO27.007, and ONC201-TX-101).

Embryo-Fetal Development

Preliminary assessments of the effects of dordaviprone on embryo-fetal development (EFD) were conducted in rats and rabbits. In non-GLP EFD studies with daily dordaviprone exposure, rabbits showed maternal toxicity at plasma exposures greater than 1.5-times those in humans administered 625 mg of dordaviprone, evidenced by adverse clinical signs and mortality. In rats, there were late resorptions and reduced fetal body weights, while female New Zealand white rabbits exhibiting fetal abnormalities at exposures lower than those associated with maternal toxicity.

In addition to findings of teratogenicity in rabbits and dose-limiting toxicity in maternal rats and rabbits from subclinical dordaviprone exposures, evidence suggests that other DRD2 antagonists,

including antipsychotic medications, may pose potential teratogenic risks. A review by Edinoff et al. highlighted potential risks associated with antipsychotics, including DRD2 antagonists, in pregnant and lactating women such as skeletal malformations, CNS defects, cleft palate, cardiac abnormalities, decreased fetal growth, and fetal death, observed in nonclinical studies (Edinoff 2022). Clinical studies have further linked antipsychotic use during pregnancy with adverse outcomes such as preterm birth, congenital malformations, and abnormally slow fetal growth (Lin 2010; Newham 2008; Newport 2007).

Given the potential risk for embryo/fetal developmental effects in humans administered DRD2 antagonists and the teratogenic findings with dordaviprone in the preliminary EFD study, along with the anticipated maternal toxicity and/or embryo/fetotoxicity in a definitive EFD study, no further EFD studies of dordaviprone were conducted. The risks are described in the proposed prescribing information.

Prenatal and Postnatal Development

Dordaviprone is intended for the treatment of patients with advanced cancer; therefore, studies on fertility and pre- and postnatal development have not been conducted, as they are not required per ICH S9 guidelines for the nonclinical evaluation for anticancer pharmaceuticals (ICH 2010).

The FDA's Assessment:
The FDA agreed that due to the significant findings in the non-GLP dose-range finding embryo-fetal development studies in rats and rabbits that additional GLP-compliant studies do not need to be conducted.

Embryo-Fetal Development
Study title/ number: A Dose Range-Finding Embryo-Fetal Development Study of ONC201 (Oral) Gavage in Rats / 20218011

Key Study Findings

- Dordaviprone administered at 125 mg/kg resulted in maternal toxicities characterized by mortalities, adverse clinical signs, and body weight loss.
- Increased pre-implantation loss was noted at 125 mg/kg. Incidences of absent eye and small renal papillae in kidney were also noted at this dose level.

GLP compliance: No

Methods

Dose and frequency of dosing:	0, 25, 62.5, or 125 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	Phosphate Buffered Saline (PBS)
Species/Strain:	Sprague Dawley CD (Crl:CD[SD])
Number/Sex/Group:	8 females/group
Study design:	Pregnant rats received ONC201 once daily during GD7 through GD17.

	Euthanization/caesarean section/necropsy were performed on GD21.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	Four HD females were found dead (GDs 16, 16, 17, 19) and 1 female was euthanized early (GD 20) due to declining clinical condition. These deaths were considered dordaviprone-related due to adverse clinical signs and body weight losses.
Clinical Signs	In the female rats that were found dead or moribund at HD, clinical signs included head tilt, dehydration, abnormal respiratory rate, labored breathing, prostration, hunched posture, erected fur, splayed limbs, thin body shape, uncoordinated movements, hyperreactivity, cold to touch, low carriage, abnormal gait, and/or decreased activity. In 3 females that survived at HD, clinical signs included shallow breathing, hunched posture, erected fur, splayed limbs, thin body condition, cold to touch, liquid discharge from the left or right eye, abnormal gait, and/or decreased activity.
Body Weights	Lower mean body weight gains were noted in the HD group for the interval of GD 7 to 21 compared to control (↓7%). This value is excluding one female (female 3227) with markedly reduced body weight gain. With inclusion of this animal, the mean body weight gains decline to ↓57% compared to control.
Macroscopic observations	Unremarkable.
Necropsy findings	All animals were confirmed pregnant. Reflecting 1 early delivery at MD and the early deaths at HD, ovarian and uterine examinations on GD 21 were based on 8, 8, 7 and 3 pregnant rats in the 0 (Control), LD, MD, HD groups, respectively. At HD, the mean number of late resorptions increased compared to control (0.3 late resorptions per litter) and the mean fetal body weights were reduced by 7% compared to controls.

Dose (mg/kg/day)	**0**	**25**	**62.5**	**125**
Number tested	**8**	**8**	**7**	**3**
Mean total resorptions	0.8	1.0	0.4	0.3
No. of late resorptions	0	0	0	0.3
Pre-implantation losses (%)	6.86	8.4	12.73	18.49
Post-implantation Loss (%)	5.86	12.17	3.8	2.56
Fetal body weight (g)	6.018	6.007	5.941	5.609

Fetal observations

	Incidences (litters/fetuses)			
Dose (mg/kg/day)	0	25	62.5	125
Number Examined (litters/fetuses)	8/88	8/85	8/92	3/35
Eye Eye, Both, Absent - Malformation	0/0	0/0	0/0	1/1
Kidney Renal papilla, Right, Small, Severe - variation	0/0	0/0	0/0	1/1

There were no abnormalities detected in any fetal external examination.

LD: low dose; MD: mid dose; HD: high dose

Study title / number: A Dose Range-Finding Embryo-Fetal Development Study of ONC201 by (Oral) Gavage in Rabbits / 20218012

Key Study Findings

- Dordaviprone administered at ≥ 62.5 mg/kg resulted in early termination of all the animals due to dordaviprone-related maternal toxicities including adverse clinical signs and maternal body weight loss.
- Incidences of fetal external and visceral abnormalities including short snout, absent teeth and misshapen brain were noted at 10 mg/kg and 25 mg/kg.

GLP compliance: No

Methods

Dose and frequency of dosing:	0, 10, 25, 62.5 or 100 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	Phosphate Buffered Saline (PBS)
Species/Strain:	Rabbit/ New Zealand White (Crl:KBL [NZW])
Number/Sex/Group:	6 females/group
Study design:	Pregnant rabbits were dosed once daily with ONC201 via oral gavage from GD 7 through GD 19. Euthanization /caesarean section/necropsy were performed on GD29.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	All of the rabbits in 62.5 and 100 mg/kg dose groups were terminated early due to dordaviprone-related adverse clinical signs. As a result of toxicity, dose administration at 100 mg/kg was terminated on the first day of dosing and all rabbits in the dosing group were euthanized. Dose administration at 62.5

<table>
<tr><td></td><td>mg/kg/day was terminated and animals were euthanized on GD 15 and GD 16. All other animals survived to scheduled euthanasia on GD 29.

Note: Dose administration was staggered by gestation age and only three of six rabbits in the 100 mg/kg dose group were administered with dordaviprone.</td></tr>
<tr><td>Clinical Signs</td><td>Dordaviprone-related clinical signs included abnormal eyeball color, abnormal feces, labored breathing, suspected dehydration, discolored urine, thin appearance and impaired righting reflex (62.5 mg/kg); splayed limbs, partly closed eyes, low carriage, convulsions, lack of coordination, discolored eyes, and hunched posture (100 mg/kg); and decreased activity, prostration, and warm body temperature (62.5 and 100 mg/kg).</td></tr>
<tr><td>Body Weights</td><td>Due to termination of the dosing group, body weight and food consumption data are not available for rabbits in the 100 mg/kg group. All the animal in the 62.5 mg/kg group had significant weight loss and reduced food consumption prior to euthanasia. There was no dordaviprone-related effect on mean maternal body weights and food consumption at $\leq$ 25 mg/kg.</td></tr>
<tr><td>Necropsy findings
Cesarean Section Data</td><td>Pregnancy was confirmed in 6, 5, 6, 5 and 4 females in the 0 (Control), 10, 25, 62.5, and 100 mg/kg dose groups, respectively. Due to the unscheduled euthanasia and terminations at 62.5 and 100 mg/kg, ovarian and uterine examinations on GD 29 were based on 6, 5, and 6 pregnant rabbits in the 0 (Control), 10, and 25 mg/kg/day dose groups, respectively.

<table>
<tr><td>Dose (mg/kg/day)</td><td>0</td><td>10</td><td>25</td></tr>
<tr><td>Number tested</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>No. of Pregnancy</td><td>6</td><td>5</td><td>6</td></tr>
<tr><td>Mean total resorptions</td><td>1.2</td><td>0.8</td><td>1.0</td></tr>
<tr><td>Mean pre-implantation losses (%)</td><td>5.01</td><td>10.89</td><td>1.28</td></tr>
<tr><td>Mean post-implantation Loss (%)</td><td>10</td><td>11.82</td><td>8.33</td></tr>
<tr><td>Mean total number of fetuses</td><td>10.8</td><td>8.4</td><td>10.2</td></tr>
</table></td></tr>
<tr><td>Necropsy findings
Offspring</td><td>
<table>
<tr><td></td><td colspan="3">Incidences (litters/fetuses)</td></tr>
<tr><td>Dose (mg/kg/day)</td><td>0</td><td>10</td><td>25</td></tr>
<tr><td>Number Examined (litters/fetuses)</td><td>6/65</td><td>5/42</td><td>6/61</td></tr>
<tr><td>Face
Nares, Both, Fused - Malformation</td><td>0/0</td><td>0/0</td><td>1/1</td></tr>
<tr><td>Face
Naris, Both, Malpositioned - Malformation</td><td>0/0</td><td>0/0</td><td>1/1</td></tr>
<tr><td>Face
Snout, Short - Malformation</td><td>0/0</td><td>0/0</td><td>1/2</td></tr>
<tr><td>Mouth
Palate, High-Arched - Variation</td><td>0/0</td><td>0/0</td><td>1/1</td></tr>
<tr><td>Mouth
Tooth, Absent - Malformation</td><td>0/0</td><td>0/0</td><td>1/2</td></tr>
<tr><td>Paw
Forepaw, Hyperflexion - Malformation</td><td>1/1</td><td>1/2</td><td>1/1</td></tr>
<tr><td>Brain
Brain, Misshapen - Malformation</td><td>0/0</td><td>0/0</td><td>1/2</td></tr>
<tr><td>Gallbladder/bile duct</td><td>0/0</td><td>0/0</td><td>1/1</td></tr>
</table></td></tr>
</table>

	Gallbladder, Bilobed - Variation: [ ] [ ] [ ] Great vessels, Truncus arteriosus, Persistent - Malformation: 0/0 1/1 0/0 Heart, Membranous Ventricular Septal Defect - Malformation: 0/0 1/1 0/0
Toxicokinetic parameters	Plasma Concentrations (ng/mL)

Study Day	Time point	Group 1 (0 mg/kg)	Group 2 (10 mg/kg)	Group 3 (25 mg/kg)	Group 4 (62.5mg/kg)
GD 19	0.5 hr	BLQ	880±313	2042±492	N/A
	2.0 hr	BLQ	293±96	1187±318	N/A
GD 15/16	Terminal	N/A	N/A	N/A	4730±1609

BLQ = below the limit of quantitation (< 10.00 ng/mL); GD = Gestation Day; N/A = Not Applicable

(Excerpted from Applicant's submission)

The FDA agrees that fertility and early embryonic studies and prenatal and postnatal studies are not warranted for the current indication of adult and pediatric patients with H3 K27M-mutant diffuse glioma. The FDA acknowledges that dordaviprone had no adverse effects on reproductive organs in repeat-dose toxicology studies; however, dordaviprone may adversely impact fertility in both males and females given its pharmacological effects. As previously mentioned, inhibition of D2R may cause hyperprolactinemia. Increase in prolactin levels can inhibit release of gonadotropin-releasing hormone (GnRH), which can decrease spermatogenesis in males and cause amenorrhea in females (Al-Chalabi M, 2023). Additionally, dordaviprone disrupts the tricarboxylic acid (TCA) cycle which contributes to sperm and egg production and early embryonic development. The TCA cycle provides the metabolic energy for sperm motility, the maturation of oocytes, and initial embryo development (Cecchino GN, 2018) (Rotimi DE, 2024). Therefore, an impairment of infertility based on mechanism of action was added to the label under Section 8.3.

5.5.5. Other Toxicology Studies

The Applicant's Position:

Study type: Cytotoxicity and Phototoxicity Assessment

Study title / study number / eCTD location: 3T3 Neutral Red Uptake Phototoxicity Assay / 19.26987.30 / m4.2.3.7.7.

Key drug-related adverse findings:

- EC_{50} for cytotoxicity was achieved at 315.4 µg/mL with solar-simulated light and 345.0 µg/mL without solar-simulated light
- Photo-irritant factor (PIF) was calculated at 1.1, which suggests minimal potential for phototoxicity under the tested conditions.
- Results indicate that dordaviprone does not meet criteria for classification as phototoxin.

GLP compliance: Yes	
Test System:	Mouse fibroblasts were used to assess cytotoxicity and phototoxicity using the neutral red uptake method to evaluate cell viability under solar-simulated light, with appropriate negative and positive controls for validity.
Study Valid:	Yes

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

X X

Stephanie Aungst, PhD, Primary Reviewer Moran Choe, PhD, Primary Reviewer

X

Claudia Miller, PhD, Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant is seeking accelerated approval of dordaviprone for the treatment of H3 K27M-mutant diffuse glioma in adult and pediatric patients. The proposed recommended dose in adult patients is 625 mg and in pediatric patients is based on body weight: 125 mg (10 to < 12.5 kg); 250 mg (12.5 to < 27.5 kg); 375 mg (27.5 to < 42.5 kg); 500 mg (42.5 to < 52.5 kg) and 625 mg

(≥ 52.5 kg). The recommended dose should be administered orally once weekly (QW) on an empty stomach (at least 1 hour before or 3 hours after food intake).

The review addressed the following issues:

The proposed recommended dosages for adults and pediatrics are acceptable. The efficacy and safety of dordaviprone were established in adults with H3 K27M-mutant diffuse glioma. Refer to review of the efficacy and safety in Section 8 for details. The efficacy and safety of dordaviprone for pediatric patients were established based on the limited efficacy data from pediatric patients included in the primary efficacy population, additional supportive safety and efficacy data in patients outside the primary efficacy population, and extrapolation from adults based on the similarity of disease between adult and pediatric patients. The population pharmacokinetic analyses (PopPK) were used to identify doses in pediatrics that matched exposure to that of adults. The doses were based on body weight as body weight significantly effects dordaviprone exposure. At the proposed recommended doses for pediatric patients who weigh 10 kg or more, dordaviprone exposures (AUC and C_{max}) are predicted to be within range of exposures predicted in adults at the proposed recommended dose. FDA recommended limiting the indication to pediatric patients 1 year of age and older as dordaviprone is primarily metabolized by CYP3A, which is generally reduced in pediatric patients < 1 year old and dordaviprone PK cannot be adequately predicted in patients < 1year old to inform a safe and effective dose in this population.

The proposed recommendation to allow the capsule contents to be mixed with a sports drink, apple juice, lemonade, or water and administered orally for pediatric patients unable to swallow capsules is acceptable. The results of the bioavailability trials with Gatorade and applesauce show that dordaviprone systemic exposures were generally in the bioequivalence limits when compared to the fasting condition and administering with these liquids is supported by the results of in vitro drug release and stability testing in these liquids. Refer to Section 4 for additional details regarding these in vitro drug release and stability tests.

FDA agrees with the recommendation to avoid the concomitant use of strong and moderate CYP3A inhibitors and inducers based on the results of the drug interaction trial with a strong CYP3A inhibitor and physiologically based pharmacokinetic modeling. The recommendation to reduce the dordaviprone dose for adults and pediatric patients who weigh 52.5 kg or more when coadministered with a strong or moderate CYP3A inhibitor is acceptable based on the results of the trial and modeling.

Dordaviprone causes concentration-dependent QTc interval prolongation and coadministration of with other QT-prolonging products may increase the risk of QTc-associated arrhythmias. The recommendation to avoid concomitant use of products known to prolong QT interval or to separate administration is acceptable.

6.1.1. Recommendations

The NDA is approvable from a clinical pharmacology perspective. The key review issues are summarized as below.

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	Safety (N = 422) and efficacy (N = 50) of dordaviprone was evaluated in multiple trials (ONC006, ONC013, ONC014), an expanded access protocol (ONC018), and a compassionate use program (ONC016). The overall response rate (ORR) was 22%. Refer to Sections 7 and 8 below for details. A randomized, double-blind placebo-controlled confirmatory trial (ONC201-108) is currently evaluating the same recommended doses administered on Day 1 and Day 2 each week.
General Dosing instructions	FDA agrees with the proposed recommended dosage of 625 mg QW for adult patients. Refer to Section 8 for additional details including a summary of efficacy and safety. Furthermore, the proposed recommended dosage is supported by target engagement and pharmacodynamic data from nonclinical studies. FDA finds the proposed recommended dosages for pediatric patients acceptable. The proposed dosage for pediatrics is predicted to provide dordaviprone exposure within range of that predicted for adults. The proposed recommended dosages may not be optimized given the limited doses and schedules evaluated in clinical trials. An alternate dosing regimen is being evaluated in the ongoing confirmatory trial. FDA agrees with the proposed recommendation to administer dordaviprone on an empty stomach, since a high-fat meal decreased dordaviprone C_{max} by 40% and available data do not allow for evaluation of the effect on the dordaviprone anti-tumor activity. For patients unable to swallow capsules, FDA agrees with the labeling recommendations to mix the capsule contents with approximately 15 to 30 mL of liquid (sports drink, apple juice, lemonade, or water) and administer orally based on the results of bioavailability trial that show that dordaviprone systemic exposure were generally in the bioequivalence limits when compared to the fasting condition and additional data provided by in vitro drug release and stability studies. Refer to Section 4 for additional information about these in vitro studies.
Dosing in patient subgroups (intrinsic factors)	No clinically significant differences in the pharmacokinetics of dordaviprone were observed in patients with mild to severe renal impairment ($CL_{cr} \geq 15$ mL/min) or with mild (total bilirubin ≤ 1.5 x ULN and AST > ULN or total bilirubin ULN to ≤ 1.5 x ULN and AST any) or moderate hepatic impairment (Child Pugh B). Therefore, no dosage modification is recommended in patients with mild or moderate hepatic impairment. The PK of dordaviprone in patients with severe

	hepatic impairment is unknown. A postmarketing study in patients with severe hepatic impairment is not recommended as severe hepatic impairment is not expected to commonly occur in this population.
Drug-drug interactions	**CYP3A Inhibitors:** Concomitant use with strong or moderate CYP3A inhibitors may increase dordaviprone plasma concentrations based on the results of a trial with a strong CYP3A inhibitor and PBPK analyses with the moderate inhibitors. Given concomitant use may increase the risk of adverse reactions, FDA agrees with the recommendation to avoid concomitant use with strong and moderate CYP3A inhibitors; alternatively, FDA recommends reducing the dose for adults and pediatric patients who weigh at least 52.5 kg and who are taking strong or moderate CYP3A inhibitors. **CYP3A Inducers:** Concomitant use with strong and moderate CYP3A inducers may decrease dordaviprone plasma concentrations based on PBPK analyses. Given concomitant use may decrease anti-tumor activity, FDA agrees with the recommendation to avoid concomitant use with strong and moderate CYP3A inducers.
QTc Assessment	Dordaviprone demonstrates concentration-dependent QTc prolongation with an estimated mean QTcF change of 11.8 msec at 1.2 times the maximum recommended dose; therefore, FDA recommends avoiding concomitant use with other products with a known potential to prolong the QTc interval. If concomitant use cannot be avoided, FDA recommends separating administration of dordaviprone and other QT-prolonging products. FDA agrees with including a Warnings and Precautions regarding QTc Interval Prolongation. Refer to section 8.2 for more information.
Labeling	FDA made multiple changes based on regulations, guidance, and current best practices. The proposed labeling is generally acceptable upon the Applicant's agreement to FDA-recommended revisions.
Bridge between the to be marketed and clinical trial formulations	The bioequivalence (BE) between Early Phase and Late Phase capsules (to be marketed formulation) of dordaviprone (Study ONC201-101; 625 mg and Study ONC201-103; 125 mg) was demonstrated.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The clinical pharmacology evaluations for dordaviprone included assessments of its absorption, distribution, metabolism, and excretion (ADME) in both nonclinical and clinical settings. Human biomaterial studies assessed cell permeability, plasma protein binding, metabolic stability and pathways, and drug-drug interaction (DDI) risks. Phase 1 clinical studies evaluated single-dose pharmacokinetics (PK) in healthy participants and patients, and multiple-dose PK in patients, as well as bioequivalence between clinical and commercial capsule formulations, metabolism/mass balance, and DDI risks. Dedicated special population PK studies were conducted in participants with renal and hepatic impairment. DDI studies evaluated the effects of extrinsic factors, such as interactions with rabeprazole (a proton pump inhibitor) and itraconazole (strong inhibitor of cytochrome P450 [CYP] 3A4 [CYP3A4]). PK evaluations also extended to adult and pediatric patients with central nervous system tumors. Population PK (POPPK) modeling developed using data from adult and pediatric cancer patients and healthy adults, and physiologically-based PK (PBPK) modeling were developed to analyze the impact of intrinsic and extrinsic factors, simulate DDI risks involving CYP3A4, 2C8, and 2D6 enzymes, and estimate pediatric doses for consistent adult exposure levels. The program also assessed QTc interval prolongation and explored exposure-response (E-R) relationships for safety and efficacy.

Pharmacokinetics

Absorption

Dordaviprone plasma exposures increase in a dose-proportional manner across the dose range of 125 to 625 mg. At the recommended dosage of dordaviprone (625 mg), the geometric mean (% geoCV) values for dordaviprone C_{max} and AUC_{inf} were 2778 ng/mL (41.7%) and 22,799 hr·ng/mL (48.2%), respectively. Plasma exposures of dordaviprone do not accumulate following once weekly dosing.

Dordaviprone administered as capsule contents dissolved in Gatorade (test) was bioequivalent to the intact capsule (reference) administered under fasted conditions. The test/reference geometric mean ratios (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}.

Dordaviprone administered as capsule contents sprinkled on applesauce (test) resulted in AUC_{last} and AUC_{inf} that were bioequivalent to the intact capsule (reference) under fasted conditions. C_{max} was slightly below the bioequivalence threshold. The test/reference geometric mean ratios (90% CIs) were 1.03 (0.94-1.13) for AUC_{last} and AUC_{inf}, and 0.78 (0.70-0.87) for C_{max}.

Distribution

The geometric mean (% geoCV) apparent volume of distribution of dordaviprone was 450 L (40.1%) in patients, indicating significant tissue distribution. Dordaviprone is bound to both

human serum albumin and alpha-1-acid glycoprotein (AAG), with higher and saturable binding to AAG at concentrations ≥10 μM.

Metabolism

Dordaviprone is primarily metabolized by CYP3A4 and to a lesser extent by CYP2D6, CYP2B6, CYP2C8, CYP2C9, and CYP3A5. The major metabolite, ONC207, is formed via oxidative N-dealkylation and is not active.

Excretion

Following administration of ^{14}C-radiolabeled dordaviprone, 90.8% of the dose was recovered in urine and feces over 288 hours, with geometric mean recovery of 70.5% in urine and 20.2% in feces. There was little measurable excretion of unchanged dordaviprone in urine and feces. The primary moiety recovered in urine was the metabolite ONC207.

Table 6.1: Applicant – Pharmacokinetic Properties of Dordaviprone

Absorption	
T_{max}*	0.5 to 5.6 hours (patients)
Effect of food (high fat meal) on dordaviprone (relative to fasting)	AUC was unchanged C_{max} decreased by ~40%
Distribution	
% bound to human plasma proteins	95% to 97%
Blood-to-plasma ratio (drug or drug-related materials)	0.67
Volume of distribution* (Vz/F)	450 L (40.1%)
Metabolism	
Metabolic pathways	N-dealkylation, oxidation, dehydrogenation, hydrogenation, or a combination thereof
Elimination	
Major route of elimination	Metabolism via CYP3A4
Clearance* (CL/F)	27.4 L/hr (48.2%)
Mean terminal half-life* ($t_{1/2}$)	11.4 hours (29.8%)
% of dose excreted in urine	70.5%, as metabolites
% of dose excreted in feces	20.2%, as metabolites

Abbreviations: AUC=area under the concentration-time curve; C_{max}=maximum concentration; CYP=cytochrome P450; geoCV=geometric coefficient of variation; POPPK=population pharmacokinetics; $t_{1/2}$=half-life; T_{max}=time to reach C_{max}.
*Parameters estimated from the dordaviprone POPPK model for adults receiving 625 mg. Parameters are presented as geometric mean (% geoCV) except T_{max} which is presented as range (minimum, maximum).

The Applicant's Position:

Dordaviprone pharmacology and clinical PK have been characterized through nonclinical and clinical studies. These assessments provide the basis for the current dose recommendations of dordaviprone for the treatment of H3 K27M-mutant diffuse glioma, which includes a 625 mg dose (five 125-mg capsules) administered once weekly for adults, and a body weight-adjusted pediatric dose to achieve exposure equivalent to the adult dose. Lower doses of dordaviprone are not supported by the E-R analyses.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of the pharmacokinetic parameters of dordaviprone. The following provides additional information to supplement the Applicant's summary.

Formulation

Three different drug products were administered in the clinical trials (Table 3). Early Phase capsules were used in Studies ONC002, ONC005, ONC006, ONC013 and ONC014 and the proposed commercial (Current (Late) Phase) capsules are being used in other trials. FDA concludes that an adequate PK bridge has been established between the Early Phase and Current (Late) Phase capsules based on the results from the dedicated BE studies.

Table 6.2 Comparison of Dordaviprone Drug Product Formulations

ONC201 Drug Product Composition		Initial Clinical	Early-Phase Clinical	Current Clinical/ Proposed Commercial
Ingredient	**Purpose**	**mg/unit**	**mg/unit**	**mg/unit**
ONC201•2HCl[1] (125 mg free base)	Active	148.8	148.8	148.80
Microcrystalline Cellulose[2], NF (b) (4)				(b) (4)
Sodium starch glycolate, NF, (b) (4)				
Magnesium stearate, NF, (b) (4)				
Total Theoretical Fill Weight				(b) (4)
Hydroxypropyl methylcellulose (HPMC) capsule, Size (b) (4) (printed with black pharmaceutical ink)		1 capsule	1 capsule	1 capsule
				(b) (4)

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods.

The PK parameters following administration of the Early Phase product were compared to that of the Current (Late) Clinical/Proposed Commercial product at doses of 625 mg (Study ONC201-101) and 125 mg (Study ONC201-103) under fasted conditions. Dordaviprone exposures (AUC and C_{max}) were within the bioequivalence (BE) limits of 0.80 and 1.25 (Table 4 and Table 5).

Table 6.3. Relative Bioavailability of Current (Late) Clinical/Proposed Commercial versus Early Phase Formulations (ONC201-101 Part B2; 625 mg dose)

	Geometric LS Mean Ratio (%) (90% CI)	
	C_{max} n=13	AUC_{last} n=13
Late Phase versus Early Phase Capsules	0.92 (0.77, 1.11)	1.05 (0.93, 1.18)

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 9.

Table 6.4. Relative Bioavailability of Current Clinical/Proposed Commercial versus Early Phase Formulations (ONC201-103 Part B2; 125 mg dose)

	Geometric LS Mean Ratio (%) (90% CI)	
	C_{max} n=36	AUC_{last} n=36
Late Phase versus Early Phase Capsules	0.99 (0.92, 1.07)	1.01 (0.96, 1.06)

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 10.

In addition, dordaviprone exists [(b) (4)] in the capsules. To support a BE study for [(b) (4)] dordaviprone.2HCl, two small scale batches were manufactured using the Phase 3 formulation (Current (Late) Phase formulation), one with the standard [(b) (4)] dordaviprone.2HCl drug substance and the other with [(b) (4)] exposure parameters (C_{max} and AUC_{last}) were BE to [(b) (4)] exposure parameters (Study ONC201-109) with ratios and 90% CIs of 1.04 (0.95 to 1.13) for C_{max} and 0.99 (0.93 to 1.05) for AUC_{last} of dordaviprone.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The initial clinical studies of dordaviprone included dose escalation studies in various solid tumor types and hematological malignancies at dose levels of 125 mg, 250 mg, 375 mg, 500 mg, and 625 mg administered orally once every 3 weeks and once weekly. At the highest clinical doses (>375 mg), dordaviprone achieved concentrations that met or exceeded IC_{50} concentrations needed for in vitro activity in H3 K27M-mutant glioma cells (0.75 to 3.31 µM (Przystal 2022),

which are consistent with concentrations needed for engagement of its direct molecular targets, DRD2 and ClpP.

Dordaviprone monotherapy has shown efficacy in reducing tumor burden in patients with recurrent H3 K27M-mutant diffuse glioma, affecting both midline and non-midline structures.

In the primary efficacy analysis set, 28% of patients responded to dordaviprone treatment according to RANO 2.0 criteria (ORR 28%; 95% CI: 16.2, 42.5), with a median time to response of 4.6 months (range: 1.6 to 15.9) and the median duration of response of 10.4 months (95% CI: 7.4, 15.4). The durable and clinically meaningful responses observed in the primary efficacy analysis set are attributable to dordaviprone monotherapy. Responses have not previously been observed in this population with any other therapy and the responses are inconsistent with the influence of pseudoprogression or ongoing effects of prior radiotherapy.

E-R efficacy analysis showed no relationship between dordaviprone exposure and ORR as assessed by Response Assessment in Neuro-Oncology (RANO) high-grade glioma (RANO-HGG), RANO-low-grade glioma (RANO-LGG), and RANO 2.0 criteria. E-R safety analysis showed no trends in any AE incidence and exposure.

The Applicant's Position:

These efficacy and safety results support the current proposed dose of dordaviprone. Lower doses of dordaviprone are not supported by the E-R analyses.

The recommended dordaviprone dose for treatment of H3 K27M-mutant diffuse glioma is 625 mg once weekly given at least 1 hour prior to or 3 hours after a meal. Dordaviprone capsule contents dissolved in Gatorade (125 mg capsule contents per 15 mL Gatorade) provided bioequivalent exposures (AUC and C_{max}) to the intact capsule. It is recommended that the contents of dordaviprone capsules be dissolved in Gatorade for patients who have difficulty swallowing whole capsules.

The FDA's Assessment:

FDA has no objection to the proposed recommended dosage of 625 mg QW for adult patients. Treatment emergent adverse events (TEAEs) leading to a dosage modification (dose reduction, interruption or discontinuation) were observed in only 7.8% of the patients (refer to Section 8.2.4). However, this dosage is not optimized as alternative dose levels or regimens were not adequately investigated during the clinical development.

A dose range of 125 mg to 625 mg of dordaviprone administered once weekly or once every 3 weeks (Q3W) was studied in the dose escalation trials (ONC002 and ONC005) in patients with advanced solid tumors and hematological malignancies. The maximum tolerated dose (MTD) was not reached and the maximum administered dose (MAD) of 625 mg QW was selected for further development. Furthermore, the once weekly dosing regimen was selected based on target engagement and pharmacodynamic data available from nonclinical studies. Refer to the final meeting minutes issued on 06/17/2021 for details.

A once daily administration of 625 mg was previously investigated and discontinued based on the results of an investigator-initiated trial in adults with relapsed/refractory acute myeloid leukemia (NCT02392572; ONC003). Two of 6 patients who received 625 mg once daily reported Grade 3 encephalopathy.

FDA acknowledges that a randomized, double blind, placebo controlled confirmatory trial (ONC201-108) is currently ongoing in the target patient population where dordaviprone will be administered at the current proposed recommended dose levels on Days 1 and Day 2 each week in adults and pediatric patients.

Administration regarding food intake

FDA agrees with the Applicant's recommendation to administer dordaviprone on an empty stomach (at least 2 hours prior to and 3 hours after a meal). Dordaviprone C_{max} decreased by 40% (no change in AUC) when administered with a high-fat meal (Study ONC201-101). Given that lower dordaviprone exposures were not adequately investigated during clinical development, it is not known if the lower C_{max} may negatively affect the anti-tumor activity.

FDA agrees with the Applicant's recommendation to administer dordaviprone by mixing the capsule contents in 15 to 30 mL of a sports drink, apple juice, lemonade, or water before administering orally for pediatric patients unable to swallow capsules whole.

- Compatibility studies were performed by adding the dordaviprone capsule contents to a sports drink, water, apple juice or lemonade to support a 24-hour solution stability (at 4 and 40 mg/mL concentrations). As demonstrated by the observed % recovery results (range 100.2 – 106.3), dordaviprone was fully solubilized in all the indicated mediums. Stability (% recovery) for samples stored at room temperature for 24 hours after reconstitution ranged from 99.9 – 102.6 with and degradation products were not detected or were below the quantification limits. Refer to the Applicant's response document (SN0014) for details.
- Geometric mean ratios and 90% CIs of dordaviprone C_{max} and AUC were generally in the bioequivalence limits of 0.80 to 1.25 when dordaviprone was administered orally by mixing the capsule contents with Gatorade or applesauce compared to the fasting condition (Study ONC201-101).

6.2.2.2. Therapeutic Individualization

Data / Applicant's Position

Based on population PK analysis, the effect of intrinsic factors including sex, race, body weight, age (adult versus pediatric), hepatic impairment, albumin, creatinine clearance, and disease status (patient vs healthy participant) were assessed using the model. Body weight, disease status, and albumin were identified as significant covariates.

Dose Modifications for Pediatric Patients Weighing Less Than 52.5 kg

The recommended dosage of dordaviprone for patients weighing at least 52.5 kg is 625 mg (five 125-mg capsules) taken orally once weekly. For pediatric patients weighing less than 52.5 kg, refer to Table 2 for recommended dosing.

Table 6.5: Applicant – Recommended Weight-Based Dosage in Pediatric Patients

Patient's Weight (kg)	Dordaviprone Capsule (125 mg)	Dose Regimen
10 kg to less than 12.5 kg	125 mg (one 125-mg capsule)	Once weekly
12.5 kg to less than 27.5 kg	250 mg (two 125-mg capsules)	Once weekly
27.5 kg to less than 42.5 kg	375 mg (three 125-mg capsules)	Once weekly
42.5 kg to less than 52.5 kg	500 mg (four 125-mg capsules)	Once weekly
52.5 kg and above	625 mg (five 125-mg capsules)	Once weekly

Dordaviprone should be taken on an empty stomach.

Administration Modifications for Patients with Swallowing Difficulties

For patients unable to swallow capsules, the capsule contents may be dissolved in approximately 15 to 30 mL of liquid (e.g., Gatorade, Powerade, apple juice, lemonade, or water) before administration.

Renal and Hepatic Impairment

No dose adjustment is recommended for mild to severe renal impairment and no dose adjustment is recommended for moderate hepatic impairment (as assessed by Child-Pugh criteria); severe hepatic impairment has not been assessed.

QT Interval Prolongation

Coadministration with other QT-prolonging products may increase the risk of QTc-associated arrhythmias. Use caution when administering dordaviprone to patients with congenital long QT syndrome, existing QTc prolongation, a history of ventricular arrhythmias, electrolyte abnormalities, heart failure, or those who are taking other QT-prolonging products. Monitor ECGs and electrolytes before initiating and periodically during treatment, as clinically indicated.

If coadministration with other QT-prolonging products is unavoidable, schedule dordaviprone doses to minimize overlap with the QT-prolonging time course of the coadministered products. Withhold or discontinue dordaviprone in patients who develop QT prolongation with signs of life-threatening arrhythmias.

The FDA's Assessment:

Pediatric patients

FDA agrees with the Applicant's proposed recommended dosages in pediatric patients who weigh 10 kg or more, since the predicted dordaviprone C_{max} and AUC in pediatric patients are generally within the range of those predicted values in adults (Figure **6**). The predicted dordaviprone AUC was approximately 35% lower in pediatric patients who weigh 10 to < 12.5 kg compared to that of adults (Figure **6** and Table **33**); however, this prediction may underestimate the AUC for this pediatric subpopulation. Most pediatric patients who weigh 10 to < 12.5 kg are likely 1 to 2 years old and these pediatric patients will likely have lower CYP3A activity (~85%) compared to that of adults (Lacriox et al 1997, Treluyer et al 2002 and Steven et al 2003). The model did not incorporate a CYP3A maturity factor and therefore, the lower CYP3A activity may result in higher dordaviprone AUC compared to that of the predicted AUC.

There is insufficient information to determine a safe and effective recommended dosage for pediatric patients who weigh < 10 kg or are < 1 year old. Most pediatric patients who weigh < 10 kg are <1 year old and CYP3A levels in this pediatric subpopulation have not typically reached the levels observed in adults, which would affect the PK of dordaviprone. Furthermore, diffuse midline glioma harboring an H3 K27M mutation is not expected to commonly occur in pediatric patients <1 year old (refer to Section 1). Hence, an age cut off of 1 year of age recommended.

For pediatric patients unable to swallow a whole capsule, FDA agrees with the Applicant's recommendation to administer dordaviprone by mixing the capsule contents in 15 to 30 mL of a sport drinks, apple juice, lemonade, or water before administering orally. Refer to Section 6.2.2.1 for additional details.

Administration Modifications for Patients with Swallowing Difficulties

FDA supports opening capsules and mixing with water, apple juice, lemonade, or a sports drink. Refer to Section 6.2.2.1 for additional details.

Renal and Hepatic Impairment

FDA agrees with the Applicant's position that a dosage modification is not recommended for patients with mild to severe renal impairment, because dordaviprone exposure (AUC and C_{max}) was not significantly affected in patients with severe renal impairment (Study ONC201-104) compared to that of patients with normal renal function.

FDA agrees the Applicant's position that a dosage modification is not recommended for patients with mild to moderate hepatic impairment, because dordaviprone exposure (AUC and C_{max}) was not significantly affected in patients with mild and moderate hepatic impairment compared to that of patients with normal hepatic function. The effects of severe hepatic impairment on dordaviprone exposure have not been evaluated; however, FDA is not issuing a PMR as severe hepatic impairment is not expected to commonly occur in this population.

QT Interval Prolongation

FDA agrees with the recommended risk mitigation strategies including avoiding the coadministration with other QT-prolonging products or staggering administration of dordaviprone and other QT-prolonging products. Dordaviprone causes concentration-dependent QTc interval prolongation with an estimated mean change in the QTcF interval at 11.8 msec following a single dose of 750 mg (1.2 times the maximum recommended dose); the QTc prolongation may be underestimated when dordaviprone is coadministered with a strong or moderate CYP3A4 inducer. Therefore, FDA agrees with the recommendation to avoid strong or moderate CYP3A inducers; alternately, the dordaviprone dose may be reduced for adults and pediatrics who weigh more than 52.5 kg if these inhibitors cannot be avoided.

6.2.2.3. Outstanding Issues

The Applicant's Position:

Based on limited data, the current body weight-based dosing scheme is recommended for pediatric patients; no dose modification recommendations in pediatric patients receiving strong or moderate CYP3A4 inhibitors can be made at this time.

The FDA's Assessment:

FDA acknowledges that dosage modifications for pediatrics patients who cannot avoid strong or moderate CYP3A inhibitors cannot be made at this time. The ongoing confirmatory trial (Study ONC01-108) is evaluating dordaviprone administered on Days 1 and 2 each week vs on Day 1 each week vs placebo. The drug-drug interaction potential and risk mitigation strategies will be re-evaluated as needed following the availability of the results from this trial.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Therapeutic dose and exposure	625 mg once weekly, C_{max}: 3075 ng/mL (107.2%) AUC: 29710 hr·ng/mL (106.4%) (Study ONC002)	
Maximum dose tested	Single dose	750 mg (healthy)
	Multiple dose	Two 625 mg doses given 4 hours apart (healthy)
Exposures achieved at maximum tested dose	Single dose, geomean (%CV geomean)	625 mg Adult Patient C_{max}: 2778 ng/mL (41.7%) 625 mg Adult Patient AUC: 22799 hr·ng/mL (48.2%) (POPPK model)
		625 mg Pediatric Patient C_{max}: 2650 ng/mL (37.8%) 625 mg Pediatric Patient AUC: 20100 hr·ng/mL (45.1%) (POPPK model)

		750 mg Healthy C_{max}: 4262 ng/mL (27.7%) 750 mg Healthy AUCinf: 20444 hr•ng/mL (34.8%) (Study ONC201-102)
Range of linear PK	Analysis in healthy adults demonstrated dose proportionality across the range of 125 mg to 750 mg (Study ONC201-101, Part A and ONC201-102)	
Accumulation at steady state	Therapeutic dose administration is not intended to achieve steady state. No detectable accumulation with once weekly dosing.	
Metabolites	ONC207: inactive, approximately 30% relative abundance in plasma and urine; 19 additional metabolites identified in plasma at <10% relative abundance. ONC207 C_{max}: 729 (19.6%) ONC207 AUC_{inf}: 21916 (24.1%) (Study ONC201-101, Part A)	
Absorption	T_{max}	Adult Patient dordaviprone: 0.5 to 5.6 hours (POPPK model)
		Pediatric Patient dordaviprone: 0.60 to 25.70 hours (POPPK model)
		Healthy dordaviprone: 0.5 to 2.0 hours ONC207: 0.5 to 8.0 hours (ONC201-101, Part A)
Distribution	V_d/F or V_d, geomean (%CV geomean)	Adult Patient V_d/F: 450 L (40.1%) (POPPK model)
		Pediatric Patient V_d/F: 452 L (36.3%) (POPPK model)
		Healthy V_d/F: 513 L (32.3%) (ONC201-101, Part A)
	% bound	Protein binding of dordaviprone was 97.1%, 97.0%, 96.1%, 95.9%, and 95.1% in human plasma 0.5, 1.0, 5.0, 10, and 20 μM, respectively, indicating a trend for slightly lower binding at higher concentrations.
Elimination	Route	Primary route is urinary excretion of metabolites (71%), with excretion of metabolites in feces as a secondary route (20%). Unchanged dordaviprone excreted in minor amounts (<0.3%) in urine, feces (ONC201-106)
	Terminal $t_{½}$, geomean (%CV geomean)	Adult Patient: 11.4 hours (29.8%) (POPPK model)
		Pediatric Patient: 10.1 hours (34.7%)
		Healthy: Dordaviprone: 9.93 hours (26.2%) ONC207: 26.9 hours (19.2%) (ONC201-101, Part A)
	CL/F or CL, geomean (%CV geomean)	Adult Patient CL/F: 27.4 L/h (48.2%) (POPPK model)
		Pediatric Patient CL/F: 31.1 (45.1%) (POPPK model)
		Healthy CL/F: 35.8 L/h (32.3%) (ONC201-101, Part A)

Abbreviations: AUC=area under the concentration-time curve; AUC_{inf}=AUC from time zero to infinity; CL=clearance; CL/F=apparent clearance; C_{max}=maximum concentration; CV=coefficient of variation; POPPK=population pharmacokinetics; T_{max}= time to reach Cmax; V_d=volume of distribution; V_d/F=apparent volume of distribution.
Note: The pediatric parameters presented apply to pediatric patients weighing ≥52.5 kg who are receiving a 625 mg dose of dordaviprone.

The Applicant's Position:

Single-dose PK has been characterized in healthy adult participants as well as adult and pediatric patients; multiple-dose PK has been characterized in adult patients.

The FDA's Assessment:

FDA generally agrees with the Applicant that the PK parameters of dordaviprone were adequately characterized in adults.

Bioanalytical methods

The bioanalytical methods for the measurement of dordaviprone and its metabolite ONC207 in plasma and urine were developed and validated at (b) (4) for early phase studies and at (b) (4) for later phase studies. Refer to 'Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 6' for details. At (b) (4) extraction of the analytes from the plasma or urine was by protein precipitation. At (b) (4) extraction of the analytes from the plasma or urine was performed by protein precipitation and liquid-liquid extraction. At both sites, separation of the analytes was accomplished by high performance liquid chromatography (HPLC) with gradient elution and the eluate was analyzed by tandem mass spectrometric detection with multiple reaction monitoring (MS/MS) using an electrospray interface.

A summary of the validation data that supported the application of the bioanalytical methods to each clinical study from which PK or drug concentration analysis was an objective is summarized in 'Summary of Biopharmaceutic Studies and Associated Analytical Methods, Appendix 1'. The validation data supported application of the bioanalytical methods to each clinical study during the development of dordaviprone. Refer to 'Appendix 1, Tables 19 - 29'.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

H3 K27M-mutant gliomas are characterized by reduced levels of repressive epigenetic marker H3 K27me3, which enables oncogenic gene expression. Immunohistochemistry analysis of tumor samples from patients treated with dordaviprone indicated an increase in H3 K27me3 levels compared to those who did not receive dordaviprone, suggesting that dordaviprone disrupts the central hallmark of the disease.

In the primary efficacy analysis set, 28% of patients showed a response to dordaviprone treatment, as assessed using Response Assessment in Neuro-Oncology (RANO) 2.0 criteria (overall response rate [ORR] 28%; 95% CI: 16.2 to 42.5), with additional efficacy details in Section 8.1.

The Applicant's Position

Evidence of a positive benefit-risk for dordaviprone is based on the efficacy, safety, and tolerability data from patients with recurrent H3 K27M-mutant diffuse glioma. In the primary efficacy analysis set, dordaviprone treatment demonstrated clinically meaningful and durable objective responses, with associated clinical benefits in patients with recurrent H3 K27M-mutant diffuse glioma.

The FDA's Assessment:

Refer to Sections 7 and 8 below for the detailed summary of efficacy and safety. Refer to Sections 6.2.1.1 and 6.3.2.2 regarding proposed recommended dosages.

Based upon the exposure response analyses for efficacy and safety,

- The results of the ER analysis for ORR are inconclusive due to the limited numbers of patients in the primary efficacy analysis dataset. No clear ER relationship was observed for OS in the overall population.
- No relationship between dordaviprone exposure and the following safety endpoints: any TEAE of Grade 3 or higher, neurological TEAE of Grade 3 or higher or TEAE of special interest was observed.

Refer to Section 19.4 for additional details.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Yes, see data presented in Section 6.2.2.1.

The Applicant's Position:

The efficacy and safety results support the current 625 mg dose, once weekly or the equivalent body weight-adjusted pediatric dose. Lower doses are not supported by the E-R analyses.

The FDA's Assessment:

FDA agrees with the Applicant's proposed recommended dosage for adults and pediatric patients who weigh 10 kg or more. As lower dose levels (< 625 mg) and alternative dosing regimens were not adequately evaluated in the clinical trials, there is inadequate data to assess if an alternative dosing regimen would improve the balance between antitumor activity and safety. A recommended dosage has not been established for patients< 1 year of age. Refer to Section 6.2.2.1 for FDA review and assessment.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations)?

Data:

No clinically significant differences in the PK of dordaviprone were observed based on age, sex, or race.

Renal Impairment

The PK of dordaviprone were assessed at a dose of 375 mg in both healthy adults and adults with severe renal impairment (eGFR <30 mL/min as calculated by the Cockcroft-Gault equation). Severe renal impairment increased dordaviprone C_{max} by 13% and AUC by approximately 50% and C_{max} by 13%. No dose adjustment of dordaviprone is recommended for patients with mild, moderate, or severe renal impairment.

Dordaviprone has not been studied in patients with end stage renal disease who are receiving dialysis.

Hepatic Impairment

The PK of dordaviprone were assessed at a dose of 125 mg in both healthy adults and adults with mild or moderate hepatic impairment (Child-Pugh Class A and B). Moderate hepatic impairment increased dordaviprone AUC by approximately 50% and Cmax by approximately 20%. No dose adjustment of dordaviprone is recommended for patients with mild or moderate hepatic impairment (Child-Pugh Class A and B).

Dordaviprone has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

The Applicant's Position:

Based on the assessment of intrinsic factors in the population PK analyses, no dose adjustment or change in dordaviprone dosing is recommended.

The FDA's Assessment:

FDA concurs with the Applicant's position that no clinically significant effects on dordaviprone PK were observed based on age (3 to 90 years), sex, race (74% White, 9% Black/African American or 5% Asian), mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN or total bilirubin > 1 to 1.5 times ULN with any AST), moderate hepatic impairment (Child Pugh B) and renal impairment. Furthermore, the exposure of dordaviprone in pediatric patients (1 year and older) who weigh at least 10 kg is predicted to be within the range of exposures predicted in adults at the recommended dosages. Refer to Section 6.2.1 for additional details.

A PMR will not be issued to evaluate the effects of severe hepatic impairment on dordaviprone PK as the occurrence of severe hepatic impairment in the target patient population is very low.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data / The Applicant's Position:

Food Effect

A high-fat meal decreased the rate of absorption (C_{max}) of dordaviprone, but the extent of exposure (AUC) remained unaffected. The geometric mean ratios (fed versus fasted) and 90% CIs for C_{max}, AUC_{last}, and AUC_{inf} were 0.61 (0.55, 0.67), 1.00 (0.95, 1.06), and 1.00 (0.95, 1.06), respectively. Dordaviprone is recommended to be taken 1 hour prior to or 3 hours after a meal.

CYP3A4 Inhibitors

Coadministration of dordaviprone with a strong CYP3A4 inhibitor resulted in an approximate 2-fold increase in Cmax and 4-fold increase in AUC; therefore, if coadministration is unavoidable, reduce dordaviprone dosing in adults to 375 mg in the presence of strong CYP3A4 inhibitors.

PBPK model simulations of moderate CYP3A4 inhibitors increased the dordaviprone Cmax and AUC by ~1.5 and 2.5-fold, respectively; therefore, if coadministration is unavoidable, reduce dordaviprone dosing in adults to 500 mg in the presence of moderate CYP3A4 inhibitors.

CYP3A4 Inducers

PBPK model simulations of strong and moderate CYP3A4 inducers reduced dordaviprone Cmax by approximately 70% and 45%, respectively, and reduced AUC by approximately 80% and 65%, respectively. Therefore, the administration of strong and moderate CYP3A4 inducers with dordaviprone should be avoided.

The FDA's Assessment:

Refer to Sections 6.2.1 and 6.2.2.2 for clinical pharmacology review and assessment.

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Primary Reviewer Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 7.1 presents a summary of clinical studies included in the NDA.

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Table 7.1: Applicant – Listing of Clinical Studies Relevant to this NDA

Study Identifiers; Report Location	Number of Centers; Locations	Status; Study Dates	Study Design	Drug, Dose, Route, Regimen	Enrollment	Sex (M/F); Age (Range)	Study Population
Clinical Pharmacology							
ONC201-109; m5.3.1.2	1; US	Complete; 21Feb2023-31Mar2023	Phase 1, open-label, randomized, 2-period, crossover, single center	Dordaviprone 125 mg; oral; single dose in each period; (b) (4) drug product capsules	N=36	28M/8F; 38 years (22-55)	Healthy; adults 18-55 years
ONC201-103; m5.3.1.2	1; US	Complete; 01Aug2022-23Nov2022	Phase 1, open-label, randomized, crossover, 2- or 3-period, single center	Dordaviprone; oral; single dose of 125 mg in each period; early phase and late phase capsules Itraconazole 200 mg; oral; once daily for 8 days (Period 3, DDI)	N=36 2 periods=18 3 periods=18	29M/7F; 40.0 years (19-52)	Healthy; adults 18-55 years
ONC201-101; m5.3.3.1	1; New Zealand	Complete; 10Sep2021-03Jun2022	Phase 1, open-label, 3-part (A, B1, B2), randomized (B1, B2), crossover (B1, B2), single center	Dordaviprone; oral; single dose in each period; A: 125, 375, and 625 mg; intact capsule B1: 125 mg as intact capsule, capsule contents sprinkled on applesauce, and capsule contents dissolved in Gatorade B2: 625 mg late phase formulation in fed and fasted state; Period 3: 625 mg early phase formulation in fasted state	N=63 By study part: A=15 B1=18 B2=30 B2/P3=13	A: 15M/0F; 28 years (20-49) B1: 18M/0F; 32 years (19-52) B2: 29M/1F; 28 years (18-53)	Healthy; adults 18-55 years

Study Identifiers; Report Location	Number of Centers; Locations	Status; Study Dates	Study Design	Drug, Dose, Route, Regimen	Enrollment	Sex (M/F); Age (Range)	Study Population
ONC201-106; m5.3.3.1	1; US	Complete; 08Apr2022-12May2022	Phase 1, mass balance, open-label, single center	[^{14}C]-dordaviprone 625 mg; oral; single dose	N=6	6M/0F; 33.5 years (29-55)	Healthy; adult males 18-55 years
ONC201-104; m5.3.3.3	1; New Zealand	Complete; 26May2022-12May2023	Phase 1, open-label, single-dose, single center	Dordaviprone 375 mg; oral; single dose	N=16 Cohort 1=8 Cohort 2=8	Cohort 1: 7M/1F; 62.5 years (52-74) Cohort 2: 7M/1F; 57.6 years (47-72)	Cohort 1: Severe renal impairment Cohort 2: Healthy, matched; adults 18-75 years
ONC201-105; m5.3.3.3	1; US	Complete; 06May2022-29Dec2022	Phase 1, open-label, single-dose, single center	Dordaviprone 125 mg; oral; single dose	N=16 Cohort 1=8 Cohort 2=8	Cohort 1: 5M/3F; 57.0 years (49-68) Cohort 2: 5M/3F; 51.5 years (42-61)	Cohort 1: Moderate hepatic impairment Cohort 2: Healthy, matched; adults 18-75 years
ONC201-107; m5.3.3.4	1; US	Complete; 14Feb2022-07Mar2022	Phase 1, open-label, single sequence crossover, single center	Dordaviprone 625 mg; oral; Days 1 and 10; Rabeprazole 20 mg; oral; once daily Days 4-10	N=16	14M/2F; 34.4 years (18-53)	Healthy; adults 18-55 years

Study Identifiers; Report Location	Number of Centers; Locations	Status; Study Dates	Study Design	Drug, Dose, Route, Regimen	Enrollment	Sex (M/F); Age (Range)	Study Population
ONC201-102; m5.3.4.1	1; New Zealand	Complete; 30Nov2022-27May2023	Phase 1, randomized, 2-part, single-center Part 1 (lead-in): open-label, 1-period Part 2 (tQTc): partly blinded, randomized, 3-period, positive- and placebo-controlled, crossover	Part 1: Dordaviprone; oral; 750 mg (single dose) or 625 mg (2 doses separated by 4 hours) Part 2: Dordaviprone; oral; 750 mg (dose was determined based on Part 1) Moxifloxacin: 400 mg; oral; single dose Placebo: oral, single dose	N=36 Part 1=6 (625 mg=3; 750 mg=3) Part 2=30	Part 1: 6M/0F; 22 years (19-31) Part 2: 30M/0F; 25 years (18-45)	Healthy; adults 18-55 years
Adequate and Well-Controlled Studies							
ONC201-108 (NCT05580562)	>145; 17 countries	Ongoing; Jan2023	Phase 3, randomized, double-blind, placebo-controlled	Dordaviprone 625 mg[a] or placebo, oral; once weekly or twice weekly (Days 1+2)	Ongoing; N=450 planned	NA	H3 K27M-mutant glioma
Uncontrolled Studies							
ONC006 (NCT02525692); m5.3.5.2	5; US	Terminated; 20Jan2016-24Apr2023	Phase 2, open-label, multicenter	Dordaviprone 625 mg, oral; once every 3 weeks (Arm A) or once weekly (Arms B-F)	N=84 By Arm: A=17 B=19 C=8 D=30 E=3 F=7	41M/43F; 48 years (17-80)	Recurrent glioblastoma, H3 K27M-mutant glioma, and diffuse midline glioma; age ≥16 years

Study Identifiers; Report Location	Number of Centers; Locations	Status; Study Dates	Study Design	Drug, Dose, Route, Regimen	Enrollment	Sex (M/F); Age (Range)	Study Population
ONC013 (NCT03295396); m5.3.5.2	9; US	Terminated; 31Oct2017-19Jul2023	Phase 2, open-label, multicenter	Dordaviprone 625 mg, oral; once weekly	N=73 By Arm: A=43 B=30	40M/33F; 33 years (20-72)	Recurrent H3 K27M-mutant glioma; adults ≥18 years
ONC014 (NCT03416530); m5.3.5.2	8; US	Terminated; 25Jan2018-24May2023; Full	Phase 1, open label, multicenter, multi-arm, dose escalation and dose expansion	Dordaviprone 625 mg[a], oral; once weekly or twice weekly (Days 1+2)	N=134 By Arm: A=22 B=24 C=15 D=25 E=25 F=11 G=12	54M/80F; 9.5 years (3-21)	Recurrent/ refractory H3 K27M-mutant glioma and newly diagnosed DIPG; pediatrics age ≥2-18 years
ONC016 (NCT05392374); m5.3.5.2	10; US	Complete; 08Sep2017-12Jun2023	Open-label, compassionate use	Dordaviprone 625 mg, oral; once weekly	N=12	8M/4F; 9 years (3-40)	H3 K27M-mutant glioma; age ≥3 years
ONC018 (NCT03134131); m5.3.5.2	36; US	Terminated; 25Jan2019-16Mar2023	Open-label, multicenter, intermediate-size expanded access	Dordaviprone 625 mg[a], oral; once weekly	N=131	64M/67F; 21 years (3-69)	H3 K27M-mutant and/or midline high grade glioma; age ≥3 years

Study Identifiers; Report Location	Number of Centers; Locations	Status; Study Dates	Study Design	Drug, Dose, Route, Regimen	Enrollment	Sex (M/F); Age (Range)	Study Population
ONC028 (NCT04617002)	27; US	Ongoing; Dec2020	Open-label, multicenter, intermediate-size expanded access	Dordaviprone 625 mg[a], oral; once weekly	Ongoing; NA	NA	Recurrent H3 K27M-mutant and/ or midline glioma
Other							
ONC201-110; m5.3.5.4	1; US	Complete; 19Jan2023-30Jan2023	Phase 1, open-label, single center	Dordaviprone 6 concentrations per 30 mL dose (2.6, 7.7, 23.3, 69.4, 250, 625 mg); oral cavity (all doses were expectorated)	N=10	3M/7F; 62 years (43-67)	Sensory panelists; Adults 25-80 years

Abbreviations: DDI=drug-drug interaction; DIPG=diffuse intrinsic pontine glioma; F=female; M=male; NA=not applicable; NDA=New Drug Application; US=United States
Study status: closed=patient evaluations are complete, but data analyses are ongoing; complete=all data analyses are complete; ongoing=patient enrollment, treatment, and/or follow-up evaluations are ongoing; terminated=enrollment and/or follow-up stopped earlier than planned.
[a] Dordaviprone dosing was scaled by body weight for patients <18 years and/or <52.5 kg.

The Applicant's Position:

The evaluation of dordaviprone includes thorough assessments of safety, efficacy, and clinical pharmacology for its proposed use in treating H3 K27M-mutant diffuse glioma in both adult and pediatric patients. Efficacy is demonstrated through a primary efficacy analysis set involving patients with recurrent H3 K27M-mutant diffuse glioma who were evaluable for monotherapy objective response and selected from 5 completed, open-label clinical studies (ONC006, ONC013, ONC014, ONC016, and ONC018) using criteria aligned with the FDA. Supportive efficacy results include clinical outcomes of additional glioma patients treated with dordaviprone in clinical studies and pharmacodynamic assessments of the major disease driver.

The safety profile was established based on an integrated safety analysis of 422 patients from 4 completed, open-label dordaviprone clinical studies in glioma (ONC006, ONC013, ONC014, and ONC018). Additional insights into the safety profile of dordaviprone are provided by clinical pharmacology studies, ongoing studies, non-glioma indication studies, and investigator-initiated trials (IITs), which support the consistency of safety results across various settings and special populations.

The FDA's Assessment:

FDA agrees with the Applicant's description of the clinical studies included in this application and considers the analysis of the prespecified integrated efficacy population derived from the 5 completed, open-label clinical studies to be an adequate and well-controlled study based on the criteria described in 21 CFR 314.126. Study ONC201-108 (NCT05580562) is ongoing and while there are early blinded safety data included in the application, there are no efficacy data from this study.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Primary Efficacy Analysis Set

Trial Design

The Applicant's Description:

In this application, the efficacy of dordaviprone was evaluated across 5 completed, open-label clinical studies (ONC006, ONC013, ONC014, ONC016, and ONC018) involving adult and pediatric patients with glioma. These studies assessed the safety and efficacy of dordaviprone in various patient populations, focusing on recurrent H3 K27M-mutant diffuse glioma. Table 8.1 provides a summary of each study contributing to the primary efficacy analysis.

Table 8.1: Applicant – Description of Efficacy Studies

Study Identifier	Study Design	Drug, Dose, Route	Number of Participants	Study Population	Sex (M/F); Median Age (Range)
ONC006	Phase 2, open-label, multicenter, multi-arm	Dordaviprone 625 mg; oral; Once every 3 weeks or once weekly	N=84 By Arm: A=17, B=19, C=8, D=30, E=3, F=7	Recurrent glioblastoma, H3 K27M-mutant glioma, or diffuse midline glioma; ≥16 years	41M/43F; 48 years (17-80)
ONC013	Phase 2, open-label, multicenter	Dordaviprone 625 mg; oral; Once weekly	N=73 By Arm: A=43 B=30	Recurrent H3 K27M-mutant glioma; ≥18 years	40M/33F; 33 years (20-72)
ONC014	Phase 1, open-label, multicenter, multi-arm, dose escalation and dose expansion	Dordaviprone 625 mg[a]; oral ±radiotherapy; Once weekly or twice weekly (Day 1+2)	N=134 By Arm: A=22, B=24, C=15, D=25, E=25, F=11, G=12	Recurrent/ refractory H3 K27M-mutant glioma, or newly diagnosed DIPG; ≥2 to 18 years	54M/80F; 9.5 years (3-21)
ONC016	Multiple single-patient compassionate use protocols	Dordaviprone 625 mg[a]; oral; Once weekly	N=12	H3 K27M-mutant glioma; ≥3 years	8M/4F; 9 years (3-40)
ONC018	Open-label, multicenter, intermediate-size expanded access	Dordaviprone 625 mg[a]; oral; Once weekly	N=131	Recurrent H3 K27M-mutant and/or midline glioma; ≥3 years	64M/67F; 21 years (3-69)

Abbreviations: DIPG=diffuse intrinsic pontine glioma; F=female; GBM=glioblastoma; M=male
[a] Dose scaled by body weight bands for patients <18 years of age and <52.5 kg.
Source: m2.5; Table 2

Radiographic assessments using magnetic resonance imaging (MRI) were performed approximately every 8 weeks.

The primary efficacy analysis set consisted of the first 50 patients with recurrent H3 K27M-mutant diffuse midline gliomas, selected from these studies using predefined criteria that aligned with the FDA. This approach enabled rigorous evaluation of the objective response in patients with recurrent H3 K27M-mutant diffuse glioma treated with dordaviprone monotherapy based on established response criteria. Efficacy endpoints were assessed using RANO criteria by blinded independent central review (BICR) and included ORR, duration of response (DOR), and time to response.

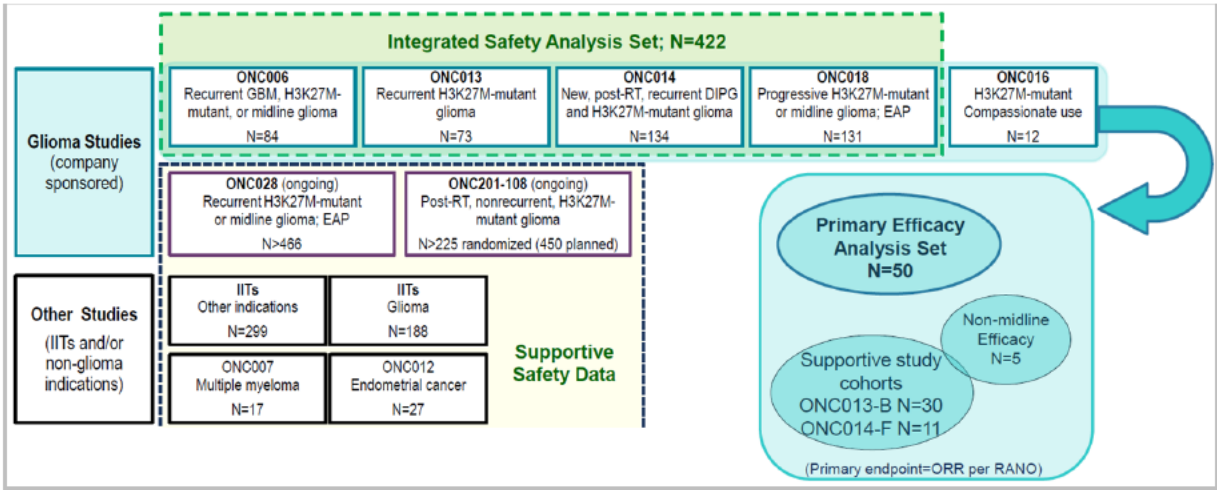
The FDA's Assessment:

FDA agrees with the Applicant's position. Due to the rarity of the disease and poor prognosis, and in order to evaluate a sufficiently homogenous patient population to assess the effect of the drug, FDA determined it was reasonable to consider safety and efficacy data from a pooled population of patients derived from single arm trials of dordaviprone monotherapy in adults and pediatric patients with recurrent H3 K27M-mutant DMG who met pre-defined eligibility criteria.

The studies included 3 single arm trials in patients with glioma: ONC006, ONC013, and ONC014, each enrolling 73-134 patients; as well as 2 expanded access protocols, ONC016 and ONC018, which enrolled 12 and 131 patients with H3 K27M-mutant glioma, respectively. The expanded access protocols each included specific eligibility criteria, required imaging assessments at pre-defined intervals (8 weeks), had specific instructions to ensure safety and consistency of treatment such as dose modifications in the event of toxicities, and employed systematic data collection. These characteristics, in conjunction with pre-defined eligibility criteria for the pooled efficacy population, enabled FDA to consider data from these expanded access protocols in addition to that from prospective clinical trials in the setting of a rare disease with a high unmet medical need.

Fifty out of the pooled total of 434 patients met the pre-defined eligibility criteria and were included in the pooled efficacy analysis (Figure 8.1). The numbers of patients in the primary efficacy population (N = 50) from each individual study are: ONC006 (N = 10), ONC013 (N = 29), ONC014 (N = 2), ONC016 (N = 1), ONC018 (N = 8).

Figure 8.1: Derivation of integrated efficacy population from 5 single arm studies of dordaviprone monotherapy in patients with glioma



Source: Chimerix, Inc. Application Orientation Meeting presentation, February 7, 2025

Eligibility Criteria

The Applicant's Description:

The efficacy of dordaviprone was evaluated in adult and pediatric patients with glioma across 5 completed, open-label clinical studies (ONC006, ONC013, ONC014, ONC016, and ONC018). To ensure a homogenous and evaluable patient subset, a primary efficacy analysis set of patients with predefined inclusion criteria was established. Patients in this set were required to have received single-agent dordaviprone, be ≥2 years of age, have H3 K27M-mutant diffuse midline glioma with progressive and measurable disease per RANO-HGG criteria, be ≥90 days post-radiation therapy, have adequate washout from prior anticancer therapies, have a KPS/LPS score of ≥60, and have stable or decreasing corticosteroid use. Patients with DIPG, primary spinal tumors, atypical histologies, or cerebrospinal dissemination were excluded.

Patients were required to show confirmed disease progression per RANO criteria and be at least 90 days post-radiotherapy before starting dordaviprone. This requirement, in addition to the washout period from previous anticancer therapies (23 days for temozolomide, 42 days for bevacizumab, and 28 days for other treatments), was to ensure any observed effects could be confidently attributed to dordaviprone in a homogeneous study population.

The FDA's Assessment:

FDA agrees with the Applicant's position. These eligibility criteria were discussed at Type C Meetings in July 2019 and May 2020, and FDA agrees that the identified population is appropriate based on the WHO Classification of CNS tumors (Louis et al, 2021), the published

literature on the biology and natural history of these tumors, and available treatments in this rare disease setting. FDA also agrees that the identified population is sufficiently homogeneous to evaluate the treatment effect of dordaviprone.

The Applicant's rationale for excluding patients with DIPG was primarily based on imaging features (e.g., typical lack of contrast enhancement, unclear margins, and amorphous geometry), as well as possibly worse prognosis compared to other diffuse midline gliomas based on inability to resect and other potential biological differences.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint was ORR, as determined by dual-reader BICR using RANO criteria. Secondary endpoints included duration of response, time to response, best overall response, disease control rate, PFS, OS, corticosteroid response rate, and performance status response rate. Patients were censored for all endpoints, except OS, upon initiation of any additional anticancer therapy.

Efficacy was primarily assessed through radiographic evaluations using MRIs and documentation of vital status. MRIs, including T1 post-contrast and T2/Fluid-Attenuated Inversion Recovery (FLAIR)–weighted images, were conducted at baseline and approximately every 8 weeks during treatment to monitor changes in target lesions and other tumors.

Efficacy was assessed using both RANO-HGG, for quantifying enhancing lesions, and RANO-LGG, for non-enhancing lesions. The RANO criteria were updated in 2023 in order to better address the heterogenous nature of diffuse midline gliomas, which often exhibit both enhancing and non-enhancing areas. RANO 2.0 provides a standardized set of criteria for all glial tumors, addressing the complexity of both high-grade and low-grade gliomas with diverse treatment modalities (Wen 2023; Banan 2021). This unified criteria, which supersedes the previous RANO protocols, allows for a more detailed and accurate assessment of tumor responses by considering both enhancing and non-enhancing tumor components. (Louis 2021). Therefore, all efficacy endpoints initially analyzed using RANO-HGG or RANO-LGG criteria were also assessed using RANO 2.0 criteria, integrating clinical outcomes with radiographic changes to provide a thorough assessment of treatment impact. Additional efficacy endpoints included performance status and corticosteroid response rates.

The FDA's Assessment:

FDA agrees with the Applicant's summary of study endpoints.

While RANO-HGG criteria were used as the primary response criteria in the clinical studies, FDA determined that the RANO 2.0 criteria are the most clinically appropriate response criteria to use in this disease setting due to the heterogeneously enhancing nature of this tumor type.

Response criteria for brain tumors have evolved over the last 25 years with improved imaging modalities and accumulated response data. The original RANO criteria (Wen et al, 2010), account only for contrast-enhancing disease in the assessment of response. These criteria may over-estimate the treatment effect (ORR) if a patient has a small enhancing lesion which resolves but a large amount of non-enhancing tumor burden which remains.

The RANO-LGG criteria, published in 2017 (Wen et al, 2017), rely primarily on non-contrast enhancing disease, since low grade tumors tend not to enhance on MRI. These criteria may underestimate response as there may be other causes of increased T2/FLAIR signal, such as post-radiation changes, post-surgical changes, edema, or corticosteroid-related changes. T2/FLAIR signal abnormality is also difficult to measure reliably due to its diffuse nature.

Thus, the RANO 2.0 criteria were established in 2023 (Wen et al, 2023) to provide unified, standardized guidelines for glioma response assessments that account for both contrast and non-contrast enhancing disease specific to a given tumor at baseline.

H3 K27M-mutant diffuse midline gliomas tend to be heterogeneously enhancing (Lovibond et al, 2023), and therefore FDA considers the RANO 2.0 criteria the most clinically relevant as they consider both enhancing and non-enhancing aspects of the tumor.

FDA does not consider disease control rate for regulatory decision-making as stable disease may reflect the natural history of the disease rather than an effect of the drug. Additionally, time to event endpoints, such as PFS and OS, are challenging to interpret in the context of a single-arm trial.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Sample Size

The planned sample size for the primary efficacy analysis was 50, which would exclude a lower 95% CI boundary of <10% with an observed 20% response rate by RANO. This planned sample size provided 95% CI with reasonable widths for the ORR estimates across a range of possible observed response rates.

Tumor Response by BICR

RANO-HGG

The tumor response endpoint definitions based on RANO-HGG criteria are as follows:

- **Overall Response Rate (ORR)**: Determined by the presence of a confirmed complete response (CR) or partial response (PR) at any time during the study, confirmed by a subsequent assessment at least 4 weeks later. ORR will be summarized with exact 95% CIs, and patients without a post-baseline assessment will be considered non-responders.

- **Best Overall Response (BOR)**: Defined as the best response recorded during the study, categorized as CR, PR, stable disease, progressive disease (PD), unevaluable, or not evaluated, and summarized by the number and percentage in each category.
- **Disease Control Rate (DCR)**: The proportion of patients achieving CR, PR, or stable disease, summarized with exact 95% CIs.
- **Duration of Response (DOR)**: Time from the first RANO-HGG response to disease progression or death in responders, summarized using the Kaplan-Meier method with medians and quartiles presented along with 95% CIs. Patients without progression at data cutoff were censored at their last disease assessment.
- **Time to Response**: Time from the first dose to the first documented response (CR or PR) in responders, summarized descriptively.
- **Progression-Free Survival (PFS)**: Time from the first dose to disease progression or death, summarized using the Kaplan-Meier method with medians and quartiles presented. Patients without documented progression or death were censored at their last assessment or upon starting any new anticancer therapy, with 95% CIs for medians and quartiles reported.

Kaplan-Meier plots will include pointwise 95% confidence bands and survival estimates at specific time points (3, 6, 9, 12, 18, 24 months) along with corresponding CIs.

RANO-LGG

All analyses conducted with RANO-HGG criteria were also performed using RANO-LGG criteria. Under RANO-LGG, an overall response includes any confirmed CR, PR, or minor response (MR).

An MR, according to RANO criteria, is determined primarily by measuring tumor shrinkage on T2/FLAIR MRIs, with the requirement that any enhancing disease remains at least stable. While the decrease in tumor size may be modest, even minor reductions can lead to significant clinical benefits for the patient. This is particularly relevant depending on the tumor's location, as reduced lesion size can relieve pressure on the brain. The clinical benefits from such minor responses may include improvements in neurological symptoms or a reduction in the daily dosage of corticosteroids required by the patient.

For RANO-LGG, the Best Overall Response (BOR) categories include CR, PR, MR, stable disease, PD, unevaluable, and not evaluated. The Disease Control Rate (DCR) encompasses CR, PR, Stable Disease, and MR, indicating the proportion of patients experiencing control of their disease under the treatment regimen.

RANO 2.0

All analyses applied to RANO-HGG criteria were also conducted using RANO 2.0 criteria, which evaluates responses based on both enhancing and non-enhancing disease, corticosteroid use, and clinical status, categorizing them as CR, PR, MR, stable disease, or PD. Overall Response Rate (ORR) by RANO 2.0 is defined as the proportion of patients achieving CR, PR, or MR across both RANO-HGG and RANO-LGG assessments; patients with PD at the time of

first response or its confirmation were not considered responders. Duration of Response (DOR) was calculated from the time of first response under RANO-HGG or RANO-LGG criteria to the time of progression under the same criteria.

Overall Survival

OS was calculated as time from the date of the first dose of dordaviprone (after recurrence after other treatments) to the date of death.

Steroid Response

Patients eligible for corticosteroid response evaluation were those receiving a baseline dexamethasone equivalent daily dose of ≥4 mg. A response was defined as a ≥50% reduction from the baseline daily dose to ≤2 mg, along with a stable or improved KPS/LPS score, confirmed at the next analysis timepoint. This endpoint assessed individuals continuously receiving at least 4 mg daily from Day -7 to Day 1, with response rates and 95% CIs provided. Time to first corticosteroid response, calculated from the first dose of dordaviprone to when response criteria were initially met, and the association of corticosteroid responses with RANO responses, were both summarized descriptively.

Performance Status Response

Patients with a baseline KPS/LPS of ≤80 were evaluable for performance status response, defined as an increase of at least 10 points from baseline, accompanied by stable or reduced corticosteroid use. The response rate and 95% exact CIs were provided. Time to the first performance status response, measured from the first dose of dordaviprone to when response criteria were first met, was summarized descriptively and only included patients who responded. Additionally, the correlation between performance status responses and RANO responses was described descriptively.

Subgroup Analyses

Subgroup analyses were performed on RANO-HGG ORR, RANO-LGG ORR, and RANO 2.0 ORR. Forest plots with response rates and associated 95% exact CIs were presented.

Association between ORR and Survival

Landmark analyses assessed the relationship between RANO 2.0 response and overall survival at 3, 5, 7, 9, and 11 months, excluding patients who died or were censored before each landmark. Survival outcomes were compared between responders and non-responders prior to each timepoint, using log-rank tests and Cox proportional hazards models to present hazard ratios and 95% CIs. Additionally, a multivariate Cox model analyzed overall survival with RANO 2.0 response as a time-varying covariate, considering patients as non-responders until their first response, and including other factors through backward selection. This approach was also applied to analyze the impact of disease control on survival, treating progression before each landmark as non-response and stability or improvement as response.

The FDA's Assessment:

FDA did not agree that a sample size justification based on 50 patients and a target ORR of 20%, with the lower limit of the 95% confidence interval using Clopper-Pearson method to exceed an ORR of 10%, would be sufficient to demonstrate the efficacy of dordaviprone, specifically the exclusion of a lower limit of 10%. In a meeting held on May 12, 2020, FDA would not commit to a specific response rate or lower bound of the 95% CI that would be considered clinically meaningful. Rather, FDA would consider the response rate in context of the totality of the evidence (e.g. duration of response, improvement of symptoms).

FDA agrees with the Applicant's description of tumor response. However, it is not clear whether the parameters used to define "steroid response" and "performance status response" are clinically meaningful and FDA considers these analyses descriptive only. Refer to Study Endpoint section above regarding the FDA comments on the acceptability of the endpoints for regulatory decision making. FDA considers results for the association between ORR and overall survival to be exploratory as these results are difficult to interpret in the absence of randomization and a control arm.

Protocol Amendments

The Applicant's Description:

The efficacy data are derived from the primary efficacy analysis set, which includes patients from 5 open-label clinical studies (ONC006, ONC013, ONC014, ONC016, and ONC018). All studies were terminated by an Administrative Protocol Amendment on 17 January 2023. The protocol amendment histories for each of these studies is briefly summarized below.

- **ONC006:** Amendments to the original protocol were implemented 7 times. Major changes included transitioning from a single arm to a multi-arm study over time (Arms A through F), updating patient eligibility criteria and objectives, lowering the minimum age requirement from 18 to 16 years, and increasing sample sizes.
- **ONC013:** The original protocol was amended 3 times. Major changes included the addition of Arm B, adding OS as a secondary endpoint, including RANO-LGG criteria, and requiring pre-study MRI scans.
- **ONC014:** The original protocol was amended 6 times. Major changes included the addition of Arms C, D, E, F, G, and H.
- **ONC016:** Participating investigators were provided with templates for a treatment protocol and informed consent document that may have been modified for their individual clinic procedures and based on the patient's age and specific diagnosis.
- **ONC018:** The original protocol was amended 3 times. Major changes included the addition of safety endpoints, increased sample size, and recurrent disease as a requirement for eligibility.

The FDA's Assessment:

FDA agrees with the Applicant's description of protocol amendments.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

Studies ONC006, ONC013, ONC014, ONC016 and ONC018 were conducted in accordance with all applicable laws of the pertinent regulatory authorities and in accordance with ICH GLP Regulations and ethical principles from the Declaration of Helsinki. The original protocols and protocol amendments for each study included in the primary efficacy analysis set were approved by an independent institutional review board/ethics committee associated with each study center. Signed informed consent was obtained from all patients before enrollment in each study.

The FDA's Assessment:

The Applicant's statements that Studies ONC006, ONC013, ONC014, ONC016, and ONC018, were conducted in accordance with Good Clinical Practice (GCP) guidelines were reviewed in each CSR.

Financial Disclosure

The Applicant's Position:

Financial disclosure information is available in Appendix 19.2. Financial disclosure information was collected from all relevant investigators.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Patient Disposition

The Applicant's Description:

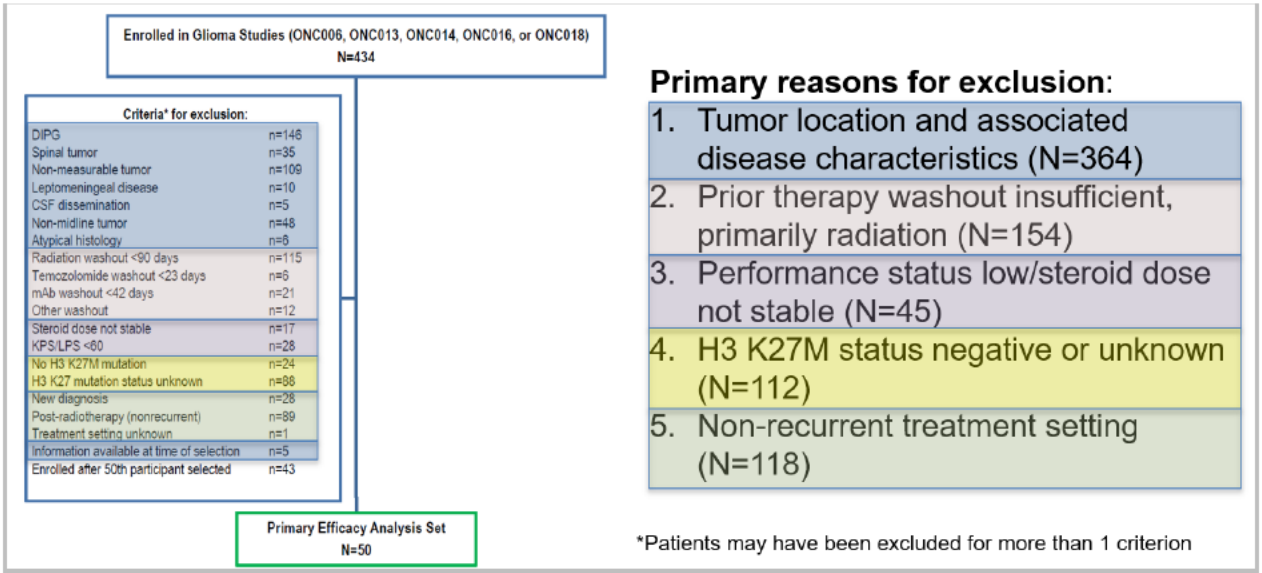
The primary efficacy analysis set consisted of 50 patients with recurrent H3 K27M-mutant diffuse midline gliomas, selected from 5 completed open-label clinical studies using predefined criteria. The primary reason for withdrawal from a study was death (86%).

The FDA's Assessment:

FDA agrees that the integrated efficacy population consisted of 50 patients who met the eligibility criteria described above. The reasons for exclusion from the primary efficacy population are listed in Figure 8.2. The general categories of exclusion included tumor location and associated disease characteristics; insufficient washout periods from prior therapy (primarily

radiation); clinical factors such as low performance status or fluctuating steroid dose; H3 K27M mutation status negative or unknown; and non-recurrent treatment setting. FDA considered the reasons for exclusion to be appropriate.

Figure 8.2: Primary reasons for exclusion from integrated efficacy population



Source: FDA analysis, adapted from NDA 219876 Summary of Clinical Efficacy, page 31)

Regarding the 5 patients without information available at time of selection, upon manual review, these patients were noted to have tumor characteristics which would have excluded them (DIPG, spinal tumors, or leptomeningeal disease [LMD]).

Regarding the 43 patients enrolled after the first 50 patients who would have met eligibility criteria, BICR-assessed images are not available for these patients; investigator-assessed response evaluations are available and summarized in Section 8.1.2 below.

Regarding patient disposition, ONC006, ONC013, ONC014, ONC016, and ONC018 were conducted between 2016 and 2023, and all patients are off study as of the data cut off of July 31, 2024. The primary reason for treatment discontinuation was progressive disease; no patients discontinued treatment due to toxicity (Table 8.2).

Table 8.2: Patient Disposition for Integrated Efficacy Population (N=50)

Patient Disposition	***Integrated Efficacy Population (N=50)***

End of Treatment Status, %	Discontinued	100
Reason for Treatment Discontinuation, %	Progressive Disease	80
	Physician or Patient Decision	4
	Sponsor request (transitioned to expanded access protocol at study closure)	4
	Lost to follow-up	2
	Other*	10
End of Study Status, %	Discontinued	100
Reason for Study Discontinuation, %	Death	74
	Withdrawal by subject	4
	Lost to follow-up	4
	Unknown	18

*Other: "unable to get clear medical follow-ups over the last 5 weeks"; "travel restrictions due to COVID-19 pandemic"; "clinical decline"; "clinical deterioration"; "non-compliance with study schedule"

Source: FDA Analysis based on NDA 219876 ADSL datasets and Clinical Study Reports

In response to an FDA information request, communicated on June 9, 2025, the Applicant clarified that the Applicant reported primary reason for study discontinuation due to death of 86% was in the Safety Analysis Set (n=422) and it was 74% in the Integrated Efficacy Analysis Population (n=50).

Protocol Violations/Deviations

Data:

During the Coronavirus Disease 2019 (COVID-19) pandemic, adjustments and omissions were made to some planned activities and assessments in all studies included in the primary efficacy analysis set to ensure patient safety. These deviations, which were considered minor, included using local providers for assessments instead of requiring patients to visit study sites, conducting remote/telehealth visits, omitting some planned procedures, and providing study treatment to accommodate for the reduced frequency of site visits. Despite these changes, the deviations had no impact on the ability to assess the safety of patients or evaluate disease response. Given the life-threatening nature of the underlying disease, regular assessments and evaluations continued based on the investigator's judgment and the standard of care.

Additionally, the protocol did not specify dosing windows for the prescribed weekly dosing intervals (once or twice weekly), and doses administrated outside of exactly 7 days from the previous dose were not recorded as protocol deviations.

Patients who continued treatment beyond progression, as allowed per protocol, were also allowed to add standard of care treatments (re-irradiation or bevacizumab) in combination with dordaviprone, as outlined in Protocol Amendments or Protocol Clarification Letters. Instances of dordaviprone use in combination with these treatments prior to these amendments were not recorded as deviations but were noted in study databases.

The incidence of protocol deviations increased following the onset of the global COVID-19 pandemic. However, attribution of these deviations as being 'COVID-related' was inconsistently recorded across different sites.

Major study-specific protocol deviations are summarized below:

- **ONC006:** The most common major deviations to inclusion criteria were prohibited medications, baseline imaging deviations (i.e., out of specified time window relative to treatment initiation), history of cardiac arrhythmia, lack of stable steroids prior to baseline imaging, and laboratory values out of range. These did not impact the ability to evaluate the study and no impact on patient safety was observed.

  Two major deviations to investigational product dosing involved planned changes to protocol-planned dosing. One patient receiving dordaviprone once every 3 weeks was escalated to once weekly dosing after confirmed progression and following evaluation of this more frequent dosing in multiple other patients. Another patient had a planned desensitization process after several low-grade allergic reactions following dosing with dordaviprone. This process involved smaller doses of dordaviprone dissolved in cherry syrup and serial diluted to be given at specific time intervals on the dosing day in an attempt to desensitize the patient to dordaviprone exposure. These deviations did not affect the interpretability of the study results.

- **ONC013:** The most common major deviations were deviations to the protocol inclusion criteria; the most common inclusion criteria violations were out of window assessments related to baseline imaging (i.e., out of specified time window relative to treatment initiation), prohibited medications, insufficient available tumor tissue/slides at screening, laboratory values outside the inclusion criteria specified range. These did not impact the ability to evaluate the study.

  Among the major deviations to inclusion criteria, one patient was enrolled in Arm B with a diffuse glioma H3 K27M-mutated that was found to be an ependymal tumor. Exclusion Criterion #2 excludes patients with atypical non-astrocytic histologies such as ependymomas. Though a major deviation, this had no impact on patients' safety or the ability to interpret the results of the study arm.

- **ONC014:** The most common major deviations were to protocol inclusion criteria; the most common inclusion criteria violations were out of window assessments related to baseline imaging (i.e., out of specified time window relative to treatment initiation), prohibited medications, insufficient washout from prior treatments, laboratory values outside the

range specified in the inclusion criteria, and patients with an age outside the protocol allowed range. These did not impact the ability to evaluate the study.

- **ONC018:** The most common major deviation from the inclusion criteria was that patients did not have progressive disease (e.g., patients were non-recurrent at baseline). Since the primary objective of this protocol was to provide dordaviprone access to patients – specifically those not eligible for ongoing dordaviprone clinical studies – enrollment was permitted before disease recurrence. These deviations did not impact the study's ability to assess treatment outcomes, nor was any effect on patient safety observed. Other major deviations included laboratory assessments out of the protocol-specified range and the presence of leptomeningeal disease. These deviations also did not affect the interpretability of the study or compromise patient safety.

The Applicant's Position:

No protocol deviation was judged to have impacted the overall conduct of the study, primary data analyses, or study conclusions.

The FDA's Assessment:

FDA agrees with the Applicant's position that the identified protocol deviations are unlikely to have a significant impact on study results.

Table of Demographic Characteristics

Data / The Applicant's Description:

Demographic characteristics of the 50 patients with recurrent H3 K27M-mutant diffuse midline glioma, who comprised the primary efficacy analysis set, include a median age of 31.0 years (range 9 to 70 years) with 8% of patients <18 years. The majority of patients were male (54%), White (80%), and not Hispanic or Latino (84%).

The FDA's Assessment:

FDA agrees with the Applicant's description of the integrated efficacy population with respect to age, race and ethnicity. Additional demographics for the integrated efficacy population are described in Table 8.3. All patients were enrolled at sites in the United States. H3 K27M-mutant DMG is a rare disease and representation of race and ethnicity are not well described in the literature, but the population appears generally representative of patients with gliomas overall (Ostrom et al, 2018).

Table 8.3: Patient Demographics, Integrated Efficacy Population (N=50)

Patient Demographics	*Integrated Efficacy Population (N=50)*

Median age, years (range)		31 (9, 70)
Age Group, %	2 to < 18 years	8
	18 to < 65 years	90
	≥ 65 years	2
Sex, %	Male	54
	Female	46
Race, %	White	80
	Black or African American	6
	Asian	2
	American Indian or Alaska Native	2
	Other/Unknown	10
Ethnicity, %	Hispanic or Latino	8
	Not Hispanic or Latino	84
	Unknown	8
Region, %	United States	100
Baseline performance score (KPS), %	90-100	34
	80	38
	60-70	28

Source: FDA analysis based on NDA 219876 ADSL datasets

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Other baseline characteristics of the 50 patients included in the primary efficacy analysis set show that 26 patients (52%) had thalamic primary tumors, and 24 patients (48%) had non-thalamic midline tumors. Multifocal disease was present in 23 patients (46%), while tumor sizes varied with 27 patients (54%) having tumors ≥10 cm^2. Most patients had one target lesion (40 patients, 80%). Performance status scores were 60 to 70 for 14 patients (28%), and 90 to 100 for 17 patients (34%), with the majority (36 patients, 72%) scoring ≥80. Treatment timing varied, with 31 patients (62%) experiencing recurrence ≥21 days prior, and the median time from prior radiation was 7.5 months (range 3 to 104 months). Dordaviprone was administered orally once weekly to 49 patients, with a 625 mg dose for adults and an equivalent body weight-adjusted

dose for pediatrics; 1 patient received a 625 mg dose every 3 weeks. Corticosteroid treatment also varied, with 16 patients (32%) receiving ≥4 mg/day of dexamethasone equivalent.

The Applicant's Position:

The baseline disease characteristics of patients included in the primary efficacy analysis set are generally representative of the overall patient population with recurrent H3 K27M-mutant diffuse glioma.

The FDA's Assessment:

FDA agrees with the Applicant's description of the integrated efficacy population with respect to baseline disease characteristics except tumor location. In response to an Information Request dated February 21, 2025, the Applicant stated that primary tumor location was determined by investigator, whereas the blinded independent central reviewer (BICR) determined tumor locations for target and non-target lesions at baseline and throughout study, but not primary tumor location. The location per investigator was derived hierarchically in three groups, with brainstem involvement taking precedence over midline ex-brainstem and midline involvement taking precedence over non-midline. By contrast, the location per BICR was derived hierarchically in two groups, with thalamic involvement taking precedence over no thalamic involvement. Upon manual review, 74% of patients had thalamic tumors, and 26% had non-thalamic midline tumors (brainstem, cerebellum, or basal ganglia).

Additional disease and treatment-related characteristics are described in Table 8.4.

Table 8.4: Baseline Disease and Treatment-Related Characteristics, Integrated Efficacy Population (N=50)

Baseline Disease and Treatment-Related Characteristics		***Integrated Efficacy Population (N=50)***
Median time from prior radiation, months (range)		7.4 (3, 102)
Median time from initial diagnosis, months (range)		10.7 (5, 104)
Disease Status, %	Recurrent	100
Primary Tumor Location, %	Thalamus	74
	Brainstem (non-DIPG)	14
	Cerebellum	10

	Basal Ganglia	2
H3 K27M-mutation identification, %	Immunohistochemistry (IHC)	92
	Sequencing (H3.1)	2
	Sequencing (H3.3)	6
Extent of prior resection, %	None	64
	Partial	22
	Total	14
Prior temozolomide use, %	Yes	88
Prior bevacizumab use, %	Yes	26
History of re-irradiation, %	Yes	6
Number of prior relapses, %	1	72
	2	24
	3	4
Steroids at baseline, %	Yes	62

Source: FDA Analysis based on NDA 219876 ADSL datasets

As described in the eligibility criteria, at least 3 months from prior radiation was required for inclusion; the median time was 7.4 months (range 3 to 102 months). Most patients received prior temozolomide (TMZ), a chemotherapeutic agent used commonly for other types of glioma; however, there are no data to suggest that TMZ monotherapy is efficacious for H3 K27M-mutant DMG. The majority of patients had only one prior relapse, and more than half were receiving steroids at baseline, which is typical for these tumors which cause significant neurological morbidity.

The H3 K27M mutation was identified in tissue samples for all patients in the integrated efficacy population, and most were identified by immunohistochemistry. While 4 patients had sequencing analyses conducted on their tumors, these are too few patients to identify any patterns in safety or efficacy which differed in patients with H3.1 vs. H3.3 histone mutations.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

Treatment compliance across the primary efficacy analysis set was not assessed.

Concomitant Medications

Overall, the concomitant medications administered were representative of those commonly prescribed for patients with glioma and were not considered to have impacted the study results.

Rescue Medications

Not applicable, rescue medications were not defined or used during the studies.

The FDA's Assessment:

FDA agrees with the Applicant's position. The most common concomitant medications in the integrated efficacy population included corticosteroids, bevacizumab, antiemetics, analgesics, and antiepileptics. In the assessment of efficacy, patients were censored for the use of any anti-cancer therapy during the treatment period, including bevacizumab. In addition, the use of corticosteroids is accounted for in the tumor response criteria (RANO 2.0 criteria), and it is unlikely that any of these concomitant medications impacted the assessment of efficacy of dordaviprone.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 8.5 summarizes the tumor response efficacy data for dordaviprone, showing the ORR and other metrics by RANO 2.0, RANO-HGG, and RANO-LGG criteria. For the primary efficacy analysis set, the ORR by RANO 2.0 criteria was 28.0% (95% CI: 16.2-42.5), with a median time to response of 4.6 months and a median response duration of 10.4 months. The ORR for RANO-HGG was 20.0% and 26.0% for RANO-LGG. Among the 4 pediatric patients, one achieved an objective response by all criteria, and another maintained stable disease.

Table 8.5: Applicant – Efficacy of Dordaviprone (Primary Efficacy Analysis Set)

	Primary Efficacy Analysis Set N=50		
	RANO 2.0 Criteria	**RANO-HGG Criteria**	**RANO-LGG Criteria**
Overall response rate, n (%), 95% CI (CR + PR [+ MR[a]])	14 (**28%**) 95% CI: 16.2– 42.5	10 (**20%**) 95% CI: 10.0 – 33.7	13 (**26%**) 95% CI: 14.6 – 40.3
Best overall response			

	Primary Efficacy Analysis Set N=50		
	RANO 2.0 Criteria	**RANO-HGG Criteria**	**RANO-LGG Criteria**
Complete response (CR)	0	1 (2%)	0
Partial response (PR)	10 (20%)	9 (18%)	6 (12%)
Minor response (MR)	4 (8%)	Not applicable	7 (14%)
Stable disease	6 (12%)[e]	10 (20%)	8 (16%)
Not evaluable	11 (22%)	8 (16%)[b]	11 (22%)[c]
Progressive disease (PD)	15 (30%)	18 (36%)	14 (28%)
Not applicable	4 (8%)[d]	4 (8%)[d]	4 (8%)[d]
Disease control rate, n (%), 95% CI (CR + PR + SD [+ MR[a]])	20 (40%) 95% CI: 26.4 – 54.8	20 (40%) 95% CI: 26.4 – 54.8	21 (42%) 95% CI: 28.2 – 56.8
Time to response, median (range)	4.6 months (1.6 – 15.9)	8.3 months (1.9 – 15.9)	3.6 months (1.6 – 17.8)
Duration of response, median, 95% CI	10.4 months 95% CI: 7.4 – 15.4	11.2 months 95% CI: 3.8 – NR	10.4 months 95% CI: 3.6 – 12.7
Continuing response estimates, % (95% CI)			
Month 6, % (95% CI)	84.6% (51.2 – 95.9)	75.0% (31.5 – 93.1)	83.3% (48.2 – 95.6)
Month 12, % (95% CI)	37.6% (11.8 – 64.0)	46.9% (12.0 – 76.3)	32.4% (8.0 – 60.5)
Month 24, % (95% CI)	12.5% (0.8 – 41.3)	23.4% (1.3 – 61.6)	0 (NC – NC)

Abbreviations: CI=confidence interval; CR=complete response; HGG=high-grade glioma; LGG=low-grade glioma; MR=minor response; MRI=magnetic resonance imaging; NC=not calculated; NR=not reached; PD=progressive disease; PR=partial response; RANO=Response Assessment in Neuro-Oncology.

Note: Integrated RANO criteria assessments were performed by dual-reader blinded independent central review. Time to response was calculated from the time of first dose of dordaviprone.

[a] Minor response is included for RANO 2.0 and RANO-LGG, but is not applicable for RANO-HGG.

[b] Five overall radiographic stable disease accompanied by increase in corticosteroids; 3 overall radiographic PD accompanied by decrease in corticosteroids.

[c] Eight overall radiographic stable disease accompanied by increase in corticosteroids; 3 overall radiographic PD accompanied by decrease in corticosteroids.

[d] Three patients did not have on-treatment monotherapy MRIs available for review; 1 patient was censored prior to the first on-treatment MRI.

[e] Included 1 patient with unconfirmed response by RANO 2.0.

Source: m2.7.3.2.2, Table 4; m5.3.5.3, Efficacy analysis data (adeff.xpt) and Time to event analysis data (adtte.xpt)

The Applicant's Position:

Dordaviprone treatment in patients with recurrent H3 K27M-mutant diffuse glioma shows clinically meaningful and durable objective responses. The authenticity of these responses is corroborated by the specific kinetics of tumor response, incorporation of RANO washout guidelines into patient selection criteria, absence of similar responses in patients with gliomas lacking the H3 K27M mutation, direct pharmacodynamic evidence of reversing the disease's driver (H3 K27me3-loss), and benefits seen in corticosteroid reduction, performance status improvement, and long-term survival endpoints predominantly among responders.

The FDA's Assessment:

FDA agrees with the Applicant's conclusion that dordaviprone treatment in patients with recurrent H3 K27M-mutant diffuse midline glioma shows clinically meaningful and durable objective responses. However, after an in-depth review of the investigator and BICR-assessed responses, FDA's assessment of ORR differs slightly from the Applicant's presentation (Table 8.6).

Table 8.6: Efficacy Results for Patients with Diffuse Midline Glioma Harboring an H3 K27M Mutation in Studies ONC006, ONC013, ONC014, ONC016, and ONC018 per RANO 2.0

Efficacy Parameter	**Dordaviprone N=50**
Overall Response Rate (95% CI)[a]	22% (12, 36)
Partial response (PR)	16%
Minor response (MR)	6%
Duration of Response	N=11
Median (95% CI)[b], months	10.3 (7.3, 15.2)
% with observed DOR ≥6 months[c]	73%
% with observed DOR ≥12 months[c]	27%

Abbreviations: BICR=blinded independent central review; CI=confidence interval; RANO=Response Assessment in Neuro-Oncology.
[a.] Confirmed overall response rate assessed by BICR; CI based on Clopper-Pearson method.
[b.] Based on Kaplan-Meier estimate.
[c.] Based on observed time.
Source: FDA analysis based on NDA 219876 ADSL, ADTTE, and ADEFF datasets

Among responders, the median time to response was 3.6 months (range 1.6, 15.6).

Based on BICR-assessed RANO 2.0 criteria, there was one additional responder based on the integrated response assessment, which takes into account corticosteroid use and performance status. Based on BICR-assessed RANO-HGG criteria (n=50), the ORR was 20% (95% CI: 10, 34), with 1 complete and 9 partial responses. Based on BICR-assessed RANO-LGG criteria (n=50), the ORR was 20% (95% CI: 10, 34), with 5 partial and 5 minor responses.

Patient-level data which informed this summary of efficacy are described in Table 8.7.

Table 8.7: Best Overall Response per RANO-HGG, RANO-LGG, and RANO 2.0 criteria per Investigator and BICR assessment for Integrated Efficacy Population Responders

Patient ID	RANO-HGG investigator-assessed BOR	RANO-HGG BICR-assessed BOR	RANO-LGG BICR-assessed BOR	RANO 2.0 BICR-assessed BOR	DOR per RANO 2.0 (days)	Included as RANO 2.0 responder in FDA analysis / Notes
ONC006-(b) (6)	PR	PR	SD	PR	861	Yes
ONC006-(b) (6)	PR	PR	PD	PD	N/A	No Patient had one BICR assessment of PR per RANO-LGG criteria (11/18/19), followed by 5 assessments of PD (12/30/19, 3/2/30, 5/4/20, 7/5/20, 9/6/20). While there were BICR assessments of PR which occurred after these occurrences of PD, the RANO 2.0 criteria state that a scan showing preliminary PD followed by a scan showing PD will be considered confirmed PD for the overall response status. Therefore, this patient was not considered to have a confirmed response.
ONC013-(b) (6)	SD	PR	PR	PR	382	Yes
ONC013-(b) (6)	PD	SD	Unconfirmed MR	Unconfirmed MR	N/A	No Patient had one BICR assessment of MR per RANO-LGG criteria (11/3/18), but patient was censored due to new anticancer treatment before confirmation of response. Because this was an unconfirmed response, this patient is not included in the calculation of ORR.
ONC013-(b) (6)	PR	PR	PD	PD	N/A	No

						Patient had a BICR assessment of SD per RANO-LGG criteria (4/8/19), followed by 7 assessments of PD for overall response (6/5/19, 7/29/19, 9/23/19, 11/21/19, 1/16/20, 3/12/20, 5/6/20). However, these time points were "not evaluable" per the integrated response criteria due to decreasing steroid dose. BICR assessments of MR occurred after these occurrences of PD/NE assessments. Therefore, while this patient was not considered to have a response per overall response criteria, this patient would be considered to have a minor response if considering the integrated response criteria which takes into account corticosteroid use and performance status.
ONC013-(b) (6)	PR	PR	MR	PR	222	Yes
ONC013-(b) (6)	SD	SD	MR	MR	27	Yes
ONC013-(b) (6)	PR	PR	SD	PR	63	Yes
ONC013-(b) (6)	PR	PR	PR	PR	336	Yes
ONC016-(b) (6)	CR	CR	PR	PR	462	Yes
ONC018-(b) (6)	PR	PR	PR	PR	281	Yes
ONC018-(b) (6)	PR	SD	MR	MR	280	Yes

ONC018-(b) (6)	SD	PR	PR	PR	312	Yes
ONC018-(b) (6)	PR	SD	MR	MR	112	Yes
ONC013-(b) (6)	SD	SD	MR	Unconfirmed MR	N/A	No Patient had a BICR assessment of confirmed MR per RANO-LGG criteria (5/12/18), but due to an overall assessment of PD per RANO-HGG criteria, patient did not have a confirmed MR per RANO 2.0 criteria.

BICR: blinded independent central review; BOR: best overall response; CR: complete response; DOR: duration of response; MR: minor response; PD: progressive disease; PR: partial response; SD: stable disease

Source: FDA analysis per NDA 219876 ADSL, ADTTE, ADEFF, SDTM RS and SDTM TR datasets

Regarding the congruence of response assessment across criteria (i.e., RANO-HGG, RANO-LGG, and RANO 2.0), in the overall efficacy population (N=50), 35 patients were non-responders by all criteria. Four (4) patients had a partial response (PR) by all criteria. Eleven (11) patients had variable assessments depending on the criteria applied, as described in Table 8.7 above. Despite the differences in criteria, primarily the evaluation of contrast-enhancing and/or non-contrast-enhancing disease, the ORR by all criteria was similar and ranged from 20-22%.

FDA considered multiple factors in the assessment of response in this population, including the appropriateness of durable ORR as an efficacy endpoint in recurrent H3 K27M-mutant DMG, the reliability of the determination of true progression at baseline, the timeline of responses, and the correlation observed between responses and clinical improvements. While there are uncertainties which remain with respect to the estimation of the exact treatment effect of dordaviprone in this setting, FDA determined that the data, in conjunction with confirmatory clinical and nonclinical evidence, provided substantial evidence of effectiveness in this rare, life-threatening disease with no available therapies.

Appropriateness of Response Rate as an Efficacy Endpoint in recurrent H3 K27M-mutant DMG

As described above in Section 8.1.1, "Study Endpoints," response criteria have evolved over the last 25 years with improved imaging modalities and accumulated response data. While RANO-

HGG criteria were used as the primary response criteria in the clinical studies, FDA determined that the RANO 2.0 criteria are the most clinically appropriate response criteria to use in this disease setting due to the heterogeneously enhancing nature of this tumor type. FDA acknowledges the limitations of brain tumor imaging; however, these limitations were mitigated by the study design (i.e., requiring at least 3 months from the time of last radiation), the collection of relevant data (e.g., pre-baseline MRI scans, data confirming true progression at baseline), and the granularity of data submitted in the application (e.g., narratives describing clinical improvements associated with responses).

An important consideration in this disease setting is the determination of whether an observed response is due to the effect of dordaviprone vs. an alternative factor, such as prior radiation. The Applicant provided supportive evidence of true progression at baseline, including the finding that all responders had at least increased tumor burden noted on the radiology report for their baseline scan (Table 8.8). In addition, among responding patients, one patient had pathological confirmation of progressive disease, 2 patients had new lesions outside their primary tumor site, and 6 had other imaging signs of progression, such as hyperperfusion, restricted diffusion, or elevated Cho/Cr ratio on MR spectroscopy (MRS). Based on the available data, the observed responses appeared to be true responses rather than a delayed effect of radiation or other treatment-related change.

Table 8.8: Supportive Evidence of True Progression at Baseline for RANO 2.0 Responders in Integrated Efficacy Population (N=11)

RANO 2.0 Responders (N=11)	Age / Sex	Prior systemic Treatment	Time from Radiation (months)	Supportive Evidence of True Progression at Baseline			
				PD at enrollment per investigator	Increased tumor burden on ≥ 2 MRIs post-radiation	New lesion or pathological confirmation	Other imaging evidence
(b) (6)	22 / F	TMZ	4.6	X	X		
	38 / M	TMZ	3.2	X			Hyperperfusion
	55 / F	TMZ	5.3	X		New lesion	
	22 / F	TMZ	7.0	X		Path confirm	
	51 / M	TMZ	5.6	X	X		
	54 / M	TMZ, TTF	3.0	X			Hyperperfusion
	37 / M	TMZ, CCNU	9.1	X	X		↑ Cho:Cr on MRS
	8 / M	dasatinib, BEV, everolimus	7.8	X	X		Restricted diffusion

(b) (6)	24 / F	TMZ	4.0	X			
	51 / M	TMZ	7.6	X	X	New lesion	Hyperperfusion
	29 / F	TMZ, TTF	4.0	X	X		Hyperperfusion

BEV: bevacizumab; CCNU: lomustine; MRS: Magnetic Resonance Spectroscopy; PD: Progressive Disease; TMZ: temozolomide; TTF: tumor-treating fields

Source: FDA analysis of NDA 219876 ADSL, ADTTE, and ADEFF datasets and clinical narratives

Timeline and Durability of Responses

In addition to the evaluation of true progression at baseline, FDA considered the timing of onset of responses with respect to initial diagnosis, receipt of last dose of radiation, and initiation of dordaviprone; duration of response; and time to initiation of another anticancer therapy (Table 8.9). Overall, patients had durable responses and, in many cases, continued on dordaviprone beyond the time of radiographic progression, as was permitted per protocol for patients who were continuing to derive benefit from treatment per the investigator.

Table 8.9: Timeline of Responses for RANO 2.0 Responders in Integrated Efficacy Population (N=11)

RANO 2.0 Responders (N=11)	Time from Initial Diagnosis to treatment start[a] (months)	Time from Radiation to treatment start (months)	RANO 2.0 Response	Time from treatment start to initial response (months)	Duration of RANO 2.0 response (months)	Reason for end of RANO 2.0 response (event/censor)	Treatment duration prior to other anticancer treatment (months)
(b) (6)	17.0	4.6	PR	4.8	28.3	PD	41.8
	6.3	3.2	PR	1.9	12.6	PD	15.2
	7.6	5.3	PR	1.9	7.3	PD	12.0
	9.2	7.0	MR	4.5	0.9	PD	15.2
	7.5	5.6	PR	15.7	2.1	Censored (at last MRI assessment without an event)	Unknown[b]
	5.5	3.0	PR	7.4	11.1	Censored (for anticancer therapy)	18.5
	11.7	9.1	PR	2.7	15.1	PD	24.3
	10.6	7.8	PR	3.5	9.2	PD	26.8
	6.7	4.0	MR	3.6	9.2	PD	16.1

(b) (6)	10.7	7.6	PR	2.6	10.3	PD	12.9
	6.6	4.0	MR	7.3	3.7	Censored (for anticancer therapy)	11.0

[a]Initiation of dordaviprone

[b]Patient considered lost to follow-up 27 months after treatment start

MR: minor response; PD: progressive disease; PR: partial response

Source: FDA analysis of NDA 219876 ADSL, ADTTE, and ADEFF datasets

Correlation Between Responses and Clinical Improvements

Tumor responses based on imaging were supported by signs of clinical improvements, per investigator assessment, in all responders (Table 8.10), most with improving focal motor weakness, cranial neuropathies or ataxia, and many with other broader improvements in functioning such as being able to work or travel again. Patients with minor responses had clinically meaningful improvements and based on the totality of data, FDA determined it was reasonable to include patients with minor responses per RANO 2.0 criteria in the calculation of ORR.

Table 8.10: Clinical Improvements Observed for RANO 2.0 Responders in Integrated Efficacy Population (N=11)

RANO 2.0 Responders (N=11)	Age / Sex	Tumor Location	RANO 2.0 Response	RANO 2.0 DOR (months)	Clinical improvements per investigator after starting dordaviprone
(b) (6)	22 / F	Thalamus	PR	28.3	Returned to college, "able to lead a normal life"
	38 / M	Thalamus	PR	12.6	Improved diplopia and paresthesias, tolerated steroid wean "for the first time in months"
	55 / F	Cerebellum	PR	7.3	Improved left facial weakness and ataxia; weaned off steroids
	22 / F	Thalamus	MR	0.9	Improved concentration, attention, executive functioning
	51 / M	Brainstem	PR	2.1	Improved diplopia, able to travel independently and maintain his job; "supporting himself financially was important to him"
	54 / M	Thalamus	PR	11.1	Improved gait stability; weaned off steroids

(b) (6)					
	37 / M	Thalamus	PR	15.1	Improved right-sided weakness; able to go back to work on his cattle farm and attend his four children's school events
	8 / M	Thalamus	PR	9.2	Improved vision, hemiparesis, and speech; able to return to school, run with an assistive device, and "thriving"
	24 / F	Thalamus	MR	9.2	"Preservation of her cognitive and physical abilities"
	51 / M	Thalamus	PR	10.3	Improved upgaze paralysis and ptosis
	29 / F	Thalamus	MR	3.7	Improved headaches; weaned off steroids

Source: FDA analysis of NDA 219876 ADSL, ADTTE, and ADEFF datasets, and clinical narratives

Data Quality and Integrity

Data / The Applicant's Position:

During the COVID-19 pandemic, all studies contributing to the primary efficacy analysis set remained active, with ongoing patient enrollment and treatment. To prioritize safety while maintaining study integrity, the sponsor issued guidelines that enabled remote assessments for imaging and laboratory tests, adapting to standard care considerations and minimizing patient risk. Despite these adjustments, regular imaging and evaluations continued, ensuring thorough data collection for key safety and efficacy evaluations. These adaptations were considered to minimally impact the interpretability of the study results and the assessment of dordaviprone's efficacy and safety in patients with glioma.

Overall, the data quality and integrity were deemed sufficient to support the conduct of the studies, the primary data analyses, and the conclusions drawn from the studies.

The FDA's Assessment:

FDA agrees with the Applicant's position. The data submitted were organized and adequate to perform a complete review of the safety of dordaviprone. FDA issued several information requests during the review cycle to obtain clarification and additional information regarding safety data included in the NDA and all requests were addressed appropriately.

Efficacy Results – Secondary and other relevant endpoints

Data:

Other Measures of Clinical Benefit

Other measures of clinical benefit included assessing the reduction in corticosteroid dose and improvement in performance status. Patients were considered evaluable for corticosteroid response if their baseline dose was ≥4 mg dexamethasone-equivalent, and evaluable for performance status response if their baseline KPS/LPS was ≤80.

The corticosteroid response rate was 43.8% (7 of 16 patients; 95% CI: 19.8-70.1), with a median time to response of 3.7 months (range: 1.9 to 5.6). The performance status response rate was 18.2% (6 of 33 patients; 95% CI: 7.0-35.3), with a median time to response of 2.7 months (range: 1.9 to 16.9). Additionally, qualitative assessments of clinical benefit reported by investigators, caregivers, and family members were included in the efficacy narratives for patients in the primary efficacy analysis set. Notably, these observations supported the use of RANO 2.0, confirming its appropriateness in capturing clinically relevant radiological changes, as clinical benefit was observed for patients with responses according to RANO-HGG and/or RANO-LGG criteria.

Survival

The OS rates after the first dose of dordaviprone as a single agent were 57.5% (95% CI: 41.7-70.5) at 12 months, and 37.6% (95% CI: 23.2-51.9) at 24 months.

The PFS rates according to RANO 2.0 criteria after the first dose of dordaviprone as a single agent were 32.4% (95% CI: 18.9-46.7) at 6 months, and 27.0% (95% CI: 14.5-41.1) at 12 months.

The Applicant's Position:

Other clinical endpoints including corticosteroid dose reduction, improved performance status, and longer survival support the clinical benefit of dordaviprone in adult and pediatric patients with recurrent H3 K27M-mutant diffuse glioma.

The FDA's Assessment:

While FDA agrees that other measures of potential clinical improvement, such as reduction in corticosteroid dose or improvement in performance status, may be valuable to assess in this population, these endpoints were considered supportive only in the context of an open-label, single-arm trial.

In addition, time-to-event endpoints such as overall survival and progression-free survival are challenging to interpret in the setting of single arm trials. Acknowledging the limitations of these analyses, FDA notes that the historical landmark estimate of median overall survival after progression is 4 to 6 months (Baugh et al, 2024; Coleman et al, 2023). The ongoing randomized trial in patients with H3 K27M-mutant glioma (Study ONC201-108) is designed to evaluated OS and PFS endpoints.

Dose/Dose Response

Data / The Applicant's Position:

Please refer to Section 6.2.2 for a discussion of dose.

The FDA's Assessment:

Refer to Section 6 for details regarding the recommended dosing regimen.

Durability of Response

Data:

According to the RANO 2.0 criteria, the median DOR in the primary efficacy analysis set was 10.4 months; see Table 8.11. The DOR was consistent when evaluated with RANO-HGG or RANO-LGG criteria, with a median DOR of 11.2 months and 10.4 months, respectively.

Table 8.11: Applicant – Duration of Response per RANO 2.0 by BICR Assessment (Primary Efficacy Analysis Set)

Duration of Response	RANO 2.0 N=50
Median (95% CI)[a], months	10.4 (7.4, 15.4)
% with observed DoR ≥6 months	84.6%
% with observed DoR ≥12 months	37.6%
% with observed DoR ≥24 months	12.5%

Abbreviations: BICR=blinded independent central review; CI=confidence interval; DoR=Duration of Response; RANO=Response Assessment in Neuro-Oncology.
[a.] Based on Kaplan-Meier estimate.
Source: m2.7.3.2.2, Table 4; m5.3.5.3, Time to event analysis data (adtte.xpt)

The Applicant's Position:

Dordaviprone demonstrated durable responses in adult and pediatric patients with recurrent H3 K27M-mutant diffuse glioma, with a response duration of 10.4 months, surpassing the expected effects of radiotherapy alone. These responses were not attributed to residual effects of prior radiotherapy or pseudoprogression, as treatment with dordaviprone began at least 90 days after the completion of radiotherapy, in accordance with RANO guidelines.

The FDA's Assessment:

Refer to "Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)" regarding FDA's assessment of durability of response.

Persistence of Effect

The Applicant's Position:

Dordaviprone was assessed in open-label clinical studies that did not include control groups, which precludes direct comparisons. Evidence supporting the sustained efficacy of dordaviprone is detailed in the previously discussed "Durability of Response" section.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

No analyses of patient-reported outcome assessments were included in this application.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Additional Analyses Conducted on the Individual Trial

Data:

Association of Objective Response with Other Measures of Clinical Benefit

RANO 2.0 response was significantly associated with OS as a time-varying covariate in a multivariate Cox Proportional Hazards model (hazard ratio 0.22 [95% CI: 0.08-0.58]; p=0.0024). Additionally, multiple enhancing target lesions and tumor size were also significant factors in the final model. Patients who had an objective response by RANO 2.0 were more likely to be alive at 12 months (100%) and 24 months (86%), and to remain progression-free at 12 months (64%).

All RANO 2.0 responders who were evaluable for the corticosteroid response endpoint (5 of 5, 100%) experienced a reduction in corticosteroid usage. Among the RANO 2.0 responders evaluable for the performance status endpoint, 63% (5 out of 8) showed an improvement in performance status.

The Applicant's Position:

Patients who responded to treatment with dordaviprone demonstrated consistent clinical benefits that extended beyond radiographic assessments, including reduced corticosteroid doses, improved performance status, and longer survival.

The FDA's Assessment:

FDA considers these analyses exploratory. Responder analyses have multiple limitations, particularly that differences between responders and non-responders may reflect patient characteristics rather than treatment effects.

The FDA has performed a subgroup analysis of ORR per BICR according to RANO 2.0 criteria. The results are presented in Table 8.12. The results should be interpreted with caution due to limited sample size.

Table 8.12: Subgroup Analysis of ORR per BICR According to RANO 2.0 in Integrated Efficacy Population (N=50)

	ORR (95% CI)
Age Group	
2 to < 18 years (n=4)	25% (0.63%, 81%)
18 to < 65 years (n=45)	22% (11%, 37%)
≥ 65 years (n=1)	0
Sex	
Male (n=27)	22% (9%, 42%)
Female (n=23)	22% (7%, 44%)
Race	
White (n=40)	23% (11%, 38%)
Black or African American (n=3)	0
Asian (n=1)	0
American Indian or Alaska Native (n=1)	0
Other/Unknown (n=5)	40% (5%, 85%)
Ethnicity	
Hispanic or Latino (n=4)	0
Not Hispanic or Latino (n=42)	21% (10%, 37%)
Unknown (n=4)	50% (7%, 93%)

ORR: overall response rate; CI: confidence interval.
Source: FDA analysis of NDA 219876 ADSL, and ADEFF datasets

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Refer to "Integrated Assessment of Effectiveness" in Section 8.1.5.

8.1.4. Assessment of Efficacy Across Trials

Data:

Efficacy Observed in Additional Efficacy Analysis Sets

The efficacy of dordaviprone was evaluated in 2 additional efficacy sets: the non-midline analysis set and 2 supportive cohorts (Study ONC013 Arm B for adults and Study ONC014 Arm F for pediatrics); see Table 8.13. Each of these analysis sets is further detailed in the subsections below.

Table 8.13: Applicant – Additional Efficacy Analysis Sets by Study

Analysis Set	ONC006	ONC013	ONC014	ONC018	ONC016	Total
Non-midline Analysis Set	4	0	1[a]	0	0	5
Supportive Cohorts	0	30 (Arm B)	11[a] (Arm F)	0	0	41

[a] No patients in ONC014 Arm F were included in the primary efficacy analysis set; 1 patient in this arm was included in the non-midline analysis set.
The all-treated analysis set was defined as all patients who received at least one dose of dordaviprone in ONC006, ONC013, ONC014, ONC018, and ONC016.
Source: m2.7.3, Table 3

Non-Midline Analysis Set

The efficacy of dordaviprone was further assessed in patients with recurrent non-midline H3 K27M-mutant diffuse glioma, defined as the non-midline analysis set. This set followed the same enrollment and data cutoff dates, and BICR process as the primary efficacy analysis set, with the key distinction in selection criteria being the exclusion of patients with midline tumor locations. A total of 5 patients with recurrent non-midline H3 K27M-mutant glioma met these criteria.

Within this non-midline analysis set, the ORR by BICR was 40% (2 of 5 patients), assessed using either RANO-LGG or RANO 2.0 criteria. Both responders were alive at the last follow-up, with an OS of at least 17.0 months and 41.2 months, respectively.

Supportive Cohorts (ONC013 Arm B and ONC014 Arm F)

In support of the efficacy findings in the primary efficacy analysis set, 2 studies included additional cohorts that prospectively enrolled patients with eligibility criteria that were largely consistent with the primary efficacy analysis set and reflective of changes in RANO guidance: ONC013 Arm B in adults and ONC014 Arm F in pediatrics. None of these patients were included in the primary efficacy analysis set.

In ONC013 Arm B, 16.7% of patients (5 of 30 patients) responded to dordaviprone with a median response duration of 15.0 months and a median OS of 14.8 months, with 26.3% of patients surviving to 24 months.

In ONC014 Arm F, 18.2% of patients (2 of 11 patients) had radiographic responses. The median OS was 8.2 months, with 27.3% of patients surviving to 12 months. One patient, who achieved over 50% tumor reduction, was assessed as having stable disease for overall response by RANO due to increased corticosteroid use. The other responding patient had a non-midline glioma and was assessed with PR by the investigator via RANO-HGG, a response duration of 8.5 months; this patient was also included in the non-midline analysis set and evaluated by BICR.

Table 8.14: Applicant – Dordaviprone Efficacy Supportive Cohorts (ONC013 Arm B and ONC014 Arm F)

	Recurrent/Progressive H3 K27M mutant Glioma	
	ONC013 Arm B (Adults) N=30	**ONC014 Arm F (Pediatric) N=11**
Best overall response (investigator assessment), n (%)		
Partial response	5 (16.7)	1 (9.1)
Stable disease	10 (33.3)	1 (9.1)[a]
Progressive disease	11 (36.7)	9 (81.8)
No assessment	4 (13.3)	0
Overall response rate (investigator assessment), n (%)		
Responders	5 (16.7)	1 (9.1)
Exact 95% CI	(5.6 – 34.7)	(0.2 – 41.3)
Disease control rate (investigator assessment), n (%)		
Controlled	15 (50.0)	2 (18.2)
Exact 95% CI	(31.3 – 68.7)	(2.3 – 51.8)

Abbreviations: CI=confidence interval; NR=not reached.
Tumor response was assessed by the investigator per RANO criteria.
[a] One patient with a >50% tumor reduction (product of diameters of the target lesion) was not reflected as a partial response by RANO criteria due to a corticosteroid dose increase from 0 to 2.5 mg of dexamethasone per day; the best response in this patient was assessed as stable disease.
Source: m2.7.3, Table 11 and Table 13; m5.3.5.3, Efficacy analysis data (adeff.xpt)

Efficacy Observed in Other Recurrent H3 K27M-mutant Glioma Patients

In the studies involving glioma patients, some patients with recurrent H3 K27M-mutant gliomas were not included in the primary efficacy analysis set, non-midline analysis set, or supportive cohorts that assessed dordaviprone's efficacy and clinical benefit. These patients were excluded either because they did not meet all inclusion criteria for the primary efficacy analysis set, or because they were enrolled after the initial 50 patients had already been included. Additionally, some patients who demonstrated benefits were excluded from the primary efficacy analysis set

due to disease characteristics associated with poor prognosis, such as DIPG, spinal disease, or leptomeningeal involvement.

Efficacy and benefits for these excluded patients are detailed in individual efficacy narratives. Reported benefits include investigator-assessed RANO responses, durable stable disease in patients with progressing tumors at study entry, reductions in tumors not qualifying for a RANO response for various reasons, such as non-measurable disease at baseline, and other clinical benefits noted by investigators. The activity of dordaviprone was consistently observed in patients with recurrent H3 K27M-mutant gliomas across both midline and non-midline tumor locations.

Notably, no responses to dordaviprone have been documented in patients whose gliomas do not carry the H3 K27M mutation.

The Applicant's Position:

The antitumor effects of dordaviprone observed in adult and pediatric patients with recurrent H3 K27M-mutant diffuse glioma in the primary analysis are supported by consistent RANO responses in both the non-midline analysis set and supportive cohorts.

Individual clinical efficacy case narratives include patients who responded to dordaviprone treatment or experienced other notable clinical benefits, including MRs. These narratives support the relevance of the clinical improvements experienced by offering additional clinical context for individual patient experiences. They also detail cases where patients might not have met all selection criteria to specifically isolate the effect of dordaviprone monotherapy, or did not meet all the formal response requirements but still showed signs of clinical benefit.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the efficacy results in patients with H3 K27M-mutant non-midline tumors (i.e., frontoparietal and temporal locations), as well as investigator assessed cohorts from ONC013 and ONC014, provide supportive data for this application. The number of patients in each of these cohorts was small and therefore these results do not independently provide substantial evidence of effectiveness of dordaviprone; however, the observation of responses in each of these additional cohorts is supportive of the primary efficacy results and was considered as contributing to confirmatory evidence necessary to establish substantial evidence of effectiveness.

Overall population treated with dordaviprone

FDA conducted additional analyses in order to understand the primary efficacy results in the context of the broader population of patients with glioma who received dordaviprone across clinical studies. Of the 434 patients with glioma enrolled across the five clinical studies (ONC006, ONC013, ONC014, ONC016, and ONC018), 377 patients received the recommended

dosage of dordaviprone. Of those, 296 patients' tumors harbored an H3 K27M mutation. Notably, there were no responders in the 24 patients who were known to be H3 K27M wildtype.

In 220 patients who received the recommended dosage of dordaviprone, harbored an H3 K27M mutation and were enrolled in the recurrent disease setting, objective responses per investigator-assessed RANO-HGG criteria were observed in adult and pediatric patients, patients with DIPG and non-DIPG, and patients with midline and non-midline locations. Measurement of ORR in the broader population is limited by heterogeneity and inclusion of patients who did not have measurable disease at baseline or were not otherwise evaluable for objective response.

Ninety-three (93) of these 220 patients met the integrated efficacy population eligibility criteria. As described in the "Patient Disposition" section, patients were excluded from the primary efficacy population if they did not meet the pre-defined criteria. The general categories of exclusion included tumor location and associated disease characteristics; insufficient washout periods from prior therapy (primarily radiation); clinical factors such as low performance status or fluctuating steroid dose; H3 K27M mutation status negative or unknown; and non-recurrent treatment setting. BICR assessments were not available for this broader population of patients. The investigator-assessed ORR per RANO-HGG criteria was 15% (14/93 patients); while slightly numerically lower than the ORR of 20% in the first 50 patients who met eligibility criteria (i.e., integrated efficacy population), the confidence intervals overlap.

Newly Diagnosed H3 K27M-mutant DMG

The larger population of patients studied across the five clinical studies (ONC006, ONC013, ONC014, ONC016, and ONC018) included patients with newly diagnosed H3 K27M-mutant DMG, both patients who had not yet received radiation (n=14) and those who had not yet progressed post-radiation (n=61). Although it is challenging to isolate the effect of the dordaviprone from radiation in this setting, responses were observed per investigator as assessed by RANO-HGG criteria (Table 8.15).

Table 8.15: ORR in Patients with Newly Diagnosed H3 K27M-mutant glioma (N=75)

Population		**ORR by investigator per RANO-HGG, N (%)**
H3 K27M-mutant glioma, received recommended dosage, newly diagnosed setting (including post-radiotherapy without recurrence/progression)		11/75 (15)
Age	Adult (≥ 17 years)	4/17 (24)
	Pediatric (< 17 years)	7/58 (12)
	Non-DIPG	5/31 (16)

Pontine vs. non-pontine location	DIPG	6/44 (14)
Midline vs. non-midline location	Midline	11/74 (15)
	Non-midline	0/1 (0)

Source: FDA analysis of NDA 219876 ADSL, ADEFF datasets

Pediatric Patients

The Applicant submitted data to assess the safety and efficacy of dordaviprone in pediatric patients in addition to adult patients with H3 K27M-mutant DMG. The primary efficacy population (N=50) includes three patients younger than 17 years of age:

- ONC014-[(b) (6)] 9-year-old male diagnosed 5 months prior to treatment, completed radiation 3 months prior to treatment, whose best overall response was stable disease and he remained on treatment for 4.5 months
- ONC014-[(b) (6)] 14-year-old male diagnosed 23 months prior to treatment, completed radiation 12 months prior to treatment, whose best overall response was progressive disease and he remained on treatment for 1.3 months
- ONC018-[(b) (6)] 9-year-old male diagnosed 10 months prior to treatment, completed radiation 8 months prior to treatment, whose best overall response was partial response and he remained on treatment for 48 months

In addition to pediatric patients in the primary efficacy population, ONC014 was a dedicated pediatric study that enrolled 134 patients across 7 arms (cohort eligibility varied by H3 K27M mutation status, disease location, and disease status), and ONC018 was an expanded access protocol that enrolled 52 patients younger than 17 years of age.

Responses were observed across the pediatric population (Table 8.16), however due to the variability and timing of prior therapies and disease status, it is challenging to draw conclusions about efficacy in the broader population of pediatric patients outside the primary efficacy population. In addition, response assessment is only available per RANO-HGG criteria.

Table 8.16: ORR in Pediatric Patients with H3 K27M-mutant glioma (N=108)

Population		**ORR by investigator per RANO-HGG, N (%)**
H3K27M-mutant glioma, received recommended dosage, age < 17 years		11/108 (10)
Disease status*	Recurrent	4/49 (8)
	Post-RT non-recurrent	5/45 (11)

	Newly diagnosed	2/13 (15)
Pontine vs. non-pontine location	Non-DIPG	5/46 (11)
	DIPG	6/62 (10)
Midline vs. non-midline location	Midline	10/106 (9)
	Non-midline	1/2 (50)

*One patient had unknown disease status

Source: FDA analysis of NDA 219876 ADSL, ADEFF datasets

Overall, the number of patients in each of these sub-analyses was generally small, and the populations heterogeneous; therefore, these results do not independently provide substantial evidence of effectiveness of dordaviprone. However, the observation of responses in each of these additional cohorts is supportive of the primary efficacy results.

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable

8.1.5. Integrated Assessment of Effectiveness

Data / The Applicant's Position:

This NDA is based on the results from the primary efficacy analysis set, which serves as an integrated assessment of effectiveness encompassing findings from 5 completed, open-label clinical studies (ONC006, ONC013, ONC014, ONC016, and ONC018). This dataset has been presented in the preceding subheadings, addressing the efficacy endpoints and outcomes.

The FDA's Assessment:

The efficacy of dordaviprone was evaluated in adult and pediatric patients with glioma across five open label, non-randomized clinical studies conducted in the U.S. (ONC006 [NCT02525692], ONC013 [NCT03295396], ONC014 [NCT03416530], ONC016 [NCT05392374], and ONC018 [NCT03134131]). Due to the rarity of the disease and poor prognosis, and in order to evaluate a sufficiently homogenous patient population to assess the effect of the drug, FDA determined it was reasonable to consider safety and efficacy data from a pooled population of patients derived from single arm trials of dordaviprone monotherapy at the recommended dosage in adults and pediatric patients with recurrent H3K27M-mutant DMG who met pre-specified criteria. Specifically, eligible patients were required to have progressive and

measurable disease per Response Assessment in Neuro-Oncology-High Grade Glioma (RANO-HGG) criteria, be ≥90 days post radiation therapy, have adequate washout from prior anticancer therapies, have a Karnofsky Performance Status/Lansky Performance Status (KPS/LPS) score ≥ 60, and have stable or decreasing corticosteroid use. Patients received a weight-based dose of dordaviprone until disease progression or unacceptable toxicity.

The integrated efficacy population included 50 patients who met the pre-defined criteria. The major efficacy outcome measure was overall response rate (ORR) assessed by blinded independent central review (BICR) according to RANO 2.0 criteria. Additional efficacy outcome measures were BICR-assessed ORR according to RANO-HGG criteria and Response Assessment in Neuro-Oncology-Low Grade Glioma (RANO-LGG) criteria, duration of response, and time to response.

The ORR assessed by BICR according to RANO 2.0 criteria was 22% (95% CI: 12, 36), with 16% partial responses and 6% minor responses. The median duration of response (DOR) was 10.3 months (95% CI: 7.3, 15.2), with an observed DOR of ≥ 6 months in 73% of responders and ≥ 12 months in 27%. In this population with a high unmet medical need, and for which there are no available therapies in any setting, a durable ORR is considered a clinically meaningful intermediate endpoint given that spontaneous responses are not observed in this disease setting and median overall survival after progression is typically 4 to 6 months (Baugh et al, 2024; Coleman et al, 2023). Potential limitations to the evaluation of objective responses in brain tumor imaging were mitigated by the study design (i.e., requiring at least 3 months from the time of last radiation), the collection of relevant data (e.g., pre-baseline MRI scans, data confirming true progression at baseline), and the granularity of data submitted in the application (e.g., narratives describing clinical improvements associated with responses).

Supportive efficacy data included BICR-assessed objective responses observed in patients with H3 K27M-mutant non-midline gliomas (i.e., hemispheric location), investigator-assessed objective responses in patients with recurrent H3 K27M-mutant DMG from other cohorts in Studies ONC013 and ONC014 (including patients with DIPG), investigator-assessed objective responses in patients with newly diagnosed H3 K27M-mutant DMG (i.e., an earlier line setting), and the lack of objective responses in patients with H3 K27M-wildtype disease.

The Applicant intends to verify and describe the clinical benefit of dordaviprone based on the results of an ongoing randomized trial in patients with newly diagnosed H3 K27M-mutant glioma (Study ONC201-108) which is >50% enrolled as of July 2025. This study is a multi-regional, double-blind, randomized controlled trial of 450 patients with H3 K27M-mutant DMG as determined by local CLIA-certified laboratory testing randomized 1:1:1 to receive dordaviprone 625 mg once weekly, dordaviprone 625 mg twice weekly, or placebo until disease progression or unacceptable toxicity. Stratification factors include age (< 21 vs. ≥ 21 years) and higher risk vs. lower risk features (higher risk category = enhancing tumor size ≥10 cm^2, multifocal lesions, brainstem location). The dual primary endpoints are OS and PFS as per RANO-HGG criteria. Two interim analyses are planned after 164 (50% information) and 246

(75% information) deaths, with a final analysis after 327 death events have been observed. The final analysis for PFS will be completed when 286 PFS events have been observed.

8.2. Review of Safety

8.2.1. Safety Review Approach

Data:

The integrated safety analysis set for dordaviprone includes data from 422 adult and pediatric glioma patients who were enrolled in 4 completed, open-label clinical studies (ONC006, ONC013, ONC014, and ONC018), as detailed in Table 8.17. Safety data are presented both for the overall set and are summarized by age category and treatment settings.

The integrated safety data were analyzed for adverse events (AEs) starting on or after the date of the first dose of dordaviprone up to 30 days after the last dose, before the initiation of additional anticancer therapies. This analysis highlights the safety profile of dordaviprone monotherapy, focusing on AEs with an onset before the initiation of additional anticancer therapies.

Table 8.17: Applicant – Summary of Patients in the Integrated Safety Analysis Sets by Study

Analysis Set	ONC006	ONC013	ONC014	ONC018	Total
Integrated Safety Analysis Set – post-baseline data through 30 days after the last dose and prior to the initiation of additional anticancer therapies	84	73	134	131	422

Patients in each of the 4 studies were monitored for safety throughout the treatment period, with significant changes in vital signs or physical findings reported as AEs. Adverse events were graded by severity per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5 guidelines.

All patients who received at least 1 dose of dordaviprone were included in the safety analysis set of the relevant study. Safety assessments included AEs, serious adverse events (SAEs), laboratory parameters (including hematology and chemistry), vital signs, physical examinations, and all concomitant medications, procedures, and additional anticancer therapies. End of treatment assessments were conducted within 30 days after the last dose of dordaviprone, unless medical conditions prevented travel. Follow-ups continued until the resolution or stabilization of any serious or reportable AEs that occurred during treatment or within 30 days of the last dose.

Additionally, supportive safety data from 9 clinical pharmacology studies involving 235 adults helped characterize the safety and PK of dordaviprone in both healthy and special populations (those with renal or hepatic impairment). The integrated safety analysis set does not include data from single-patient compassionate use protocols, ongoing studies, non-glioma indication studies, or IITs. However, these sources did provide additional SAE data for the use of dordaviprone

across a broader population, which is included in the NDA package.

In the integrated safety analysis set, the most frequently reported AEs (>20% of patients; all causalities) in glioma patients were fatigue, headache, vomiting, and nausea, with less frequent but still notable AEs (>10% to 20%) including gait disturbance, hemiparesis, lymphocyte count decreased, dysarthria, muscular weakness, hyperglycemia, dysphagia, dizziness, alanine aminotransferase (ALT) increased, and constipation. The majority of these events were mild to moderate in intensity, with many considered not related to dordaviprone. The most common (>5% patients) Grade ≥3 AEs were hydrocephalus and disease progression. Treatment-related SAEs occurred in 3.6% of patients, with no treatment-related deaths reported.

Overall, dordaviprone administered at the proposed once weekly dose for adults (625 mg) and pediatric patients (dose scaled by body weight) with glioma demonstrated a manageable and well-tolerated safety profile, with few dose reductions or discontinuations due to treatment-related issues.

The Applicant's Position:

A thorough review of the integrated safety analysis set, which includes data from 422 adult and pediatric glioma patients, provides an adequate overview of the safety profile for dordaviprone monotherapy and its proposed indication. The supportive data from clinical pharmacology studies, single-patient compassionate use protocols, ongoing studies, non-glioma indication studies, and IITs reinforce the safety conclusions for dordaviprone in the target patient population.

The FDA's Assessment:

FDA agrees with the Applicant's position that the integrated safety analysis set for dordaviprone includes data from 422 patients with glioma who were enrolled in 4 open-label clinical studies (ONC006, ONC013, ONC014, and ONC018).

Safety was not systematically collected in ONC016, an expanded access protocol, and therefore those 12 patients, including one patient included in the primary efficacy population, are not included in the integrated safety analysis set.

Of the 422 patients in the integrated safety analysis set, 46 patients received a dose other than the recommended dose or the equivalent body weight-adjusted dose for patients weighing < 52.5 kg (<RP2D, N=34; >RP2D, N=12).

Therefore, FDA considers the **overall safety population** to include **376 patients** with glioma who received dordaviprone monotherapy at the recommended dose or the equivalent body weight-adjusted dose for patients weighing < 52.5 kg.

The **primary efficacy safety population** includes **49 patients** with H3 K27M-mutant recurrent diffuse midline glioma (DMG) who received dordaviprone monotherapy at the recommended

dose. One patient in the primary efficacy population received a dose of 625 mg once every 3 weeks and was excluded from the safety analyses.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 8.18 summarizes dordaviprone exposure for the integrated safety analysis set. The majority of patients (89%) received dordaviprone at a dose of 625 mg (or the equivalent body weight-adjusted dose in pediatrics) once weekly; 8% were assigned to a lower dose or dosing frequency due to the dose escalation/titration study design; and 2.8% received 625 mg (or the equivalent body weight-adjusted dose in pediatrics) twice weekly on 2 consecutive days. Of the 422 patients treated, 34.1% had treatment exposure for at least 6 months, and 16.4% were exposed for at least 1 year.

Table 8.18: Applicant – Dordaviprone Exposure (Integrated Safety Analysis Set)

	Adult Post-RT Non-Recurrent N=17	Adult Recurrent N=225	Pediatric[a] Newly Diagnosed N=28	Pediatric Post-RT Non-Recurrent N=69	Pediatric Recurrent N=82	Overall N=422
Dose, n (%)						
<RP2D	1 (5.9)	18 (8.0)	6 (21.4)	6 (8.7)	3 (3.7)	34 (8.1)
RP2D	14 (82.4)	207 (92.0)	22 (78.6)	57 (82.6)	75 (91.5)	376 (89.1)
>RP2D	2 (11.8)	0	0	6 (8.7)	4 (4.9)	12 (2.8)
Duration of time (months) on dordaviprone [b]						
Mean (SD)	13.3 (13.19)	6.4 (9.74)	7.8 (3.69)	10.9 (11.89)	4.2 (6.13)	7.1 (9.69)
Median	9.6	2.6	7.1	6.8	2.6	3.6
Q1, Q3	3.6, 13.3	1.4, 6.6	5.3, 9.8	3.3, 14.9	1.2, 4.7	1.7, 8.5
Min, Max	2.8, 46.7	0.0, 86.2	0.0, 17.5	1.0, 61.4	0.0, 48.1	0.0, 86.2
Duration category, n (%)						
≥1 month	17 (100)	193 (85.8)	27 (96.4)	68 (98.6)	67 (81.7)	373 (88.4)
≥2 months	17 (100)	124 (55.1)	27 (96.4)	63 (91.3)	46 (56.1)	278 (65.9)
≥3 months	16 (94.1)	104 (46.2)	27 (96.4)	53 (76.8)	33 (40.2)	233 (55.2)
≥6 months	9 (52.9)	61 (27.1)	19 (67.9)	37 (53.6)	18 (22.0)	144 (34.1)
≥9 months	9 (52.9)	45 (20.0)	9 (32.1)	28 (40.6)	10 (12.2)	101 (23.9)
≥12 months	6 (35.3)	35 (15.6)	3 (10.7)	19 (27.5)	6 (7.3)	69 (16.4)
≥18 months	4 (23.5)	20 (8.9)	0	13 (18.8)	1 (1.2)	38 (9.0)
≥24 months	3 (17.6)	12 (5.3)	0	7 (10.1)	1 (1.2)	23 (5.5)
Total dose reductions, n (%)	**1 (5.9)**	**12 (5.3)**	**5 (17.9)**	**9 (13.0)**	**2 (2.4)**	**29 (6.9)**

	Adult Post-RT Non-Recurrent N=17	Adult Recurrent N=225	Pediatric[a] Newly Diagnosed N=28	Pediatric Post-RT Non-Recurrent N=69	Pediatric Recurrent N=82	Overall N=422
Dose reductions associated with weight loss	0	0	1 (3.6)	5 (7.2)	1 (1.2)	7 (1.7)
Duration of time (months) on dordaviprone prior to the use of other anticancer therapy[c]						
Mean (SD)	11.8 (13.36)	4.6 (8.37)	6.5 (3.64)	9.7 (12.01)	3.3 (4.28)	5.6 (8.81)
Median	4.8	1.9	5.5	4.9	1.7	2.6
Q1, Q3	3.5, 13.3	1.1, 4.6	3.9, 8.8	2.6, 11.0	1.2, 3.7	1.3, 5.5
Min, Max	1.6, 46.7	0.0, 86.2	0.0, 13.6	0.0, 59.8	0.0, 26.8	0.0, 86.2
Duration category, n (%)						
≥1 month	17 (100)	175 (77.8)	27 (96.4)	66 (95.7)	63 (76.8)	349 (82.7)
≥2 months	16 (94.1)	101 (44.9)	26 (92.9)	60 (87.0)	39 (47.6)	243 (57.6)
≥3 months	15 (88.2)	79 (35.1)	24 (85.7)	45 (65.2)	25 (30.5)	188 (44.5)
≥6 months	7 (41.2)	39 (17.3)	13 (46.4)	30 (43.5)	11 (13.4)	100 (23.7)
≥9 months	7 (41.2)	29 (12.9)	7 (25.0)	22 (31.9)	8 (9.8)	73 (17.3)
≥12 months	5 (29.4)	23 (10.2)	2 (7.1)	16 (23.2)	5 (6.1)	51 (12.1)
≥18 months	3 (17.6)	9 (4.0)	0	10 (14.5)	1 (1.2)	23 (5.5)
≥24 months	3 (17.6)	5 (2.2)	0	7 (10.1)	1 (1.2)	16 (3.8)

Abbreviations: RP2D=recommended Phase 2 dose (625 mg [or scaled by body weight] once weekly); RT=radiotherapy

[a] One patient in this group was 21 years old.

[b] Duration of time on dordaviprone (months) = last dose minus first dose + 1 day.

[c] Duration of time on dordaviprone prior to other use of other anticancer therapy(months)=last dose prior to use of other therapy minus first dose + 1 day.

Source: ISS Table 1.2; m5.3.5.3, Subject level analysis data (adsl.xpt)

The Applicant's Position:

The number of glioma patients treated and the extent of their exposure to the recommended dordaviprone dose of 625 mg, or the equivalent body weight-adjusted pediatric dose, administered once weekly allow for an adequate assessment of the safety profile of dordaviprone monotherapy in patients representative of the intended target population.

The FDA's Assessment:

FDA agrees with the Applicant's position that 376 patients with glioma received dordaviprone monotherapy at the recommended dose or the equivalent body weight adjusted dose for patients weighing < 52.5 kg. While 45% of patients in the overall population received dordaviprone for less than 3 months, this short duration of therapy was primarily driven by patients with recurrent disease. The median OS in the recurrent setting is approximately 4 to 6 months, with median progression-free survival of < 2 months based on historical estimates, thus these results reflect the natural history of this aggressive cancer.

Relevant characteristics of the safety population:

Data:

Within the integrated safety analysis set, the median patient age was 21.5 years (range: 3 to 80 years), with an age distribution as follows: 31% aged 2 to 11 years, 11.4% aged 12 to 17 years, 53.8% aged 18 to 64 years, and 3.8% aged 65 years or older. The racial composition was 75.1% White, 7.8% Black/African American, 3.8% Asian, 3.1% from other racial groups, with 10.2% unknown or not reported. Additionally, 12.1% were Hispanic or Latino. Most patients (66.6%) had a KPS/LPS of 80 to 100.

Relevant disease characteristics included primary tumor locations in the brainstem (45.5%), midline (excluding brainstem; 43.6%), and non-midline regions (10.9%). Furthermore, 34.4% of patients had DIPG, 29.1% presented with multifocal disease, 75.1% had a known H3 K27M mutation, and 72.7% had experienced disease recurrence.

The median time from initial diagnosis was 328 days for pediatric patients and 381 days for adults with recurrent disease. For those with non-recurrent disease, the median time was 118 days for pediatrics and 141 days for adults.

Nearly all patients (93.4%) received radiotherapy prior to enrollment in a dordaviprone clinical study. Temozolomide was the most frequently used antineoplastic agent before starting dordaviprone, especially among patients with recurrent disease (adults 91.6%; pediatrics 24.4%).

The Applicant's Position:

The patient population included in the integrated safety analysis set is generally representative of the target patient population in the proposed indication.

The FDA's Assessment:

FDA agrees with the Applicant's position that the demographic and disease characteristics are generally representative of the target patient population in the proposed indication.

The Applicant described the integrated safety analysis set of 422 patients with glioma who received dordaviprone at any dose.

Table 8.19 includes the demographic and disease characteristics for the 376 adult and pediatric patients with glioma across four open-label clinical studies (ONC006, ONC013, ONC014, and ONC018) who received dordaviprone at the recommended dose or the equivalent body weight-adjusted dose for patients weighing < 52.5 kg.

Table 8.19: Demographics and Disease Characteristics of Overall Safety Population

	Overall Safety Population (N=376)
Median age, years (range)	23 (3, 80)

		Overall Safety Population (N=376)
Age Group, %	2 to < 18 years	41
	18 to < 65 years	55
	≥ 65 years	4
Sex, %	Male	48
	Female	52
Race, %	White	74
	Black or African American	9
	Asian	4
	American Indian/Alaska Native	<1
	Native Hawaiian/Pacific Islander	<1
	Other/Multiple/Unknown	12
Ethnicity, %	Hispanic or Latino	13
	Not Hispanic or Latino	78
	Unknown	9
Region, %	United States	100
Baseline performance score (KPS), %	90-100	34
	80	32
	60-70	27
	< 60	7
	Missing	<1
Median time from prior radiation, months (range)		5.9 (0.2, 102.3)
Median time from initial diagnosis, months (range)		9.4 (0.1, 336.7)
Disease Status, %	Recurrent	75
	Newly Diagnosed	6
	Post-radiation, non-recurrent	19

		Overall Safety Population (N=376)
	Unknown	<1
Primary Tumor Location per investigator, %	Midline Ex-Brainstem	46
	Brainstem	45
	Non-Midline	9
DIPG, %	DIPG	33
	Non-DIPG	67
Spinal disease present, %	Yes	8
	No	92
Multifocal disease present, %	Yes	30
	No	70
	Missing	<1
H3 K27M mutation	H3 K27M mutation	79
	H3 K27M wildtype	6
	Unknown	15
Extent of prior resection, %	None	68
	Partial	21
	Total	11
Prior temozolomide use, %	Yes	61
Prior bevacizumab use, %	Yes	17
History of re-irradiation, %	Yes	11
Number of prior relapses, %	0	25
	1	56
	2	13

		Overall Safety Population (N=376)
	3	3
	4	2
	Missing	<1
Steroids at baseline, %	Yes	51

Source: NDA 219876, ISS ADSL dataset

The median age was 23 years (range: 3 to 80): 30% were 2 to 11 years old, 11% were 12 to 17 years old, 55% were 18 to 64 years old, and 3.7% were 65 years or older. Fifty-two percent (52%) were female; 74% White, 10% unknown race or race not reported, 9% Black or African American, 4% Asian, 2.9% other or multiple races; and 13% were of Hispanic or Latino ethnicity. Karnofsky/Lansky Performance Status (KPS/LPS) score was 80 to 100 in 66% of patients, 60 to 70 in 27%, and <60 in 7%.

Relevant disease characteristics included primary tumor locations in the midline (91%) and non-midline regions (9%); 33% had diffuse intrinsic pontine glioma (DIPG); 30% presented with multifocal disease; 79% had an H3 K27M mutation; 75% had recurrent disease.

Compared to the primary efficacy population, the overall safety population comprises a broader population of patients, including patients with more variable ages (range 3 to 80 years; including 154 patients younger than 18 years), time from initial diagnosis, and disease status (including newly diagnosed, post-radiation non-recurrent, and recurrent).

Adequacy of the safety database:

Data:

The safety analyses and conclusions in this submission are based on the integrated safety analysis set, which includes 422 adult and pediatric patients with glioma from 4 open-label clinical studies (ONC006, ONC013, ONC014, and ONC018). Standard baseline and safety evaluations included demographics and baseline characteristics, extent of exposure, AE summaries (including subgroup analyses), SAE narratives, clinical laboratory assessments (hematology, chemistry), patient disposition, and deaths.

The Applicant's Position:

The population studied and safety data evaluated are considered adequate to support the NDA for the proposed indication.

The FDA's Assessment:

FDA agrees with the Applicant's position that the safety population evaluated in clinical studies ONC006, ONC013, ONC014, and ONC018 adequately represents the target population, including demographics, disease, and other baseline characteristics. The safety narratives were also adequate to allow further assessment of relevant safety signals.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Description:

There are no major concerns about the quality and integrity of the submitted datasets and case narratives that comprise the core safety analysis in the integrated safety analysis set; and data from the submitted clinical study reports was sufficiently complete for a comprehensive analysis of the safety data.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Categorization of Adverse Event

The Applicant's Description:

Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA 24.0) to classify events under primary system organ class (SOC) and preferred term (PT).

Treatment-emergent adverse events (TEAEs) were defined as AEs reported as starting on or after the date of first dose of dordaviprone up to 30 days after last dose. Only TEAEs were included in the summary tables.

To focus on the safety of dordaviprone monotherapy and minimize the potential impact of additional anticancer therapies following progression, safety data present AEs that started on or after the date of first dose of dordaviprone up to 30 days after the last dose and prior to initiation of additional anticancer therapies.

AEs with missing or partially missing start dates were considered as reported during a particular timeframe unless it can be ruled out based on available date components. Missing severity data were not imputed and were reported as unknown. Events that were missing a relationship to dordaviprone were considered related for the purposes of reporting. AEs assessed as possibly or probably related were summarized as "related" and AEs assessed as unlikely related were summarized as "not related." Multiple occurrences of the same event in a single patient were counted once at the maximum severity (worst grade) and most related.

Patients included in the integrated safety analysis set were treated in clinical studies without comparator arms and therefore the causal relationship of AEs to underlying disease, concomitant medications, or dordaviprone cannot be definitively determined.

Adverse Events of Special Interest

Due to potential effects of D2 antagonism, specific AEs such encephalopathies (noninfectious encephalopathy/delirium), extrapyramidal syndrome, torsade de pointes/QT prolongation, and embolic and thrombotic events were analyzed as AEs of special interest (AEOSIs) in the integrated safety analysis set. These events are summarized following standardized MedDRA queries (SMQ) (narrow terms) at the top level and by PT.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Routine Clinical Tests

The Applicant's Description:

Standard baseline and safety evaluations included demographics and baseline characteristics, extent of exposure, AE summaries (including subgroup analyses), clinical laboratory (hematology, chemistry), patient disposition, and death.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.4. Safety Results

Deaths

Data:

Within the integrated safety analysis set, 39 patients (9%) experienced a TEAE (onset during treatment with dordaviprone or within 30 days of the last dose, and before the initiation of additional anticancer therapies) that led to death; see Table 8.20 below.

Disease progression (20 patients; 5%) and similar terms (neoplasm, neoplasm progression, neoplasm malignant, and brain stem glioma) (5 patients; 1%) were the most frequently reported reasons for death.

None of the AEs leading to death were considered to be related to dordaviprone.

Table 8.20: Applicant – AEs Leading to Death (Integrated Safety Analysis Set)

System Organ Class Preferred Term	Adult Post-RT Non-Recurrent N=17	Adult Recurrent N=225	Pediatric[a] Newly Diagnosed N=28	Pediatric Post-RT Non-Recurrent N=69	Pediatric Recurrent N=82	Overall N=422
Patients with at least one fatal AE, n (%)	2 (11.8)	12 (5.3)	3 (10.7)	8 (11.6)	14 (17.1)	39 (9.2)
Cardiac disorders	0	1 (0.4)	0	0	1 (1.2)	2 (0.5)
Cardiac arrest	0	1 (0.4)	0	0	1 (1.2)	2 (0.5)
General disorders and administration site conditions	1 (5.9)	6 (2.7)	2 (7.1)	6 (8.7)	9 (11.0)	24 (5.7)
Disease progression	1 (5.9)	4 (1.8)	2 (7.1)	5 (7.2)	8 (9.8)	20 (4.7)
Death	0	2 (0.9)	0	1 (1.4)	1 (1.2)	4 (0.9)
Neoplasms benign, malignant and unspecified	0	1 (0.4)	0	2 (2.9)	2 (2.4)	5 (1.2)
Neoplasm	0	0	0	2 (2.9)	0	2 (0.5)
Neoplasm progression	0	0	0	0	1 (1.2)	1 (0.2)
Brain stem glioma	0	0	0	0	1 (1.2)	1 (0.2)
Neoplasm malignant	0	1 (0.4)	0	0	0	1 (0.2)
Nervous system disorders	1 (5.9)	1 (0.4)	0	1 (1.4)	1 (1.2)	4 (0.9)
Encephalopathy	0	1 (0.4)	0	0	0	1 (0.2)
Hydrocephalus	0	0	0	0	1 (1.2)	1 (0.2)
Haemorrhage intracranial	0	0	0	1 (1.4)	0	1 (0.2)
Paroxysmal sympathetic hyperactivity	1 (5.9)	0	0	0	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0	3 (1.3)	1 (3.6)	1 (1.4)	1 (1.2)	6 (1.4)
Respiratory distress	0	1 (0.4)	0	0	1 (1.2)	2 (0.5)
Aspiration	0	0	1 (3.6)	0	0	1 (0.2)
Dyspnoea	0	0	0	1 (1.4)	0	1 (0.2)
Pneumonia aspiration	0	1 (0.4)	0	0	0	1 (0.2)
Respiratory failure	0	1 (0.4)	0	0	0	1 (0.2)

Abbreviations: AE=adverse event; RT=radiotherapy; TEAE=treatment-emergent adverse event.
Note: This table includes TEAEs, defined as AEs reported as starting on or after the date of first dose of dordaviprone and through 30 days after the last dose and prior to the initiation of additional anticancer therapies. If a patient has multiple occurrences of an AE or within a system organ class, the patient is presented only once in the respective count.
Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 24.0.
[a] One patient was 21 years of age.
Source: ISS Table 3.2.4; m5.3.5.3, Adverse event analysis data (adae.xpt)

In addition, 12 patients experienced a fatal AE after the initiation of additional anticancer therapies or more than 30 days after the last dose of dordaviprone. These events included disease progression (5 patients); respiratory failure (2 patients); and neoplasm, neoplasm progression,

sepsis, encephalopathy, hydrocephalus, and dyspnea (1 patient each). Disease progression was not considered an AE for studies in the integrated safety analysis set, though was sometimes reported.

The Applicant's Position:

The most common cause of death was disease progression (4.7% of patients), which is expected within the studied disease population. Although disease progression was not required to be reported as an AE, it accounted for the majority of patients with fatal AEs (6% of patients). There were no treatment-related fatal events. Dordaviprone is generally safe and well-tolerated in both adult and pediatric patients with H3 K27M-mutant diffuse glioma. Given its favorable safety profile, the investigators sometimes opted (and the studies permitted) to continue dosing of dordaviprone following disease progression.

The FDA's Assessment:

FDA agrees with the Applicant's summary of deaths in the integrated safety analysis set (N=422).

In the overall safety population (N=376), 33 patients (9%) experienced a Grade 5 TEAE (onset within 30 days of the last dose of dordaviprone, and before the initiation of additional anticancer therapies); 11 additional patients experienced a fatal AE after the initiation of additional anticancer therapy. Twenty-six (26) patients had Grade 5 AEs of disease progression (preferred terms included: disease progression, neoplasm, neoplasm progression, neoplasm malignant, brainstem glioma). Eighteen (18) patients had other Grade 5 adverse events, including death (n=3), respiratory failure (n=3), respiratory distress (n=2), dyspnea (n=2), aspiration (n=2), cardiac arrest (n=2), encephalopathy (n=1), sepsis (n=1), intracranial hemorrhage (n=1), and hydrocephalus (n=1).

In the primary efficacy safety population (N=49), one patient had a Grade 5 TEAE (Patient ONC013-LCI-03; fatal event of encephalopathy).

FDA reviewed the narratives for each of the fatal TEAEs in the overall safety population and Table 8.21 provides a brief summary of the narrative of each Grade 5 AE and FDA's assessment of the causality in greater detail. Notably, the majority of patients with DIPG/DMG with advanced disease experience difficulty swallowing given the location of their tumor; other common symptoms for patients receiving palliative care as reported in a study of patients with DIPG include issues with mobility, communication, consciousness and breathing.

Table 8.21: Grade 5 TEAEs in the Overall Safety Population (N=376), excluding disease progression

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
Occurred prior to initiation of another cancer agent (N=13)			
ONC006-(b) (6)	36-year-old White male with recurrent H3 K27M-mutant DMG s/p subtotal resection, temozolomide and radiation, who developed headache on Study Day 278; dordaviprone was discontinued on Study Day 296 due to disease progression. He died due to **Grade 5 aspiration pneumonia** on Study Day 316. The investigator attributed the event as unlikely related to dordaviprone.	Aspiration pneumonia in the setting of disease progression, unlikely related to dordaviprone	No
ONC013-(b) (6)	28-year-old White male with recurrent thalamic H3 K27M-mutant DMG s/p surgery, radiation, temozolomide, and bevacizumab, who developed gait disturbance on Study Day 22. Two days later he developed increased somnolence, difficulty walking, CT showed interval development of intraparenchymal hemorrhage along the VP shunt catheter and hydrocephalus with stable tumor size. The shunt was re-programmed on Study Day 25 and his symptoms improved; however, he had ongoing neurologic decline over the next 2 weeks, and his family opted to pursue hospice care. He died on Study Day 48 due to **Grade 5 encephalopathy**. The investigator attributed the events as likely related to the underlying disease and not related to dordaviprone.	Likely disease-related, but imaging did not show disease progression, therefore challenging to rule out contribution of dordaviprone to the adverse event	Yes
ONC013-(b) (6)	48-year-old White male with recurrent thalamic H3 K27M-mutant DMG s/p radiation, temozolomide, and bevacizumab, who developed fluctuating worsening of his underlying muscle weakness and peripheral sensory neuropathy from Study Days 94 through 147. His last day of dordaviprone was	Disease progression, unlikely related to dordaviprone	No

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
	Study Day 155. On Study Day 160, he was found unresponsive in his living room and taken to the hospital, however despite resuscitation efforts, he died due to an event of **Grade 5 death** the same day. An autopsy showed the cause of death was high grade glioma. The investigator attributed the event as unlikely related to dordaviprone.		
ONC013-[redacted] (b) (6)	21-year-old male with recurrent DMG s/p radiation, temozolomide and selinexor, who developed shortness of breath on Study Day 63, ultimately requiring intubation. A chest X-ray showed pneumonia with likely superimposed acute respiratory distress syndrome. The next day, a CT showed progressive disease. He had declining respiratory status, and he was transitioned to comfort care on Study Day 70; he died due to **Grade 5 respiratory distress** the same day. The investigator attributed the event as not related to dordaviprone.	Infectious pneumonia in the setting of disease progression, unlikely related to dordaviprone	No
ONC014-[redacted] (b) (6)	5-year-old White female with newly diagnosed DIPG who developed Grade 3 renal calculi on Study Day 113; the event resolved after stent placement. She then developed Grade 3 aspiration and hypoxia on Study Day 143; chest X-ray showed bilateral pneumonia. She was treated with antibiotics and discharged on Study Day 147, but had ongoing symptoms of respiratory distress at home and transitioned to hospice comfort care. She died on Study Day 152 due to **Grade 5 aspiration**. The investigator attributed the event as not related to dordaviprone.	Aspiration pneumonia in the setting of underlying brain tumor, unlikely related to dordaviprone	No
ONC014-[redacted] (b) (6)	10-year-old Black male with DIPG who developed increased dysphagia, lethargy, and decreased appetite on Study Day 63; he was	Hydrocephalus and disease progression,	No

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
	admitted to the hospital and CT showed hydrocephalus. The medical team deemed he was unsafe for transfer or continuation of treatment due to disease progression. The family elected to transition to end of life care and he died at home on Study Day 69 due to **Grade 5 AEs of dyspnea and death**. The investigator attributed the event as not related to dordaviprone.	unlikely related to dordaviprone	
ONC014-[redacted] (b) (6)	15-year-old Black female with H3 K27M-mutant DMG of the brainstem who developed recurrence and started dordaviprone approximately 1 year after diagnosis. She had a baseline performance status of 50 and was receiving 8 mg of dexamethasone at enrollment. On Study Day 21 (six days after her last dose of study treatment), she became unresponsive while riding in the backseat of the car and required CPR and epinephrine before return of spontaneous circulation. She was admitted to the intensive care unit and was found to have disease progression. She died (**Grade 5 AE of death**) one week later.	Disease progression, unlikely related to dordaviprone	No
ONC018-[redacted] (b) (6)	9-year-old Black male with DIPG who developed dyspnea one month after starting dordaviprone. He was seen in the ED and treated with oxygen and diazepam and discharged home. He was seen in clinic the next day and was overall stable, however, 7 days later he presented with **Grade 5 cardiac arrest** and died following "supportive care." It was unknown whether autopsy was performed. The investigator attributed the death as unlikely related to study treatment.	Likely disease-related, but limited information available, therefore challenging to rule out contribution of dordaviprone to the adverse event	Yes
ONC018-[redacted] (b) (6)	19-year-old White male with DIPG who developed disease progression on Study Day 169. He died (**Grade 5 AE of death**) on Study Day 186; an autopsy was performed but	Disease progression, unlikely related to dordaviprone	No

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
	results were not available. The investigator attributed the death as unlikely related to study treatment.		
ONC018-(b) (6)	32-year-old White male with H3 K27M-mutant DMG had an event of asystole resulting in death (**Grade 5 cardiac arrest**) seven months after starting dordaviprone. Per the safety report narrative, "The subject's sister reported that the death was due to asystole as a result of the brain tumor." It is unknown whether an autopsy was performed. The investigator attributed the death as unlikely related to study treatment.	Likely disease-related, but limited information available, therefore challenging to rule out contribution of dordaviprone to the adverse event	Yes
ONC018-(b) (6)	4-year-old female with H3 K27M-mutant DMG who became unresponsive at home ("tensing extremities, eyes wide open, did not respond to tactile or verbal stimuli") on Study Day 151. In the ED, CT imaging showed intracranial hemorrhage with "acute and subacute regions of hemorrhage in the posterior fossa with intraventricular extension; heterogeneous tumor was noted within posterior fossa involving the pons, cerebellum and vermis". Despite supportive care measures, she did not improve, and the family elected to pursue comfort care. She died on Study Day 180 due to **Grade 5 AEs of intracranial hemorrhage and disease progression**. The investigator attributed the death as not related to study treatment.	Likely disease-related, but imaging did not show disease progression, therefore challenging to rule out contribution of dordaviprone to the adverse event	Yes
ONC018-(b) (6)	9-year-old Hispanic White male with DIPG who developed respiratory distress requiring hospital admission 1 month after starting study treatment. CT imaging showed worsening hydrocephalus and disease progression; study treatment was discontinued due to progressive disease. He died due to	Disease progression, unlikely related to dordaviprone	No

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
	Grade 5 respiratory distress 10 days after admission. An autopsy was not performed. The investigator attributed the death as unlikely related to study treatment.		
ONC018-(b) (6)	18-year-old Black female with DIPG who developed Grade 3 dyspnea on Study Day 70, which resolved within 2 days. On Study Day 120, she died at home due to "tumor progression and resultant herniation" (**Grade 5 respiratory failure**). It is unknown whether an autopsy was performed. The investigator attributed the death as not related to study treatment.	Disease progression, unlikely related to dordaviprone	No
Occurred after initiation of another cancer agent (N=5)			
ONC006-(b) (6)	20-year-old White female with recurrent brainstem glioma (H3 K27M status unknown) who developed increased left-sided weakness and dysphagia on Study Day 15; dordaviprone was discontinued on Study Day 22 due to disease progression. She started bevacizumab on Study Day 27, but had progressive symptoms including dizziness, headache, left-sided weakness, dysphagia, and hypoxia. She developed a Grade 3 lung infection (Chest X-ray showed multifocal pneumonia) and was treated with antibiotics, but ultimately died due to **Grade 5 respiratory failure** on Study Day 35. The investigator attributed the event as unlikely related to dordaviprone.	Disease progression, unlikely related to dordaviprone	No
ONC014-(b) (6)	9-year-old female with DIPG who discontinued study treatment on Study Day 210 due to progressive disease. Subsequently, she was started on another anti-cancer agent (PI3K inhibitor). Twenty-three (23) days after her last dose of dordaviprone, she developed fever and was admitted for respiratory distress requiring intubation. At that time, her "family	Sepsis occurred >3 weeks after discontinuation of dordaviprone and in the setting of receiving	No

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in USPI
	verbalized to make the patient a do not resuscitate (DNR)." She died on the same day due to **Grade 5 sepsis**. The investigator attributed the event as unlikely related to dordaviprone.	another anti-cancer agent	
ONC018-(b) (6)	7-year-old White male with DIPG who developed disease progression approximately 3 months after starting dordaviprone. He died at home while in hospice care due to progressive disease (**Grade 5 AEs of dyspnea and disease progression**). The investigator attributed the events as not related to dordaviprone.	Disease progression, unlikely related to dordaviprone	No
ONC018-(b) (6)	55-year-old White male with H3 K27M-mutant HGG who developed disease progression on Study Day 270 and discontinued dordaviprone. He died 25 days later while in hospice care due to **Grade 5 respiratory failure.** No autopsy was performed. The investigator attributed the event as not related to dordaviprone.	Disease progression, unlikely related to dordaviprone	No
ONC018-(b) (6)	11-year-old White female with H3 K27M-mutant HGG who developed headache and vomiting on Study Day 97. MRI showed increased tumor size with a slight increase in ventriculomegaly. She was started on bevacizumab on Study Day 98. She continued to have intermittent headaches and repeat MRI on Study Day 116 showed obstructive hydrocephalus with herniation. She "was made do not resuscitate/do not intubate" and she died the next day due to **Grade 5 hydrocephalus**. The investigator attributed the event as unlikely related to dordaviprone.	Disease progression, unlikely related to dordaviprone	No

Source: Clinical Study Reports for ONC006, ONC013, ONC014, and ONC018 submitted in NDA 219876

Section 6 (Adverse Reactions) of US product labeling includes safety data for the overall safety population (n=376). Fatal adverse reactions, excluding those definitively attributable to

progressive disease or extraneous cause, occurred in 1% of patients, including cardiac arrest (0.5%), intracranial hemorrhage (0.3%), and encephalopathy (0.3%).

Serious Adverse Events

Data:

Table 8.22 summarizes treatment-emergent SAEs that occurred in >1% of patients overall for the integrated safety analysis set. In total, 144 patients (34.1%) experienced at least one SAE. The most commonly reported SAE (>5% of patients) was hydrocephalus (5.9%). Serious adverse events considered by the investigator to be at least possibly related to dordaviprone were reported for 15 patients (3.6%). The most common treatment-related SAEs were vomiting (4 patients), fatigue (2 patients), and pulmonary embolism (2 patients). All other treatment-related SAEs were reported in one patient each.

Table 8.22: Applicant – Treatment-Emergent SAEs in >1% of Patients Overall (Integrated Safety Analysis Set)

System Organ Class Preferred Term	Adult Post-RT Non-Recurrent N=17	Adult Recurrent N=225	Pediatric[a] Newly Diagnosed N=28	Pediatric Post-RT Non-Recurrent N=69	Pediatric Recurrent N=82	Overall N=422
Patients with any SAE, n (%)	6 (35.3)	68 (30.2)	17 (60.7)	21 (30.4)	32 (39.0)	144 (34.1)
Nervous system disorders	5 (29.4)	36 (16.0)	11 (39.3)	11 (15.9)	15 (18.3)	78 (18.5)
Hydrocephalus	1 (5.9)	8 (3.6)	5 (17.9)	4 (5.8)	7 (8.5)	25 (5.9)
Headache	2 (11.8)	5 (2.2)	2 (7.1)	1 (1.4)	3 (3.7)	13 (3.1)
Seizure	0	7 (3.1)	2 (7.1)	0	2 (2.4)	11 (2.6)
Encephalopathy	0	6 (2.7)	0	1 (1.4)	0	7 (1.7)
Dysarthria	0	2 (0.9)	1 (3.6)	1 (1.4)	1 (1.2)	5 (1.2)
General disorders and administration site conditions	1 (5.9)	10 (4.4)	5 (17.9)	7 (10.1)	13 (15.9)	36 (8.5)
Disease progression	1 (5.9)	4 (1.8)	2 (7.1)	5 (7.2)	8 (9.8)	20 (4.7)
Respiratory, thoracic and mediastinal disorders	0	14 (6.2)	5 (17.9)	4 (5.8)	6 (7.3)	29 (6.9)
Dyspnoea	0	4 (1.8)	2 (7.1)	1 (1.4)	1 (1.2)	8 (1.9)
Pulmonary embolism	0	6 (2.7)	0	0	0	6 (1.4)
Gastrointestinal disorders	1 (5.9)	8 (3.6)	5 (17.9)	6 (8.7)	7 (8.5)	27 (6.4)
Vomiting	0	3 (1.3)	4 (14.3)	5 (7.2)	5 (6.1)	17 (4.0)
Dysphagia	1 (5.9)	2 (0.9)	0	1 (1.4)	3 (3.7)	7 (1.7)
Infections and infestations	0	5 (2.2)	5 (17.9)	4 (5.8)	1 (1.2)	15 (3.6)
Urinary tract infection	0	2 (0.9)	2 (7.1)	2 (2.9)	0	6 (1.4)

System Organ Class Preferred Term	Adult Post-RT Non-Recurrent N=17	Adult Recurrent N=225	Pediatric[a] Newly Diagnosed N=28	Pediatric Post-RT Non-Recurrent N=69	Pediatric Recurrent N=82	Overall N=422
Musculoskeletal and connective tissue disorders	0	7 (3.1)	2 (7.1)	0	5 (6.1)	14 (3.3)
Muscular weakness	0	5 (2.2)	1 (3.6)	0	2 (2.4)	8 (1.9)
Renal and urinary disorders	0	3 (1.3)	3 (10.7)	4 (5.8)	2 (2.4)	12 (2.8)
Urinary retention	0	1 (0.4)	1 (3.6)	1 (1.4)	2 (2.4)	5 (1.2)
Injury, poisoning, and procedural complications	0	7 (3.1)	0	0	1 (1.2)	8 (1.9)
Fall	0	5 (2.2)	0	0	0	5 (1.2)
Cardiac disorders	0	3 (1.3)	0	0	2 (2.4)	5 (1.2)
Cardiac arrest	0	1 (0.4)	0	0	2 (2.4)	3 (0.7)

Abbreviations: AE=adverse event; RT=radiotherapy; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Note: This table only includes TEAEs, defined as a newly occurring or worsening AE after the first dose of dordaviprone, through 30 days after the last dose, and prior to initiation of other anticancer therapies. If a patient has multiple occurrences of an AE or within a system organ class, the patient is presented only once in the respective count. Adverse events were coded using the Medical Dictionary for Regulatory Activities, Version 24.0.
[a] One patient was 21 years of age.
Source: ISS Table 3.2.3; m5.3.5.3, Adverse event analysis data (adae.xpt)

The Applicant's Position:

Dordaviprone is generally safe and well-tolerated in both adult and pediatric patients with H3 K27M-mutant diffuse glioma, with a low incidence of treatment-related SAEs (3.6%).

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of treatment-emergent SAEs. Given that these data are derived from single arm trials, the attribution of relatedness to dordaviprone is challenging to assess. According to standard labeling practice, US product labeling includes a summary of treatment-emergent SAEs rather than treatment-related SAEs.

In the overall safety population (N=376), SAEs occurred in 33% of patients. SAEs in >2% of patients included hydrocephalus (5%), vomiting (4.3%), headache (3.2%), seizure (2.4%), and muscular weakness (2.1%).

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Only 3 patients (0.7%) discontinued dordaviprone treatment due to AEs.

The Applicant's Position:

Dordaviprone is generally safe and well-tolerated in both adult and pediatric patients with glioma, exhibiting a favorable and manageable safety profile, as demonstrated by the low incidence of discontinuations due to TEAEs.

The FDA's Assessment:

FDA agrees with the Applicant's position that the number of discontinuations due to AEs was low. However, the collection of safety data with respect to dose modifications differed across studies. In response to an Information Request dated May 15, 2025, the Applicant reviewed the narratives and records/clinical database for patients with adverse events which resulted in an action taken of "dose reduction or delay" or "study medication discontinued or dose reduced" to determine the actual action taken for those adverse events.

Upon review of these data, in addition to the safety data submitted in the original application datasets, FDA determined that permanent discontinuation of dordaviprone due to an adverse reaction occurred in 2.1% of patients. Adverse reactions which resulted in permanent discontinuation in >1 patient included confusional state.

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

Data:

In the integrated safety analysis set, 33 patients (7.8%) experienced a TEAE that led to discontinuation, reduction or interruption of dordaviprone prior to the initiation of additional anticancer therapy.

Of these, 10 patients (2.4%) experienced a TEAE that was considered related to dordaviprone. The following treatment-related AEs impacted dordaviprone dosing (discontinuation, reduction, or interruption): alanine aminotransferase increased, neutrophil count decreased, and neutropenia (in 2 patients each), and hypersensitivity, vomiting, weight decreased, ataxia, confusional state, and pulmonary embolism (in 1 patient each).

The Applicant's Position:

Dordaviprone is generally safe and well-tolerated in both adult and pediatric patients with glioma, exhibiting a favorable safety profile, as demonstrated by the low incidence of dose modifications due to TEAEs.

The FDA's Assessment:

FDA agrees with the Applicant's position that the number of dose interruptions and reductions is relatively low in comparison to other anti-cancer products.

In the overall safety population (N=376), dosage interruptions of dordaviprone due to an adverse reaction occurred in 6% of patients. Adverse reactions which required dosage interruption in >1

patient included increased alanine aminotransferase, increased aspartate aminotransferase, decreased lymphocyte count, muscular weakness, and aspiration pneumonia.

Dose reductions of dordaviprone due to an adverse reaction occurred in 2.7% of patients. Adverse reactions which required dose reductions in >1 patient included decreased neutrophil count and increased alanine aminotransferase.

Significant Adverse Events

Data:

Common All Grade and Grade ≥3 Adverse Events

Table 8.23 summarizes the TEAEs that occurred in >10% of patients overall for the integrated safety analysis set. The most common (>5% patients) AEs that were Grade ≥3 in intensity were hydrocephalus and disease progression. The investigator considered the majority of Grade ≥3 events to be not related to dordaviprone and more likely due to the disease under study.

Table 8.23: Applicant – TEAEs in >10% of Patients in Decreasing Order of Frequency (Integrated Safety Analysis Set)

	Integrated Safety Analysis Set, N=422			
	All Causality		Treatment-Related	
Preferred Term	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Patients with at least one AE	394 (93.4)	208 (49.3)	217 (51.4)	41 (9.7)
Fatigue	140 (33.2)	12 (2.8)	78 (18.5)	7 (1.7)
Headache	134 (31.8)	16 (3.8)	28 (6.6)	0
Vomiting	104 (24.6)	11 (2.6)	44 (10.4)	4 (0.9)
Nausea	101 (23.9)	3 (0.7)	61 (14.5)	0
Gait disturbance	66 (15.6)	18 (4.3)	3 (0.7)	0
Hemiparesis	66 (15.6)	18 (4.3)	10 (2.4)	0
Lymphocyte count decreased	62 (14.7)	15 (3.6)	34 (8.1)	8 (1.9)
Dysarthria	54 (12.8)	11 (2.6)	5 (1.2)	1 (0.2)
Muscular weakness	53 (12.6)	17 (4.0)	5 (1.2)	1 (0.2)
Hyperglycaemia	52 (12.3)	3 (0.7)	5 (1.2)	0
Dysphagia	50 (11.8)	10 (2.4)	2 (0.5)	1 (0.2)
Dizziness	49 (11.6)	2 (0.5)	13 (3.1)	0
Alanine aminotransferase increased	46 (10.9)	5 (1.2)	27 (6.4)	3 (0.7)
Constipation	45 (10.7)	0	6 (1.4)	0

Abbreviations: AE=adverse event; TEAE=treatment-emergent adverse events.
Note: This table only includes TEAEs, defined as a newly occurring or worsening AE after the first dose of study treatment and through 30 days after the last dose of study treatment and prior to initiation of additional anticancer therapy. Multiple occurrences of an event within a patient are counted only once. Based on investigator assessment of causality.
Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 24.0.
Source: ISS Table 3.2.1, ISS Table 3.2.2, ISS Table 3.2.6, ISS Table 3.2.7; m5.3.5.3, Adverse event analysis data (adae.xpt)

The Applicant's Position:

Dordaviprone is generally safe and well-tolerated in both adult and pediatric patients with glioma, with the majority of treatment-related AEs being mild to moderate in intensity. The proposed prescribing information includes the most frequently reported AEs, along with relevant warnings and precautions for informed use of dordaviprone.

The FDA's Assessment:

FDA generally agrees with the Applicant's presentation of the most common adverse events except as outlined below.

The most common adverse reactions (≥20%) were fatigue, headache, vomiting, nausea, and musculoskeletal pain (Table 8.24). Other clinically important adverse reactions observed in less than 10% of patients treated with dordaviprone were peripheral neuropathy, seizure, diarrhea, tremor, and venous thromboembolic events.

Table 8.24: Adverse Reactions (≥10%) in Patients with Glioma Who Received Dordaviprone in ONC006, ONC013, ONC014, and ONC018

Adverse Reaction	**Dordaviprone (N=376)**	
	All Grades (%)	**Grade 3 or 4 (%)**
General Disorders		
Fatigue[a]	34	3.2
Gait disturbance	16	3.7
Nervous System Disorders		
Headache[b]	32	4.3
Cranial nerve disorders[c]	16	1.3
Hemiparesis	15	4.5
Dysarthria	13	2.7
Dizziness	13	0.5
Ataxia	10	1.3
Gastrointestinal Disorders		
Vomiting	24	2.7
Nausea	24	0.8
Dysphagia	13	2.1
Constipation	11	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	20	2.9
Muscular weakness	13	4.5

Metabolism and Nutrition Disorders		
Hyperglycemia	12	0.8
Infections and Infestations		
Rash[e]	11	0.8

[a.] Includes asthenia.
[b.] Includes head discomfort and sinus headache.
[c.] Includes accessory nerve disorder, auditory nerve disorder, facial nerve disorder, facial paralysis, facial paresis, glossopharyngeal nerve disorder, hypoglossal nerve disorder, IIIrd nerve disorder, IIIrd nerve paralysis, IVth nerve disorder, IVth nerve paralysis, tongue paralysis, trigeminal nerve disorder, trigeminal neuralgia, VIth nerve disorder, VIth nerve paralysis, and VIth nerve paresis.
[d.] Includes back pain, pain in extremity, arthralgia, neck pain, non-cardiac chest pain, myalgia, bone pain, musculoskeletal chest pain, musculoskeletal stiffness, and spinal pain.
[e.] Includes dermatitis, dermatitis acneiform, dermatitis bullous, eczema, erythema multiforme, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

Source: NDA 219876 ADSL and ADAE datasets

Treatment Emergent Adverse Events and Adverse Reactions

Data:

The most common AEs (>20% of patients; all causalities) in patients with glioma were fatigue, headache, vomiting, and nausea. These events were generally mild or moderate (Grade 1 or Grade 2) in intensity. AEs occurring in >10% to 20% of patients were gait disturbance, hemiparesis, lymphocyte count decreased, dysarthria, muscular weakness, hyperglycemia, dysphagia, dizziness, alanine aminotransferase increased, and constipation. The majority of these events were considered not related to dordaviprone and were generally mild to moderate in intensity; see data presented earlier in the "Significant Adverse Events" section (Table 8.22).

For details on Grade ≥3 AEs, see data presented earlier in the "Significant Adverse Events" section (Table 8.22).

Table 8.25 summarizes the incidence of treatment-emergent AEs by individual study and for the overall integrated safety analysis set.

Table 8.25: Applicant – Summary of TEAEs in Patients with Glioma by Study (Integrated Safety Analysis Set)

Category, n (%)	ONC006 N=84	ONC013 N=73	ONC014 N=134	ONC018 N=131	Integrated N=422
Any AE	76 (90.5)	69 (94.5)	131 (97.8)	118 (90.1)	394 (93.4)
Treatment-related AE	38 (45.2)	37 (50.7)	82 (61.2)	60 (45.8)	217 (51.4)
Grade 3 or higher AE	23 (27.4)	37 (50.7)	81 (60.4)	67 (51.1)	208 (49.3)
Treatment-related Grade 3 or higher AE	2 (2.4)	6 (8.2)	15 (11.2)	18 (13.7)	41 (9.7)
Serious AE	21 (25.0)	24 (32.9)	53 (39.6)	46 (35.1)	144 (34.1)
Treatment-related SAE	2 (2.4)	0	6 (4.5)	7 (5.3)	15 (3.6)
AE leading to death	4 (4.8)	3 (4.1)	13 (9.7)	19 (14.5)	39 (9.2)
Treatment-related AE leading to death	0	0	0	0	0
AE leading to impact on dosing [a]	7 (8.3)	6 (8.2)	15 (11.2)	5 (3.8)	33 (7.8)

Category, n (%)	ONC006 N=84	ONC013 N=73	ONC014 N=134	ONC018 N=131	Integrated N=422
Treatment-related AE leading to an impact on dosing [a]	1 (1.2)	1 (1.4)	6 (4.5)	2 (1.5)	10 (2.4)

Abbreviations: AE=adverse event; TEAE=treatment-emergent adverse events.
[a] Impact on dosing includes dose reduction, dose interruption, and discontinuation.
Note: This table includes TEAEs, defined as AEs reported as starting on or after the date of first dose of dordaviprone up to 30 days after the last dose and prior to initiation of additional anticancer therapies.
Sources: ISS Table 3.2.1, ISS Table 3.2.2, ISS Table 3.2.3, ISS Table 3.2.4, ISS Table 3.2.5, ISS Table 3.2.6, ISS Table 3.2.7, ISS Table 3.2.8, ISS Table 3.2.9, ISS Table 3.2.10;
m5.3.5.3, Adverse event analysis data (adae.xpt)
m5.3.5.2: ONC006 CSR Table 10; ONC013 CSR Table 11; ONC014 CSR Table 13; ONC018 CSR Table 13

The Applicant's Position:

Dordaviprone is generally safe and well tolerated in both adult and pediatric patients with glioma, exhibiting a favorable and manageable safety profile. The majority of the reported AEs were considered not related to dordaviprone, and were events expected to occur in brain tumor patients. The proposed prescribing information includes the most frequently reported AEs, along with relevant warnings and precautions for informed use of the drug product.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Refer to Table 8.24 above for a summary of the most common adverse events in the overall safety population (N=376).

The adverse event profile was generally similar in the overall safety population (N=376) and the primary efficacy population (N=50), with slightly higher percentages in the efficacy population likely related to the smaller absolute number of patients (Table 8.26).

Table 8.26: Overall Safety Profile of Dordaviprone in Safety and Efficacy Populations

	Overall Safety Population (N=376)[a]	Efficacy Population (N=50)
Any Grade TEAE, %	93	96
Grade ≥ 3 TEAE, %	49	60
SAEs, %	33	44
Dose modifications, %	11	12
Fatal AEs[b], %	1	2

[a]Patients with glioma across 4 open-label clinical studies (ONC006, ONC013, ONC014, and ONC018) who received dordaviprone 625 mg once weekly (or equivalent body weight-adjusted dose)

[b]Excluding disease progression or other extraneous cause

Source: NDA 219876 ADSL and ADAE datasets

Laboratory Findings

Data:

Table 8.27 summarizes maximum treatment-emergent laboratory grades for key laboratory parameters for patients in the integrated safety analysis set. Treatment-emergent laboratory abnormalities that occurred in at least 20% of patients were ALT increased, hemoglobin decreased, neutrophils decreased, leukocytes decreased, aspartate aminotransferase increased, and calcium decreased. Notably, concurrent elevations of ALT and bilirubin occurred in 1 patient, however review of the case suggested multiple other etiologies, and these elevations returned to normal range with continued dordaviprone dosing.

Clinically relevant laboratory abnormalities were reported as AEs. The majority of these AEs were reported as Grade 1 and 2 in intensity. Dose modifications were required for 2.1% of patients due to laboratory-associated AEs.

Table 8.27 Applicant – Treatment-Emergent Graded Laboratory Results: Maximum On-Treatment Grade Prior to Other Anticancer Therapies (Integrated Safety Analysis Set)

Lab Parameter	Grade	Adult Post-RT Non-Recurrent N=17	Adult Recurrent N=225	Pediatric[a] Newly Diagnosed N=28	Pediatric Post-RT Non-Recurrent N=69	Pediatric Recurrent N=82	Overall N=422
ALT (increased)	n	17	191	27	67	68	371
	Grade 1	6 (35.3)	28 (14.7)	11 (40.7)	15 (22.4)	14 (20.6)	74 (19.9)
	Grade 2	1 (5.9)	11 (5.8)	1 (3.7)	3 (4.5)	2 (2.9)	18 (4.9)
	Grade 3	0	5 (2.6)	0	0	1 (1.5)	7 (1.9)
	Grade 4	0	0	1 (3.7)	0	0	1 (0.3)
AST (increased)	n	17	190	27	67	68	370
	Grade 1	4 (23.5)	23 (12.1)	9 (33.3)	22 (32.8)	15 (22.1)	73 (19.7)
	Grade 2	0	2 (1.1)	0	0	0	2 (0.5)
	Grade 3	0	1 (0.5)	1 (3.7)	0	1 (1.5)	3 (0.8)
	Grade 4	0	0	0	0	0	0
Total Bilirubin (increased)	n	17	191	27	67	67	370
	Grade 1	0	5 (2.6)	2 (7.4)	2 (3.0)	2 (3.0)	11 (3.0)
	Grade 2	2 (11.8)	2 (1.0)	0	0	0	4 (1.1)
	Grade 3	2 (11.8)	3 (1.6)	0	7 (10.4)	4 (6.0)	16 (4.3)
	Grade 4	0	0	0	0	0	0

Lab Parameter	Grade	Adult Post-RT Non-Recurrent N=17	Adult Recurrent N=225	Pediatric[a] Newly Diagnosed N=28	Pediatric Post-RT Non-Recurrent N=69	Pediatric Recurrent N=82	Overall N=422
Alkaline Phosphatase (increased)	n	17	191	27	67	68	371
	Grade 1	0	4 (2.1)	3 (11.1)	17 (25.4)	8 (11.8)	32 (8.6)
	Grade 2	0	0	1 (3.7)	5 (7.5)	0	6 (1.6)
	Grade 3	0	0	0	1 (1.5)	0	1 (0.3)
	Grade 4	0	0	0	0	0	0
Creatinine (increased)	n	17	193	27	67	69	374
	Grade 1	0	4 (2.1)	0	0	0	4 (1.1)
	Grade 2	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	1 (0.5)	0	0	0	1 (0.3)
Albumin (decreased)	n	17	191	27	66	68	370
	Grade 1	1 (5.9)	9 (4.7)	2 (7.4)	2 (3.0)	2 (2.9)	17 (4.6)
	Grade 2	1 (5.9)	4 (2.1)	1 (3.7)	2 (3.0)	0	8 (2.2)
	Grade 3	0	0	1 (3.7)	0	1 (1.5)	2 (0.5)
	Grade 4	NA	NA	NA	NA	NA	NA
Calcium (decreased)	n	17	192	27	67	69	373
	Grade 1	6 (35.3)	28 (14.6)	7 (25.9)	11 (16.4)	11 (15.9)	63 (16.9)
	Grade 2	0	0	0	1 (1.5)	0	1 (0.3)
	Grade 3	0	1 (0.5)	0	0	0	1 (0.3)
	Grade 4	0	2 (1.0)	0	4 (6.0)	2 (2.9)	8 (2.1)
Calcium (increased)	n	17	192	27	67	69	373
	Grade 1	1 (5.9)	2 (1.0)	1 (3.7)	5 (7.5)	3 (4.3)	12 (3.2)
	Grade 2	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	1 (1.4)	1 (0.3)
Potassium (decreased)	n	17	193	27	67	69	374
	Grade 1	2 (11.8)	23 (11.9)	4 (14.8)	10 (14.9)	8 (11.6)	47 (12.6)
	Grade 2	NA	NA	NA	NA	NA	NA
	Grade 3	0	0	0	1 (1.5)	0	1 (0.3)
	Grade 4	0	1 (0.5)	0	0	0	1 (0.3)
Potassium (increased)	n	17	193	27	67	69	374
	Grade 1	2 (11.8)	3 (1.6)	4 (14.8)	11 (16.4)	0	20 (5.3)
	Grade 2	0	4 (2.1)	1 (3.7)	3 (4.5)	0	8 (2.1)

Lab Parameter	Grade	Adult Post-RT Non-Recurrent N=17	Adult Recurrent N=225	Pediatric[a] Newly Diagnosed N=28	Pediatric Post-RT Non-Recurrent N=69	Pediatric Recurrent N=82	Overall N=422
	Grade 3	0	1 (0.5)	0	1 (1.5)	0	2 (0.5)
	Grade 4	0	0	0	0	0	0
Sodium (decreased)	n	17	193	27	67	69	374
	Grade 1	2 (11.8)	25 (13.0)	5 (18.5)	10 (14.9)	7 (10.1)	49 (13.1)
	Grade 2	1 (5.9)	0	0	1 (1.5)	1 (1.4)	3 (0.8)
	Grade 3	0	0	0	1 (1.5)	0	1 (0.3)
	Grade 4	0	0	0	0	0	0
Hemoglobin (decreased)	n	17	193	27	67	68	373
	Grade 1	4 (23.5)	35 (18.1)	7 (25.9)	21 (31.3)	12 (17.6)	79 (21.2)
	Grade 2	0	6 (3.1)	3 (11.1)	3 (4.5)	1 (1.5)	13 (3.5)
	Grade 3	0	1 (0.5)	0	1 (1.5)	0	2 (0.5)
	Grade 4	0	0	0	0	0	0
Leukocytes (decreased)	n	17	193	27	67	68	373
	Grade 1	3 (17.6)	23 (11.9)	11 (40.7)	12 (17.9)	9 (13.2)	58 (15.5)
	Grade 2	1 (5.9)	5 (2.6)	6 (22.2)	11 (16.4)	1 (1.5)	24 (6.4)
	Grade 3	0	0	0	1 (1.5)	0	1 (0.3)
	Grade 4	0	0	0	0	0	0
Lymphocytes (decreased)	n	17	193	27	67	68	373
	Grade 1	0	0	0	0	0	0
	Grade 2	2 (11.8)	22 (11.4)	8 (29.6)	7 (10.4)	7 (10.3)	46 (12.3)
	Grade 3	2 (11.8)	11 (5.7)	6 (22.2)	4 (6.0)	1 (1.5)	24 (6.4)
	Grade 4	0	1 (0.5)	1 (3.7)	0	0	2 (0.5)
Neutrophils (decreased)	n	17	193	27	67	68	373
	Grade 1	4 (23.5)	23 (11.9)	9 (33.3)	19 (28.4)	9 (13.2)	64 (17.2)
	Grade 2	1 (5.9)	3 (1.6)	5 (18.5)	10 (14.9)	1 (1.5)	20 (5.4)
	Grade 3	0	2 (1.0)	1 (3.7)	4 (6.0)	0	7 (1.9)
	Grade 4	0	0	0	0	0	0

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; NA=not applicable
Notes: Grades for laboratory parameters utilized CTCAE v5.0. Treatment-emergent is defined as an increase from the baseline grade or a graded result with no corresponding baseline.
Denominators include patients/tests with at least one on-treatment grade/result.
Source: ISS Table 4.2.2; m5.3.5.3, Laboratory results analysis data (adlb.xpt)

The Applicant's Position:

Overall, there is a low incidence of Grade ≥3 laboratory abnormalities. Although elevations in hepatic laboratory parameters were reported, these events were infrequent and did not reflect a pattern suggestive of serious drug-induced liver injury.

The FDA's Assessment:

FDA generally agrees with the Applicant's presentation of the most common laboratory abnormalities except as outlined below.

The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased calcium, and increased alanine aminotransferase (Table 8.28).

Table 8.28: Select Laboratory Abnormalities (≥10%) that Worsened from Baseline in Patients with Glioma Receiving Dordaviprone in ONC006, ONC013, ONC014, and ONC018

Laboratory Abnormality[a]	Dordaviprone[b]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Hemoglobin decreased	25	0.6
Neutrophils decreased	24	1.5
Lymphocytes decreased	19	7
Chemistry		
Alanine aminotransferase increased	28	2.4
Aspartate aminotransferase increased	22	0.9
Calcium decreased	20	2.7
Sodium decreased	14	0.3
Potassium decreased	13	0.3
Glucose decreased	11	0
Alkaline phosphatase increased	11	0.3

[a] Severity as defined by the National Cancer Institute CTCAE Version 5.0.
[b] The denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 325 to 330 patients.

Source: NDA 219876 ADSL and ADLB datasets

Vital Signs

Data:

Clinically relevant abnormal findings in vital signs, ECGs, or physical examinations were to be reported as AEs.

The Applicant's Position:

Any clinically significant abnormalities identified in an individual patient related to vital signs or physical examination were to be reported as AEs and were not otherwise systematically collected. Vital sign data were collected in clinical pharmacology studies. Collectively, these data did not identify any overall safety concerns.

The FDA's Assessment:

FDA agrees with the Applicant's position. In the overall safety population (n=376), the median baseline weight was 64.5 kilograms (range 11.8 to 199.1), and baseline height was 154.9 cm (range 88.5 to 195.6). Adverse events related to vital signs included: bradycardia or sinus bradycardia (n=7), tachycardia or sinus tachycardia (n=19), hypertension or systolic hypertension (n=28), hypotension or orthostatic hypotension (n=4), and pyrexia (n=25).

Electrocardiograms (ECGs) and QT

Data:

Study ONC201-102, a thorough QTc study, evaluated the ECG effects of a single dose of dordaviprone compared to placebo and moxifloxacin (a positive control) in healthy adults. The study demonstrated that dordaviprone at a dose of 750 mg led to a placebo-corrected QT interval increase (ΔΔQTcF) of 11.75 msec (90% CI: 9.84-13.67) at T_{max} (0.75 hours post-dose). A similar increase of 11.28 msec (90% CI: 9.54-13.01) was predicted for the therapeutic dordaviprone dose of 625 mg. These findings were consistent across multiple time points, with QTcF prolongation peaking at 13.8 msec at 5 hours post-dose. No QTcF intervals exceeded 480 msec post-administration, and no serious cardiac AEs were reported.

Further analysis from other studies supported these findings. In a DDI study with rabeprazole (Study ONC201-107), minor increases in QTcF were observed within the first 4 hours post-dose, returning to near baseline by 24 hours; no cardiac AEs were reported. Additionally, in the integrated safety analysis set, 3 participants (0.7%) experienced AEs of QT prolongation, all of which were non-serious and of Grade 1 intensity; two of these events were considered possibly related to dordaviprone by the investigator, however they occurred ≥6 days post dose.

The Applicant's Position:

Based on results from the dedicated thorough QTc study (ONC201-102), dordaviprone is associated with the potential risk of clinically significant QT interval prolongation. Warnings and precautions have been included in the proposed prescribing information.

The FDA's Assessment:

Dordaviprone causes a concentration-dependent QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (e.g., torsades de pointes) or sudden death. In the pooled safety population, of the 82 patients who underwent at least one post-baseline ECG assessment,

6% experienced an increase in QTc of >60 msec compared to baseline after receiving dordaviprone and 1.2% had an increase in QTc to >500 msec.

US product labeling for dordaviprone recommends monitoring ECGs and electrolytes prior to starting dordaviprone and then periodically during treatment as clinically indicated. US product labeling also warns that significant prolongation of the QT interval may occur when dordaviprone is taken concomitantly with other products that have a known potential to prolong the QT interval, and therefore to increase the frequency of monitoring when administering dordaviprone to patients taking other products that have a known potential to prolong the QT interval and in patients with congenital long QT syndrome, existing QTc prolongation, a history of ventricular arrhythmias, electrolyte abnormalities, heart failure, or who are taking strong or moderate CYP3A4 inhibitors.

Refer to the QT IRT full report for additional details.

Immunogenicity

Data:

Data from the integrated safety analysis set indicate that <1% of patients have experienced a serious allergic reaction or symptoms of hypersensitivity requiring hospitalization.

The Applicant's Position:

Relevant warnings and precautions have been included in the proposed prescribing information to adequately address this potential risk.

The FDA's Assessment:

FDA agrees with the Applicant's position. In the pooled safety population (n=376), Grade 3 hypersensitivity reactions occurred in 0.3% of patients receiving dordaviprone.

Two patients in the overall safety population experienced an AE of hypersensitivity, as follows:

- ONC013-(b) (6) 72-year-old male with recurrent H3 K27M-mutant DMG developed Grade 1 drug hypersensitivity on Study Day 201. The investigator attributed the event as unlikely related to dordaviprone.
- ONC018-(b) (6) 13-year-old female with recurrent H3 K27M-mutant DMG developed Grade 3 hypersensitivity on Study Day 22. The event occurred two days after the last dose of dordaviprone. She was admitted for treatment of a DVT on Study Day 21 and was started on enoxaparin. The investigator attributed the event as not related to dordaviprone.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Adverse Events of Special Interest

Data:

Due to potential effects of D2 antagonism, specific AEs such encephalopathies (noninfectious encephalopathy/delirium), extrapyramidal syndrome, torsade de pointes/QT prolongation, and embolic and thrombotic events were monitored as AEOSIs throughout the overall program. These events are summarized following SMQ (narrow terms) at the top level and by PT.

Extrapyramidal syndrome

Within the integrated safety analysis set,1.2% of patients experienced events included in the extrapyramidal syndrome SMQ (trismus, dyskinesia, and hypertonia), with 3 reports of trismus including one Grade 3 event. None of these events were considered related to dordaviprone by the investigator. The incidence of extrapyramidal events was consistent across all age groups and treatment settings.

Noninfectious encephalopathy/delirium

Within the integrated safety analysis set, 2.4% of patients experienced events in the encephalopathy SMQ (8 cases of encephalopathy and 2 cases of delirium), with only one Grade 1 delirium event that was considered possibly related to dordaviprone by the investigator. Encephalopathy was predominantly reported in adults with recurrent disease (7 of the 8 cases).

Grade ≥3 encephalopathy occurred 1.4% of patients in the integrated safety analysis set. Though encephalopathy may be observed with disease progression and associated clinical decline in patients with glioma making attribution difficult, it is recommended that patients be monitored for signs and symptoms of encephalopathy (such as altered mental state, loss of memory or cognitive ability, inability to concentrate, lethargy, and progressive loss of consciousness).

Torsade de pointes/QT prolongation

Within the integrated safety analysis set, 3 participants (0.7%) experienced AEs of QT prolongation; all of these events were nonserious and Grade 1 in severity. Two of these events were considered possibly related to dordaviprone by the reporting investigator. The sponsor considered the events unlikely related because these events occurred at least 6 days following dordaviprone dosing.

The results of a dedicated thorough QTc study (ONC201-102) indicated a potential risk of clinically significant QT interval prolongation with dordaviprone; please refer to the "Electrocardiograms and QT" section above.

Embolic and thrombotic events

Embolic and thrombotic SMQ terms are the most frequently reported AEOSIs (19.0% of patients overall) in the integrated safety analysis set. This can be explained by the inclusion of hemiparesis and hemiplegia, both of which are clinical symptoms of glioma, in the SMQ search

terms, as well as the known high risk (up to 30%) of venous thromboembolism in the setting of high-grade glioma (Burdett 2023; Jo 2023). Most of the events were Grade 1 or 2 in severity; and though hemiparesis was the most commonly reported 'embolic and thrombotic' AE (15.6%, all causality), it was only considered by the investigator to be related to dordaviprone in 2.4% of patients.

Grade ≥3 embolic and thrombotic events were reported for 27 patients (6.4%), including a total of 6 patients (1.4%) reporting pulmonary embolism; the investigator considered pulmonary embolism to be at least possibly related to dordaviprone in 2 patients (0.5%). The incidence of embolic and thrombotic events by treatment setting ranged from 14.5% (pediatric post-RT nonrecurrent) to 23.5% (adult nonrecurrent). All 6 cases of pulmonary embolism were in adults with recurrent disease.

The Applicant's Position:

Thrombotic and embolic events were the most commonly reported AEOSIs in the integrated safety analysis set, with a reported incidence of 19%. However, when hemiparesis, a common clinical symptom of glioma, is excluded from the list of terms, the incidence of thromboembolic events decreases to 3%. Given the already high baseline risk of venous thromboembolism in patients with high-grade glioma, the current data does not indicate an increased risk for thrombotic and embolic events.

Although there were only 3 AEs of QT prolongation in the integrated safety analysis set, the results from the dedicated thorough QTc study (ONC201-102) suggest a potential risk of clinically significant QT interval prolongation with dordaviprone. Thus, warnings and precautions regarding this risk have been included in the proposed prescribing information.

The FDA's Assessment:

FDA agrees with the Applicant's position that the following adverse events were considered as events of special interest in this development program: extrapyramidal syndrome, noninfectious encephalopathy, QTc prolongation (refer to ECGs and QT section above), and venous thromboembolic events.

Extrapyramidal syndrome

Neurologic effects of anti-dopaminergic agents may include movement disorders characterized as extrapyramidal symptoms. Acute manifestations may include dystonia, akathisia, tremor, parkinsonism, and dyskinesias. In animal studies of dordaviprone, neurologic toxicities included tremor, seizures, excessive salivation, rigidity, abnormal gait, and twitching (see Section 5 for details).

In the overall safety population (n=376), movement disorders occurred in 26 patients (7%). However, due to the location of the tumors in the midline of the brain, it is challenging to differentiate the etiology of these adverse events (i.e., due to tumor location vs. due to

dordaviprone therapy). The most common movement disorder TEAE was "tremor," which occurred in 18 patients (4.8%), and most were Grade 1 TEAEs with the exception of three Grade 2 TEAEs and one Grade 3 TEAE. The Grade 3 TEAE of tremor occurred in a 23-year-old male with recurrent DMG and seizures who developed right-sided tremor in the setting of tachycardia and hypertension; he was treated with benzodiazepines and antibiotics; the tumor was stable on imaging, but due to its location in the left basal ganglia, thalamus, midbrain, pons and medial temporal lobe, it is challenging to rule out an impact of the tumor on the neurologic symptoms.

Encephalopathy

Encephalopathy is a broad term which implies a disturbance of brain function and can be due to a variety of causes, including the underlying brain tumor. In the overall safety population (n=376), related adverse events included confusional state (n=18), somnolence (n=12), lethargy (n=10), encephalopathy (n=8), depressed level of consciousness (n=7), delirium (n=2), mental status changes (n=2), and neurological decompensation (n=1). All Grade 3 or higher events were attributed as unrelated to dordaviprone by the investigator. It is challenging to rule out a potential contribution of dordaviprone to these events, however, it is most likely that the anatomic disease location led to these neurologic symptoms.

Venous thromboembolic events

Adverse events of venous thromboembolism occurred in 3.2% of patients in the overall safety population (Table 8.29), including 2.1% Grade 3 events (no Grade 4 or 5 events). FDA did not include events of hemiparesis or hemiplegia in this analysis as these events are nearly universal for patients with midline brain tumors due to neuroanatomy.

Table 8.29: TEAEs of venous thromboembolic events in the overall safety population (N=376)

Adverse Event Term	Narrative Details
Pulmonary embolism	6 adult patients with H3 K27M-mutant DMG experienced serious Grade 3 treatment-emergent adverse events of pulmonary embolism. 1. 34-year-old male with history of DVT on subtherapeutic enoxaparin (due to risk of intracranial hemorrhage) and recent hospitalization for fall and rib fracture; developed Grade 3 pulmonary embolism on Study Day 32 associated with Grade 3 pulmonary infarction; attributed as unrelated; patient continued same dose of dordaviprone. 2. 53-year-old male with history of DVT and recent hospitalization for tumor hemorrhage; developed Grade 3 pulmonary embolism on Study Day 33 which the investigator attributed to disease progression and

	not related to dordaviprone; treatment was interrupted and ultimately not resumed due to death from disease progression. 3. 43-year-old male with no prior history of venous thromboembolic events developed Grade 3 pulmonary embolism on Study Day 85; he was started on apixaban and recovered; attributed as unrelated; patient continued same dose of dordaviprone. 4. 52-year-old male with no prior history of venous thromboembolic events developed Grade 3 pulmonary embolism on Study Day 180; he was started on rivaroxoban and recovered; attributed as unrelated; patient continued same dose of dordaviprone. 5. 30-year-old female with history of obesity, hypercholesterolemia, hepatic steatosis, polycystic ovarian syndrome, and leg swelling developed Grade 3 pulmonary embolism on Study Day 84; she was started on apixaban and dordaviprone dose was reduced; attributed as possibly related although patient other risk factors included cancer and other comorbidities. 6. 39-year-old female with history of DVT and recently completed 6-month course of anticoagulation; developed Grade 3 pulmonary embolism on Study Day 7; dordaviprone was interrupted and dose reduced, and patient recovered; attributed as possibly related to dordaviprone but other risk factors including cancer and recent discontinuation of apixaban seven days prior.
Embolism	4 patients with H3 K27M-mutant DMG experienced treatment-emergent adverse events of embolism. 1. 56-year-old female with history of treatment with rivaroxaban developed left leg swelling on Study Day 64, ultrasound showed a DVT (Grade 3), and she was started on enoxaparin; dordaviprone was interrupted during hospitalization then resumed at the same dose; the event was attributed as unrelated to dordaviprone and due to underlying risk factors. 2. 59-year-old male developed right leg swelling and pain on Study Day 107, ultrasound showed a DVT (Grade 2), and he was started on rivaroxaban; dordaviprone was continued at the same dose; the event was attributed as unrelated to dordaviprone. 3. 13-year-old female developed Grade 3 extremity pain on Study Day 21; she had arm swelling and pain and an ultrasound showed thrombosis of the left brachial vein (Grade 2 embolism); the event was attributed as possibly related to dordaviprone. She was treated with enoxaparin. However, on Study Day 27, she developed a Grade 3 intracranial hemorrhage in the left temporoparietal lobe with midline shift. The patient recovered. She developed progressive disease on Study Day 48.

	4. 14-year-old female developed Grade 3 embolism (bilateral thigh deep vein thrombosis) on Study Day 85 after experiencing acute onset right thigh pain after a 5-hour airplane flight. She was treated with enoxaparin, and the event resolved; the event was attributed as unrelated to dordaviprone.
Deep vein thrombosis	43-year-old female with recurrent H3 K27M-mutant DMG developed Grade 2 deep vein thrombosis on Study Day 19. Dordaviprone was continued at the same dose and the investigator attributed the event as unrelated to the study drug.
Cerebral venous sinus thrombosis	5-year-old female with recurrent DIPG developed Grade 1 cerebral venous sinus thrombosis on Study Day 112, six days after the last dose of dordaviprone and in the setting of progressive disease. The investigator attributed the event as unrelated to the study drug.

In addition, one event of cerebrovascular accident occurred in a 21-year-old male with newly diagnosed H3 K27M-mutant DMG who developed left-sided weakness and dysarthria on Study Day 128 (NIHSS 9; started on aspirin 81 mg daily; Grade 3 event) which the investigator attributed the event as unlikely due to the study drug. Study drug dosing was interrupted briefly and resumed at a reduced dose on Day 144, the patient recovered and continued study drug at the reduced dose.

Venous thromboembolism (VTE) is a common complication in patients with primary brain tumors, with up to 20% of patients per year having a VTE event (Riedl et al, 2020). The rate observed in the overall safety population for dordaviprone is lower than this baseline rate and several patients had additional underlying risk factors (e.g., prior VTE event, obesity, plane travel). Therefore, based on the available data, there does not appear to be an increased risk of venous thromboembolism for patients receiving dordaviprone.

8.2.5.2 Other Potential Risks

Data / The Applicant's Position:

Coadministration of dordaviprone with moderate or strong CYP3A inhibitors or inducers should be avoided when possible due to clinically relevant drug-drug interactions. If unable to avoid administration of strong and moderate CYP3A4 inhibitors, reduce the dose of dordaviprone in adults.

Teratogenicity: Dordaviprone was teratogenic in embryo-fetal development studies in animals with systemic exposures lower than the expected human exposure based on the recommended dose. Based on this data, it is considered a potential human teratogen. Use in pregnancy is not recommended unless the benefit of treatment outweighs the risk.

The proposed prescribing information includes the most frequently reported AEs, along with relevant warnings and precautions for informed use of the drug product.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data / The Applicant's Position:

No analyses of patient-reported outcome assessments are included in this application.

The FDA's Assessment:

Not applicable

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Age

Patients aged ≥65 years had the lowest incidence of Grade ≥3 AEs (6.3% of patients, compared to 44.5% to 60.3% in other age groups); however, there were only 16 patients enrolled in that age group.

Adverse events reported in pediatric patients were generally similar to those reported in adults (18 to <65 years). Dehydration was only reported for pediatric patients and pulmonary embolism was only reported in adults. Grade ≥3 events of disease progression were reported for more younger patients (<12 years of age, 11.5%) than older patients.

Sex

The incidence of Grade ≥3 AEs was generally comparable across SOCs, with a higher incidence of AEs in the investigations SOC for females (12.1%) than males (5.0%).

The Applicant's Position:

There are no expected differences in safety outcomes between adults and pediatrics or between the sexes.

The FDA's Assessment:

FDA agrees with the Applicant's position. Forty-one percent (41%) of the overall safety population were pediatric patients; 30% were 2 to 11 years old, 11% were 12 to 17 years old. The incidence of adverse events was generally similar in adult and pediatric patients. Adverse events which occurred more frequently in children (≥10% difference in all grade TEAEs) included headache (43% vs. 32%), dysarthria (25% vs. 13%), ataxia (20% vs. 10%), vomiting (45% vs. 24%), and constipation (21% vs. 11%). Additional AEs which occurred in >10% of pediatric patients included increased weight (16%), decreased appetite (13%), pyrexia (13%), cough (12%), hydrocephalus (12%), diplopia (11%), extremity pain (11%), and abdominal pain (11%). High grade laboratory abnormalities worsened from baseline that occurred more

frequently in children (≥2% difference in Grades 3 or 4 lab abnormalities) included decreased calcium (5% vs. 2.7%) and increased bilirubin (9% vs. 4.6%).

Subgroup differences in safety can be challenging to appreciate and characterize in single arm trials. A PMR will be issued to verify and describe the clinical benefit of dordaviprone in patients with H3 K27M-mutant DMG. The ongoing randomized trial of dordaviprone will generate valuable safety data by enabling direct comparison of drug-related toxicities against the natural history of the underlying disease through its randomized study populations.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No specific safety studies were conducted for this application.

The FDA's Assessment:

Not applicable

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No human carcinogenicity studies were conducted for this application.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

Data:

No human reproduction or pregnancy studies were conducted for this application.

The Applicant's Position:

Dordaviprone is considered to be a potential teratogen based on nonclinical data.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

Data / The Applicant's Position:

No assessments of growth in pediatric patients were conducted for this application.

The FDA's Assessment:

FDA agrees with the Applicant's position. Given the uniformly fatal nature of the disease and short life expectancy of patients with recurrent H3 K27M-mutant DMG, it would be challenging to assess any detriments to long-term growth in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Dordaviprone withdrawal and/or rebound symptoms were not reported for any patients included in the integrated safety analysis set.

The Applicant's Position:

No cases of drug abuse have been reported in clinical studies. Drug abuse or dependence is not expected based on pharmacological class, mechanism of action, and the known pharmacologic profile of dordaviprone.

The potential for abuse of DRD2 antagonists is generally considered low. Unlike commonly abused substances that directly stimulate dopamine receptors to induce euphoria or other rewarding/pleasurable effects, DRD2 antagonists do not typically produce such effects. In fact, they often have the opposite effect, causing side effects that are generally not considered desirable, such as fatigue, dizziness, or blunting of emotions.

In the event of an overdose, individuals should be monitored for adverse effects and receive appropriate supportive care. There are no specific treatment recommendations.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Dordaviprone is not currently registered, approved, or marketed in the US or any other country.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

Data:

Additional safety data for dordaviprone is being collected in the Phase 3 ACTION study (ONC201-108), which will be ongoing during the initial post-marketing period.

The Applicant's Position:

The post-marketing safety profile of dordaviprone is anticipated to mirror the safety data captured during clinical studies and presented in the NDA, underscoring the favorable and manageable safety profile of dordaviprone across diverse patient populations.

The FDA's Assessment:

FDA agrees with the Applicant's position. Dordaviprone is expected to be administered by oncologists; management of and monitoring for adverse effects of anti-cancer medications, including potentially serious adverse effects, is standard practice in oncology. FDA does not anticipate that the safety of this product will differ significantly in the post-market setting.

8.2.11. Integrated Assessment of Safety

Data / The Applicant's Position:

The safety profile of dordaviprone is based on the results of the integrated safety analysis set, which included 422 adult and pediatric patients with glioma from 4 completed, open-label studies (ONC006, ONC013, ONC014, and ONC018). This comprehensive dataset has been presented in the preceding subheadings, addressing the safety profile of dordaviprone.

In addition to this integrated analysis, supportive safety data have been provided from clinical pharmacology studies, ongoing studies, IITs, and studies involving non-glioma indications, further validating the safety profile of dordaviprone across a broader range of clinical contexts.

The FDA's Assessment:

FDA agrees with the Applicant's position. The overall safety population included 376 adult and pediatric patients with glioma who received dordaviprone at the recommended weight-based dose across 4 open-label clinical studies (ONC006, ONC013, ONC014, and ONC018). Study ONC016 was an expanded access protocol and did not comprehensively assess safety.

Of the 376 patients who received dordaviprone, 35% were exposed for 6 months, and 17% were exposed for at least 1 year. The median age was 23 years (range: 3 to 80): 30% were 2 to 11 years old, 11% were 12 to 17 years old, 55% were 18 to 64 years old, and 3.7% were 65 years or older. Fifty-two percent (52%) were female; 74% White, 10% unknown race or race not

reported, 9% Black or African American, 4.0% Asian, 2.9% other or multiple races; and 13% were of Hispanic or Latino ethnicity. Karnofsky/Lansky Performance Status (KPS/LPS) score was 80 to 100 in 66% of patients, 60 to 70 in 27%, and <60 in 7%. Relevant disease characteristics included primary tumor locations in the midline (91%) and non-midline regions (9%); 33% had diffuse intrinsic pontine glioma (DIPG); 30% presented with multifocal disease; 79% had an H3 K27M mutation; 75% had recurrent disease.

Serious adverse reactions occurred in 33% of patients who received dordaviprone. Serious adverse reactions in >2% of patients included hydrocephalus (5%), vomiting (4.3%), headache (3.2%), seizure (2.4%), and muscular weakness (2.1%). Fatal adverse reactions occurred in 1% of patients who received dordaviprone, including cardiac arrest (0.5%), intracranial hemorrhage (0.3%), and encephalopathy (0.3%).

Permanent discontinuation of dordaviprone due to an adverse reaction occurred in 2.1% of patients. Adverse reactions which resulted in permanent discontinuation of MODEYSO in >1 patient included confusional state.

Dosage interruptions of dordaviprone due to an adverse reaction occurred in 6% of patients. Adverse reactions which required dosage interruption in >1 patient included increased alanine aminotransferase, increased aspartate aminotransferase, decreased lymphocyte count, muscular weakness, and aspiration pneumonia.

Dose reductions of dordaviprone due to an adverse reaction occurred in 2.7% of patients. Adverse reactions which required dose reductions in >1 patient included decreased neutrophil count and increased alanine aminotransferase.

The most common adverse reactions (≥20%) were fatigue, headache, vomiting, nausea, and musculoskeletal pain. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased calcium, and increased alanine aminotransferase. Other clinically important adverse reactions observed in less than 10% of patients treated with MODEYSO were peripheral neuropathy, seizure, diarrhea, tremor, and venous thromboembolic events. The product label will include Warnings for hypersensitivity, QTc prolongation, and embryofetal toxicity.

The review team considered that the safety profile of dordaviprone was acceptable when assessed in the context of a life-threatening disease. In addition, although dordaviprone can cause serious and severe toxicities, the safety concerns are described in product labeling, and dordaviprone will be prescribed by oncologists who are trained to monitor and treat serious treatment-related toxicities. There were no significant safety concerns identified during the NDA review requiring additional risk management tools such as a Risk Evaluation and Mitigation Strategy (REMS).

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

This NDA was primarily supported by an integrated efficacy population developed from five open label, non-randomized clinical studies conducted in the U.S. In general, deriving inference from a small integrated population of patients from non-randomized studies has inherent limitations, with interpretability of efficacy results limited by several factors including uncertainties related to small sample size, selection bias, and heterogeneity of individual studies.

Although uncertainties exist especially with the small sample size, the estimated response rate was considered clinically meaningful, and the study follow-up for DOR was sufficiently mature to characterize the duration of response. Pre-specified eligibility criteria were used to derive a relatively homogeneous patient population for efficacy analyses, which reduced concerns related to selection bias. The pooled studies are largely aligned with eligibility criteria, treatment dosing, use of prior or concomitant medication, and tumor assessment methods, which mitigated concerns regarding overall between-study heterogeneity in duration of follow-up and study populations, including demographics and baseline disease characteristics. Additionally, two of the five pooled studies included fewer than 5 patients eligible for pooling. To better understand the between-study heterogeneity in treatment effect while accounting for both sample size and observed response rates, FDA conducted a sensitivity analysis by applying inverse variance weighting to estimate the pooled ORR using the three studies with more than 5 patients eligible for pooling and included in the primary efficacy population. FDA also compared this weighted estimate to the unweighted pooled ORR from the same three studies as well as all five studies. The numerical similarity among the estimates further reduced concerns regarding the impact of heterogeneity in treatment effect across studies.

Considering the rarity of the disease and poor prognosis, FDA determined that it is reasonable to review integrated efficacy data pooled from multiple non-randomized studies of dordaviprone monotherapy in adults and pediatric patients.

The pre-specified primary endpoint in this integrated efficacy analysis was ORR per RANO-HGG according to BICR. However, given that RANO 2.0 criteria are the most clinically appropriate response criteria to use in this disease setting due to the heterogeneously enhancing nature of this tumor type, but were published after the five pooled studies were conducted, ORR per RANO 2.0 criteria was reported as the primary efficacy outcome measure in product labeling and the supportive efficacy results per RANO-HGG and RANO-LGG criteria were also provided.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The Applicant has provided substantial evidence of effectiveness to support the accelerated approval of dordaviprone under 21 CFR part 314 subpart H, for the treatment of adult and

pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy.

The efficacy of dordaviprone was evaluated in adult and pediatric patients with glioma across five open label, non-randomized clinical studies conducted in the U.S. (ONC006 [NCT02525692], ONC013 [NCT03295396], ONC014 [NCT03416530], ONC016 [NCT05392374], and ONC018 [NCT03134131]). Due to the rarity of the disease and poor prognosis, and in order to evaluate a sufficiently homogenous patient population to assess the effect of the drug, FDA determined it was reasonable to consider safety and efficacy data from a pooled population of patients derived from single arm trials of dordaviprone monotherapy at the recommended dosage in adults and pediatric patients with recurrent H3K27M-mutant DMG who met pre-specified criteria. Specifically, eligible patients were required to have progressive and measurable disease per Response Assessment in Neuro-Oncology-High Grade Glioma (RANO-HGG) criteria, be ≥90 days post radiation therapy, have adequate washout from prior anticancer therapies, have a Karnofsky Performance Status/Lansky Performance Status (KPS/LPS) score ≥ 60, and have stable or decreasing corticosteroid use. Patients received a weight-based dose of dordaviprone until disease progression or unacceptable toxicity.

The integrated efficacy population included 50 patients who met the pre-defined criteria. The major efficacy outcome measure was overall response rate (ORR) assessed by blinded independent central review (BICR) according to RANO 2.0 criteria. Additional efficacy outcome measures were BICR-assessed ORR according to RANO-HGG criteria and Response Assessment in Neuro-Oncology-Low Grade Glioma (RANO-LGG) criteria, duration of response, and time to response.

The ORR assessed by BICR according to RANO 2.0 criteria was 22% (95% CI: 12, 36), with 16% partial responses and 6% minor responses. The median duration of response (DOR) was 10.3 months (95% CI: 7.3, 15.2), with an observed DOR of ≥ 6 months in 73% of responders and ≥ 12 months in 27%. In this population, the observed durable responses are considered substantial as there are no available therapies, spontaneous responses are not observed in this disease setting, and median overall survival after progression is typically 4 to 6 months (Baugh et al, 2024; Coleman et al, 2023).

Drug approval requires substantial evidence of effectiveness through adequate and well-controlled studies, which are described in 21 CFR 314.126., There was a clear statement of objectives for the analyses that provided evidence of safety and effectiveness in this application, with a pre-specified statistical analysis plan which was reviewed by FDA, including pre-defined eligibility and response criteria. The study design incorporating data from single arm studies with standardized eligibility criteria was considered appropriate for this rare disease with no available therapy and a well characterized natural history. With respect to patient selection, all patients had progressive measurable disease after up-front standard of care treatment including radiotherapy, and all patients received dordaviprone monotherapy on study. Bias was minimized with pre-specification of inclusion criteria for the integrated efficacy population based on relevant clinical characteristics; in addition, supportive analyses which characterized the results in the context of the broader population enrolled across the single arm studies provided confidence in the results in the primary efficacy population. Finally, the response assessments were reliable and adequate

to assess the effect of the drug using appropriate statistical methods. Potential limitations to the evaluation of objective responses in brain tumor imaging are described herein; however, these limitations were mitigated by the study design (i.e., requiring at least 3 months from the time of last radiation), the collection of relevant data (e.g., pre-baseline MRI scans, data confirming true progression at baseline), and the granularity of data submitted in the application (e.g., narratives describing clinical improvements associated with responses).

The submitted evidence meets the statutory evidentiary standard for accelerated approval. An ORR of sufficient magnitude and duration is an endpoint reasonably likely to predict clinical benefit in patients with H3 K27M-mutant diffuse midline glioma, and this endpoint has supported the accelerated approvals of other therapies for patients with solid tumors harboring oncogenic driver mutations.

The Applicant intends to verify and describe the clinical benefit of dordaviprone based on the results of an ongoing randomized trial in patients with newly diagnosed H3 K27M-mutant glioma (Study ONC201-108) designed to evaluated OS and PFS endpoints, which is >50% enrolled as of July 2025. As this trial does not include pediatric patients with diffuse intrinsic pontine glioma, which is the most common subset of H3 K27M-mutant DMG among pediatric patients, additional clinical trial data will be required to support verification of benefit in this group of patients.

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence. Confirmatory evidence included BICR-assessed objective responses observed in patients with H3 K27M-mutant non-midline gliomas (i.e., hemispheric location), investigator-assessed objective responses in patients with recurrent H3 K27M-mutant DMG from other cohorts in Studies ONC013 and ONC014 (including patients with DIPG), investigator-assessed objective responses in patients with newly diagnosed H3 K27M-mutant DMG (i.e., an earlier line setting), and the lack of objective responses in patients with H3 K27M-wildtype disease. These clinical data are further supported by the biologically relevant mechanism of action of dordaviprone and evidence of restoration of histone H3 K27M trimethylation in tumor samples from patients treated with dordaviprone (Venneti et al, 2023).

The review team considered the safety profile of dordaviprone acceptable when assessed in the context of a life-threatening disease. The most common adverse reactions (≥20%) were fatigue, headache, vomiting, nausea, and musculoskeletal pain. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased calcium, and increased alanine aminotransferase. Other clinically important adverse reactions observed in less than 10% of patients treated with dordaviprone were peripheral neuropathy, seizure, diarrhea, tremor, and venous thromboembolic events. The product label will include Warnings for hypersensitivity, QTc prolongation, and embryofetal toxicity.

Although dordaviprone can cause serious and severe toxicities, the safety concerns are described and mitigated through instructions in product labeling; additionally, dordaviprone will be prescribed by oncologists who are trained to monitor and treat serious treatment-related

toxicities. There were no significant safety concerns identified during the NDA review requiring additional risk management tools such as a Risk Evaluation and Mitigation Strategy (REMS).

This is the first approval of a systemic therapy specifically for patients with diffuse midline glioma harboring an H3 K27M mutation. Based on the favorable benefit-risk assessment for use of dordaviprone in this population with a serious, life-threatening disease, accelerated approval is recommended for the following indication:

For the treatment of adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy.

8.4.1. Approach to Substantial Evidence of Effectiveness

1. Verbatim indication:

   Treatment of adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR

   c. ☐ Evidence that supported SEE from a prior approval *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)*[2]

3. Complete response, if applicable
   a. ☒ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)
[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)
[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

X	X
Primary Statistical Reviewer Arup Sinha, PhD	Statistical Team Leader Xiaoxue Li, PhD
X	X
Primary Clinical Reviewer Elizabeth Duke, MD	Clinical Team Leader Diana Bradford, MD

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indications.

10 Pediatrics

The Applicant's Position:

All relevant information from the pediatric population is presented in prior sections. The approved pediatric study plan was submitted in m1.9.6.

The FDA's Assessment:

The Applicant provided substantial evidence of safety and effectiveness to support the accelerated approval of dordaviprone in pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy.

Additional information is needed to verify and describe the clinical benefit of dordaviprone in pediatric patients with H3K27M-mutant diffuse midline glioma, including patients with DIPG. Therefore, a PMR was issued under the provisions of accelerated approval as follows:

> Conduct a clinical trial in pediatric patients (<17 years of age) with H3 K27M-mutant diffuse midline glioma, inclusive of a sufficient number of patients with Diffuse Intrinsic Pontine Glioma (DIPG), intended to verify and describe the clinical benefit of dordaviprone in the pediatric population. Endpoints evaluated should include overall response rate (ORR), duration of response (DOR), and overall survival (OS).

11 Labeling Recommendations

Data:

This NDA reflects the first submission of proposed labeling by the applicant.

The Applicant's Position:

There are no significant labeling changes at this time.

The FDA's Assessment: The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
1 INDICATIONS AND USAGE		FDA revised the proposed indication statement (b) (4) to age, "1 year of age and older" because at age less than one year, CYP3A enzymes are immature, regardless of the patient's weight.
2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection		FDA specified that the presence of H3 K27M mutation should be confirmed from tumor specimens.
2.2 Recommended Testing Before Starting MODEYSO		FDA removed (b) (4) and therefore, it is not required to repeat this up front in labeling.
2.3 (b) (4)		FDA combined this section with recommended dosage.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

2.3 Recommended Dosage and Administration		FDA revised this subsection for clarity and brevity, including administration instructions and the recommended dose. FDA added subheadings for vomiting and missed dose for clarity.
2.4 Dosage Modifications for Adverse Reactions		FDA added new subsection for dosage modifications for adverse reactions including a table for weight-based dosage modifications and a table for dosage modifications for adverse reactions by severity grade.
2.5 Dosage Modifications for CYP3A4 Inhibitors		FDA added a new subsection for recommended dosage of MODEYSO when taken concomitantly with a strong or a moderate CYP3A4 inhibitor.
3 DOSAGE FORMS AND STRENGTHS		Minor revisions for clarity.
5 WARNINGS AND PRECAUTIONS		FDA revised the text in section 5 for clarity, brevity and consistency with the Guidance Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format (October 2011). FDA deleted the Applicant's proposed (b) (4) FDA added details to subsection 5.2 QTc Interval Prolongation for safety. Subsection 5.3 Embryo-fetal Toxicity was revised for consistency with oncology labeling practice.
6 ADVERSE REACTIONS 6.1 Clinical Trials Experience		FDA revised the pooled safety population to N=376 to include only patients with a diagnosis of glioma who received the recommended dose and schedule of MODEYSO across 4 four open-label clinical studies (ONC006, ONC013,

		ONC014, and ONC018). The format was revised for consistency with oncology labeling practice and all incidences of adverse reactions were adjudicated.
7 DRUG INTERACTIONS		FDA revised the text for consistency with FDA's Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products-Content and Format, Guidance for Industry Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (December 2016).
8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy 8.2 Lactation 8.3 Females and Males of Reproductive Potential 8.4 Pediatric Use 8.5 Geriatric Use		Subsections 8.1 Pregnancy, 8.2 Lactation, and 8.3 Females and Males of Reproductive Potential were revised for consistency with the Guidance Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format (July 2020). Infertility statement was added. Subsection 8.4 Pediatric Use: description of the basis for use in pediatric patients was revised for clarity and brevity. Subsection 8.5 Geriatric Use: revised for consistency with 21 CFR 201.57(c)(9)(v). FDA omitted subsections 8.6 Renal Impairment and 8.7 Hepatic Impairment due to the lack of actionable information for consistency with 21 CFR 201.56(d)(4).
10 OVERDOSAGE		FDA omitted section 10 due to the lack of actionable information for consistency with 21 CFR 201.56(d)(4).
11 DESCRIPTION		The proposed text was edited and revised for consistency with 21 CFR 201.57(c)(12).

12 CLINICAL PHARMACOLOGY		Subsection 12. 1 Mechanism of Action was revised to specify that dordaviprone restores histone H3 K27 trimethylation in H3 K27M-mutant diffuse glioma, and for consistency with 21 CFR 201.57(c)(2)(iv). Subsection 12.2 Pharmacodynamics FDA revised the statement for cardiac electrophysiology and added a statement regarding dordaviprone exposure-response relationships and the time course of pharmacodynamic response for consistency with the 21 CFR 201.57(c)(13)(i)(B) requirements. Subsection 12.3 Pharmacokinetics (PK) FDA added maximum concentration (Cmax) and total systemic exposure (AUC) following dordaviprone administration. FDA included information on food effect, pediatric patients, renal impairment, hepatic impairment and drug interactions.
13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility		FDA stated that carcinogenesis studies were not performed with dordaviprone, and that dordaviprone is not genotoxic.
13.2 Animal Toxicology and/or Pharmacology		FDA included toxicity details from the dog study.
14 CLINICAL STUDIES		FDA revised the text for clarity, brevity and for consistency with oncology labeling practice. All numbers were adjudicated, and landmark duration of response limited to two time points.
16 HOW SUPPLIED/STORAGE AND HANDLING		FDA presented this information in a tabular format to improve clarity.

17 PATIENT COUNSELING INFORMATION		FDA revised this section for consistency with the advice in the full prescribing information.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The risks of dordaviprone are acceptable in the indicated patient population with a serious and life-threatening condition; the safe use of dordaviprone can be adequately implemented in the post-marketing setting through product labeling. No additional risk management strategies are recommended.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following post-marketing requirements (PMRs) and post-marketing commitment (PMC) will be included in the approval letter. Refer to Approval Letter for timelines.

PMR 4861-1: Complete a multiregional, randomized clinical trial in patients with H3 K27M-mutant diffuse midline glioma, intended to verify and describe the clinical benefit of dordaviprone through assessment of overall survival (OS) as a primary endpoint.

PMR 4861-2: Conduct a clinical trial in pediatric patients (<17 years of age) with H3 K27M-mutant diffuse midline glioma, inclusive of a sufficient number of patients with Diffuse Intrinsic Pontine Glioma (DIPG), intended to verify and describe the clinical benefit of dordaviprone in the pediatric population. Endpoints evaluated should include overall response rate (ORR), duration of response (DOR), and overall survival (OS).

PMC 4861-3: Conduct an appropriate analytical and clinical validation study to support the development of an in vitro diagnostic device using clinical trial data that demonstrates that the device is essential to the effective and safe use of dordaviprone for the treatment of adult and pediatric patients with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness:

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
X	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes _X__ No
X	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _X__ No
X	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _X__ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

R. Angelo de Claro, MD

Deputy Office Director, OOD (Acting)

Deputy Director, OCE (Acting)

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:

There were 5 covered clinical studies; financial disclosure information was submitted in m1.3.4.

***Covered Clinical Study (Name and/or Number):**
ONC006, ONC013, ONC014, ONC016, ONC018

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: _65_		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): __0__		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): __1__		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: __0__ Significant payments of other sorts: __0__ Proprietary interest in the product tested held by investigator: __0__ Significant equity interest held by investigator in study: __1__ Sponsor of covered study: _Oncoceutics, Inc. / Chimerix, Inc_		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) __0__		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant and confirmed/edited by the FDA.

The FDA's Assessment:

Financial disclosure information was collected for the investigators and sub-investigators participating in Studies ONC006, ONC013, ONC014, ONC016, ONC018.

In assessing the impact of this potential conflict, given that Dr. Cloughesy enrolled zero patients in the integrated efficacy population (n=50) and <2% of patients in the overall population of patients with glioma (N=422), and since the ORR endpoint was determined by BICR, FDA considers any potential bias related to the conflict would be mitigated.

Overall, FDA finds that any possible bias due to financial interests as disclosed by investigators was minimal and unlikely to affect the interpretation of the study.

19.3. Nonclinical Pharmacology/Toxicology

Data and Applicant's Position:

The nonclinical pharmacology and toxicology data for dordaviprone are presented in Section 5.

The FDA's Assessment:

Refer to Section 5.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:

Population PK analysis was conducted by the Applicant to characterize the PK of dordaviprone and evaluate the clinically relevant intrinsic and extrinsic covariate factors that could affect dordaviprone PK exposures. In the final population PK model, baseline bodyweight, albumin and disease status (patients vs healthy participants) were identified as significant covariates. Subjects with lower bodyweight, higher albumin tend to have higher PK exposures of dordaviprone. No clinically significant differences in dordaviprone PK exposures were observed based on age, sex, race, mild hepatic impairment, or mild/moderate renal impairment. PK simulations based on the final population PK analysis were performed to compare drug exposures across different bodyweight and age groups at the proposed recommended doses. As the current population PK analysis did not include any pediatric patients younger than 2 years old, which limits its ability to predict drug exposures due to the expression level of CYP3A4 in this age group, PK simulation was performed for patients aged 2 years or older. Dordaviprone exposures in pediatric patients who weigh more than 10 kg are generally predicted to be within range of those predicted in adults at the proposed recommended doses; with the exception of pediatric patients who weigh 10 to 12.4 kg. PK exposures for pediatric patients who weigh 10-12.4 kg receiving dose of 125 mg were predicted to be lower than adults at the proposed doses. This difference may be overestimated given CYP3A4 activity in pediatric patients who weigh 10 kg to 12.4 kg may be less than that of adults; lower CYP3A4 activity would likely lead to higher

dordaviprone exposure. The PK analysis cannot account for the reduced CYP3A4 activity in pediatric patients.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

General Information		
Objectives of PPK Analysis		• Characterize the PK of dordaviprone cross studies • Assess sources of PK variability • Predict individual exposure for E-R assessment
Study Included		ONC002, ONC005, ONC006, ONC013, ONC014, ONC201-101
Dose(s) Included		Every 3 weeks: 125 mg, 250 mg, 500 mg, 625 mg Weekly: 250 mg, 375 mg, 500 mg, 625 mg Single dose: 125 mg, 375 mg, 625 mg
Population Included		Healthy adult participants, adult and pediatric cancer patients
Population Characteristics	General	Age: median 31 years (range: 3 to 90 years) Weight: median 70.3 kg (range: 11.8 to 158 kg) N=219 (53.0%) male N=307 (74.3%) White, N=37 (9.0%) Black or African American, N= 19 (4.6%) Asian, N= 3 (0.7%) Native Hawaiian or other Pacific Islander, N= 2 (0.5%) Multiple, N=1 (0.2%) American Indian/Alaska Native
	Organ Impairment	Hepatic (NCI): N=349 (84.5%) Normal, N=57 (13.8%) Mild, N=2 (0.5%) Moderate, N=1 (0.2%) Severe, N=4 (1.0%) missing Renal (CrCL,): median 137 mL/min (range: 30.4 to 661 mL/min)
	Pediatrics (if any)	Age: median 9.0 years (range: 3 to 21 years) Weight: median 33.2 kg (range: 11.8 to 136 kg), N=1 (1%) 10 to 12.4 kg, N=37 (37%) 12.5 to 27.4 kg, N=19 (19%) 27.5 to 42.4 kg, N=18 (18%) 42.5 to 52.4 kg, N=25 (25%) 52.5+ kg (from model application)
No. of Patients, PK Samples, and BLQ		N=413 participants with N=5416 samples, N=340 (6.3%) samples pre-treatment BLQ, and N= 1510 (27.9%) post treatment BLQ samples
Sampling Schedule	Rich Sampling	ONC002 (Patient) C1D1: pre-dose, 0.5, 2, 4-, 6-, 48-, and 168-hours post-dose C2D1: pre-dose ONC005 (Patient) C1D1, C1D8, C1D15 and C1D22: pre-dose; 0.5, 2, 4, 6, 24, and 48 hours C2D1: pre-dose ONC201-101 (Healthy) Part A: Predose, 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 post-dose

		Part B1 and B2: Predose, 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 post-dose
	In ITT Population	ONC006 C1D1: pre-dose, 2 hours post-dose ONC013 C1D1: pre-dose, 2-, 24-, 48-, and 72-hours post-dose C1D8 and D15: pre-dose ≥C2: D1 pre-dose (even cycles only) ONC014 C1D1: pre-dose, 0.5, 2-, 4-, 24-, and 48-hours post-dose C1D8 and D15: pre-dose C2D1: pre-dose
Covariates Evaluated	Static	Body size, sex, age, CrCL at baseline, hepatic function, Karnofsky/Lansky performance status at baseline, disease status
	Time-varying	albumin, dose regimen, Concomitant medications, including CYP3A4-modifying drugs, acid-reducing drugs (PPIs, H2 antagonists, and other acid reducers), and dexamethasone

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM Version 7.5.1	Acceptable
Model Structure	2-compartment disposition model with first-order absorption with a lag time, and linear elimination.	Acceptable
Model Parameter Estimates	Table 16	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All parameters were estimated with acceptable precision. IIV on KA had the greatest shrinkage, likely due to differences in PK sampling schemes around T_{max} between patient and healthy populations	Acceptable
BLQ for Parameter Accuracy	27.9% of post-treatment observations were BLQ, therefore a likelihood imputation method (M3 imputation) was tested, the resulting model did not minimize, therefore no further pursuit of M3 imputation was made	Acceptable
GOF, VPC	Figure 1 and Figure 2	Acceptable
Significant Covariates and Clinical Relevance	Figure 3	Acceptable Renal and hepatic functions were evaluated as covariates, and none of them were identified as significant covariates.

Analysis Based on Simulation (optional)	The results of PK simulation based on final population PK model was summarized in Table 17. All pediatric weight groups except the 10 to 12.4 kg weight group had median Cmax ratios (adult Cmax as reference) of 0.8 or higher. In reference to the AUC of the adult subjects, two pediatric groups had a median AUC ratio of 0.8 or higher (27.5-42.4 kg and 52.2+ kg). All other pediatric groups had a median AUC ratio of less than 0.8.	As there were only 2 pediatric subjects with bodyweight 10-12.4 kg involved in the simulation, the results of the simulation should be interpreted with caution.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	No clinically significant differences in the PK of dordaviprone were observed based on age, sex, or race. No dose adjustments are recommended for patients with hepatic impairment or renal impairment.	Based on population PK analysis, no dose adjustments are recommended for patients with mild or moderate renal impairment, with mild hepatic impairment.

Table 19.1: Applicant – Parameter Estimates for the Refined Final PPK Model with the Updated Dataset

Parameters	**Estimate**	**%RSE**	**95 % CI**	
CL/F (L/hr)	29.7	3.13	27.9 – 31.5	
V2/F (L)	30.0	5.15	27.0 – 33.0	
KA (hr^{-1})	0.438	3.90	0.405 – 0.471	
ALAG (hr)	0.250	0.0300	0.249 – 0.250	
Q/F (L/hr)	27.8	3.80	25.8 – 29.9	
V3/F (L)	195	3.06	183 – 206	
BWT ~ volume (Exponent)	1.03	4.58	0.936 – 1.12	
BWT ~ clearance (exponent)	0.634	7.58	0.540 – 0.729	
Albumin ~ CL/F (exponent)	1.95	15.3	1.36 – 2.53	
Albumin ~V2/F (exponent)	3.87	11.1	3.03 – 4.71	
Healthy volunteer ~ V2/F (fractional change)	-0.873	4.50	-0.950 – -0.796	
Albumin ~V3/F (exponent)	0.766	24.8	0.394 – 1.14	
Random Effects	**Estimate (%CV)**	**%RSE**	**95% CI**	**Shrinkage (%)**

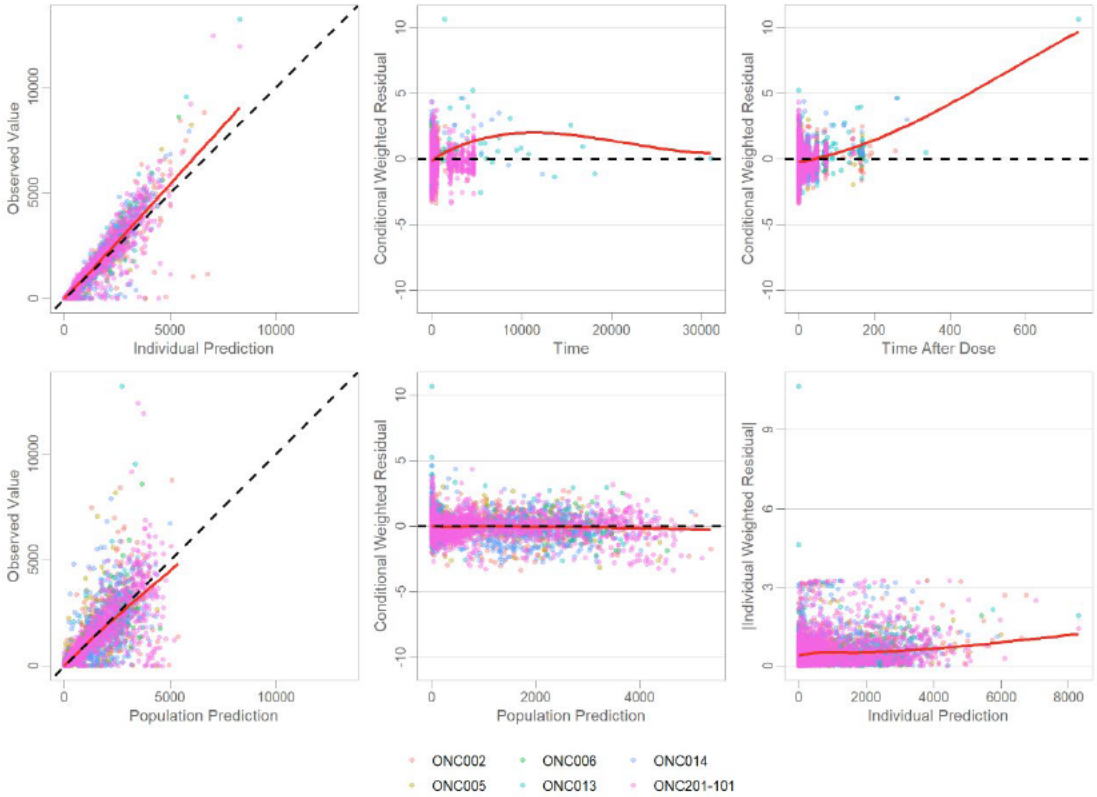
Parameters	Estimate	%RSE	95 % CI	
IIV on CL/F	53.0	5.44	47.2 – 58.5	10.7%
IIV on V2/F	225	12.9	172 – 287	22.8%
IIV on KA	18.8	18.1	10.2 – 24.6	57.8%
IIV on V3/F	26.1	9.72	20.6 – 30.7	36.2%
Residual Error	**Estimate**	**%RSE**		
Additive error (ng/mL)	2.60	25.8	1.29 – 3.91	10.2%
Proportional Error (%)	30.7	3.19	28.7 – 32.6	10.2%

Abbreviations: %CV=percent coefficient of variation; ALAG=absorption lag time; BWT=body weight at baseline; CI=confidence interval; CL/F=apparent clearance; IIV=interindividual variability; KA=absorption rate constant; PPK=population pharmacokinetic; Q/F=apparent intercompartmental clearance; RSE=relative standard error; V2/F=apparent volume of distribution for the central compartment; V3/F=apparent volume of distribution for the peripheral compartment

Notes: Parameter precision (95% CI) were calculated based on NONMEM covariate step. IIV was estimated on the variance scale in NONMEM and presented as %CV here using the approximation sqrt(exp[variance]-1).

Source: CHIM-ONC201_diagnostics_run315.Rmd

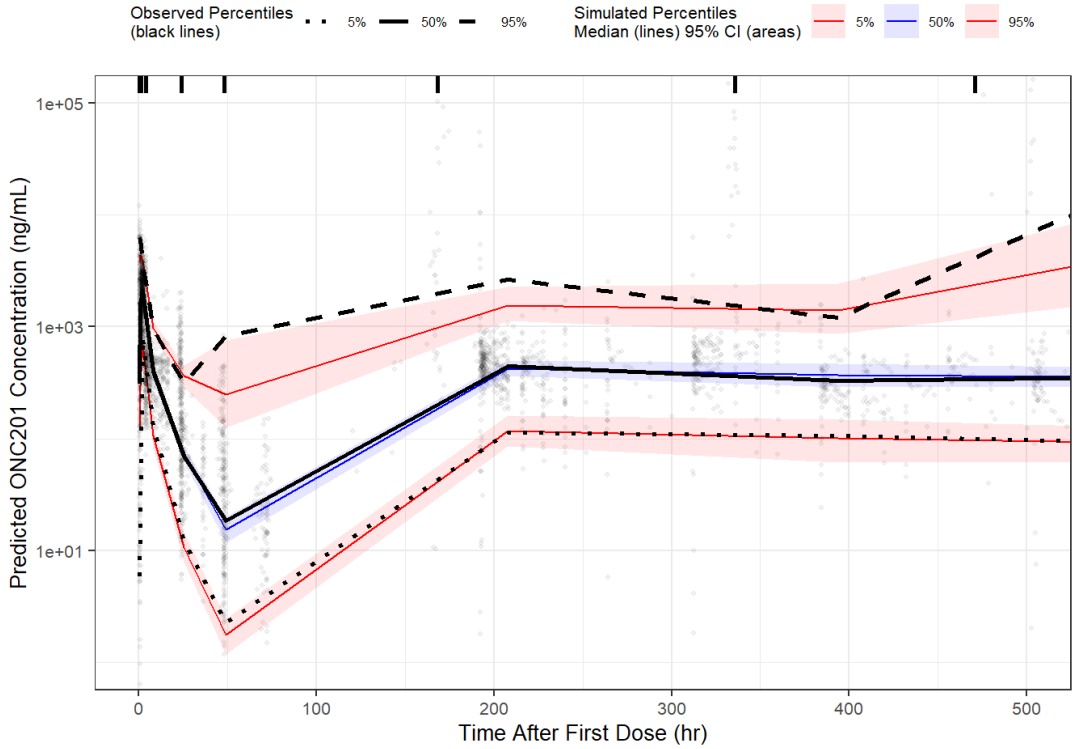
Figure 19.1: Applicant – Goodness-of-Fit Plots for the Final PPK Model (OBS-PRED/IPRED, CWRES-TIME/PRED)



Abbreviations: GOF=goodness of fit; LOESS=locally weighted scatterplot smoothing; PPK=population pharmacokinetic

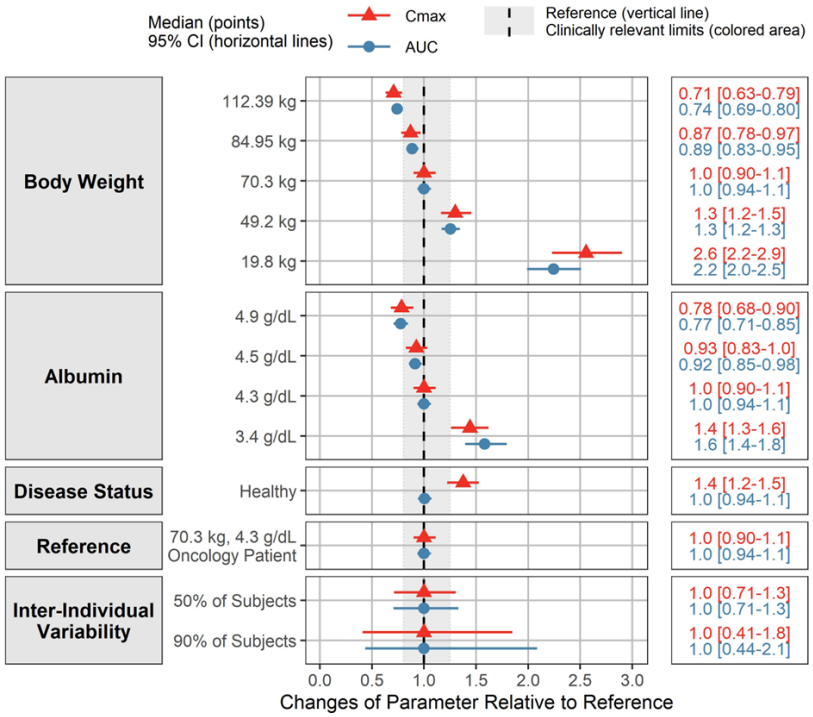
Notes: Dots are individual data points, solid lines are smoothed LOESS lines, and dashed black lines are lines of unity.
Source: CHIM-ONC201_diagnostics_run315.Rmd

Figure 19.2: Applicant – Prediction-corrected VC for the Refined Final PPK Model



Abbreviations: CI=confidence interval; p5=5th percentile; p95=95th percentile; PPK=population pharmacokinetic; VPC=visual predictive check
Notes: Black lines represent p5 (dotted), median (solid), and p95 (dashed) of the observed data. Solid red lines represent the p5 and p95 of the simulated data, and red shading represents the 95% CI of those percentiles. The solid blue line represents the median of the simulated data, and blue shading represents the 95% CI of the median. Gray dots represent individual observed dordaviprone (ONC201) concentrations.
Source: CHIM-ONC201_diagnostics_run315.Rmd

Figure 19.3: Applicant – Impact of Significant Covariates on Exposure (C_{max} and AUC)



Abbreviations: AUC=area under the concentration-time curve; CI=confidence interval; C_{max}=maximum concentration; PPK=population pharmacokinetics.

Notes: Reference subject is defined as an oncology patient with a body weight of 70.3 kg and baseline albumin of 4.3 g/dL. Body weight and albumin groupings represent the 5th, 25th, 50th, 75th, and 95th percentiles of the covariate value in the PPK dataset. Interindividual variability is displayed as the 50% and 90% prediction intervals for a reference subject. Clinically relevant limits are considered 0.8 to 1.25.

Source: Chimerix_ONC201_ForestPlot_2024.R

Table 19.2. Summary of Simulated Dordaviprone Exposures in Adults and Pediatric Subjects by Applicant.

	Adult (N=667)	Ped 10-12.4 kg (N=2)[a]	Ped 12.5-27.4 kg (N=138)	Ped 27.5-42.4 kg (N=83)	Ped 42.5-52.4 kg (N=45)	Ped 52.5+ kg (N=65)
C_{max} (ng/mL)						
Mean (CV%)	3300 (49.7%)	1470 (10.2%)	2840 (49.2%)	3170 (47.0%)	2900 (49.2%)	3020 (46.1%)
Median [Min, Max]	3060 [205, 11900]	1470 [1360, 1570]	2550 [519, 7730]	3070 [495, 6850]	2780 [282, 7090]	2690 [719, 6790]
95% PI	803 - 7260	1370 - 1570	934 - 6400	817 - 5760	688 - 5590	873 - 6220
$AUC_{0\text{-}168}$ (hr*ng/mL)						
Mean (CV%)	26900 (68.0%)	8470 (65.1%)	20000 (65.1%)	25000 (55.5%)	20600 (62.8%)	22400 (61.2%)
Median [Min, Max]	22200 [5120, 172000]	8470 [4570, 12400]	16000 [3470, 69900]	21300 [4230, 62600]	17200 [5300, 74200]	20000 [4930, 69800]
95% PI	8040 - 75100	4760 - 12200	5860 - 54800	5470 - 49800	7220 - 59800	7100 - 60100

Source: CHIM-PMX-ONC201-2784_Pediatric-Simulations-weight-bands_June2024.rmd
Abbreviations: Ped=pediatric; N=number of subjects; C_{max}=maximum concentration; AUC=area under the curve; CV=coefficient of variation; PI=prediction interval
[a] given the small number of subjects in this group, results should be interpreted with caution

The FDA's Assessment:

The result of population PK analysis for dordaviprone in adult and pediatric subjects were checked by the reviewer. The results of the population PK modeling were generally acceptable due to the agreement between prediction and observation. As there were only two pediatric subjects with bodyweight 10-12.4 kg involved in the PK simulation and reduced CYP3A levels in pediatric patients less than 1 years old compared to that of adults, the simulation results for pediatric subjects with bodyweight 10-12.4 kg should be interpreted with caution.

19.4.1.3. PPK Review Issues

Organ impairments (mild renal impairment vs normal renal function, moderate renal impairment vs normal renal function, mild hepatic impairment vs normal hepatic function) were evaluated as covariates on clearance of dordaviprone, and none of them were identified as significant covariates.

19.4.1.4. Reviewer's Independent Analysis

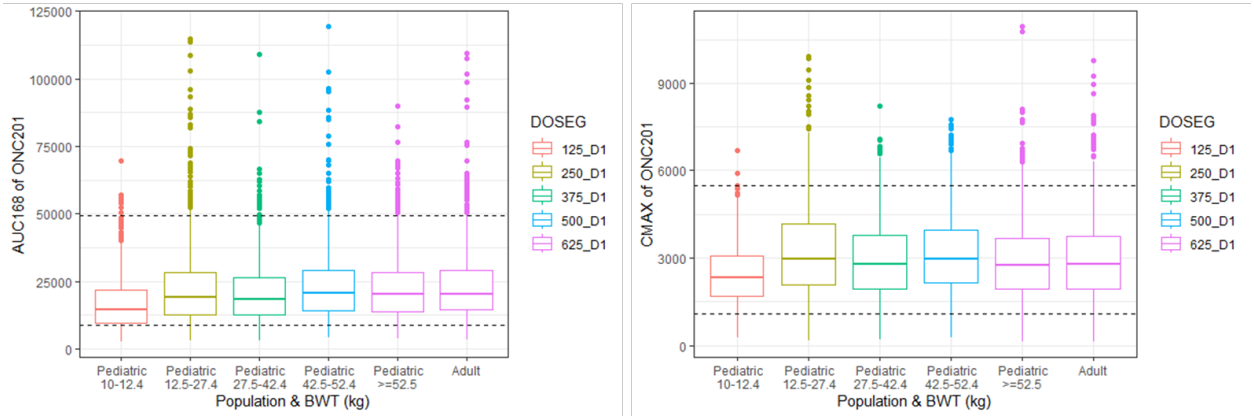
Based on the final population PK model of dordaviprone, simulations of dordaviprone exposures for pediatric and adult patients were performed to compare the exposures of bodyweight and age groups at proposed doses. One thousand subjects in each age and dose group were sampled from NHANEs dataset. Simulation results were summarized and shown in Figure 4 and Table 18. Dordaviprone AUC0-168h and Cmax for pediatric subjects with bodyweight 10-12.4 kg are predicted to be 30% and 16% lower than adults at the proposed doses.

Table 19.3. Summary of Simulated Dordaviprone Exposures in Pediatric and Adult Subjects by Reviewer.

Population	Pediatrics					Adult
Bodyweight Group (kg)	10-12.4	12.5-27.4	27.5-42.4	42.5-52.4	>=52.5	>=52.5
Dose Group (mg)	125	250	375	500	625	625
GeoMean AUC168	14464	18894	18265	20336	19893	20681
GeoRatio* AUC168	0.70	0.91	0.88	0.98	0.96	-
GeoMean Cmax	2213	2817	2638	2816	2586	2631
GeoRatio* Cmax	0.84	1.07	1.00	1.07	0.98	-

Source: Reviewer's analysis.

Figure 19.4. Comparison of Simulated Dordaviprone Exposures in Pediatric and Adult Subjects by Reviewer.



Source: Reviewer's analysis.

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

Exposure-response analysis was performed by the Applicant to characterize the relationship between dordaviprone exposures and efficacy endpoints including ORR and OS from Study ONC006, ONC013 and ONC014. Total of 39 subjects, including 3 pediatric subjects (Age: 8, 14 and 17 years old) in the primary efficacy analysis were included in the E-R analysis for ORR, and no significant E-R relationships were identified. The results of E-R analysis for ORR are inconclusive due to limited numbers of subjects in the primary efficacy analysis dataset. No clear ER relationship was observed in for OS in the overall population.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		To explore the relationship between dordaviprone exposure and efficacy via: • Objective response rate (ORR) in the primary efficacy analysis set • Overall survival (OS) in patients from ONC006, ONC013, and ONC014
Study Included		ONC006, ONC013, ONC014. These studies collected the efficacy endpoints of interest and allowed for assessment of efficacy in adult and pediatric patients
Endpoint		ORR and OS
No. of Patients (total, and with individual PK)		N= 39 (ORR) N= 196 (OS)
Population Characteristics	General	**ORR** Age: 31.0 years median (range: 9.0 to 70.0 years) Weight: 87.4 kg median (range: 42.9 to 153 kg) Sex: n=21 (53.8%) male Race: n=30 (76.9%) White, n=3 (7.7%) Black or African American, n=1 (2.6%) Asian, n=1 (2.6%) American Indian/Alaska Native, n=4 (10.3%) Other/Unknown **OS** Age: 19.0 years median (range: 3.0 to 75.0 years) Weight: 62.8 kg median (range: 11.8 to 158 kg) Sex: n=89 (45.4%) male Race: n=137 (69.9%) White, n=18 (9.2%) Black or African American, n=10 (5.1%) Asian, n=1 (0.5%) American Indian/Alaska Native, n=30 (15.3%) Other/Unknown
	Pediatrics (if any)	**ORR** N=3 (7.7%) Age: 14 years median (range: 9.0 to 17.0 years) Weight: 45.3 kg median (range: 42.9 to 71.1 kg) **OS** N=92 (46.9%) Age: 9.5 years median (range: 3.0 to 17.0 years)

	Weight: 32.8 kg median (range: 11.8 to 115.6 kg)	
Dose(s) Included	125 mg to 625 mg	
Exposure Metrics Explored	$AUC_{0\text{-}168}$, C_{max}	
Covariates Evaluated	Age, body weight, sex, race, number of relapses, Karnofsky/Lansky Performance score at baseline, concomitant medication use, diagnosis status, DIPG status, H3 K27M mutation status	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	ORR: Univariate evaluation using logistic regression OS: Cox proportional hazards model	Acceptable
Model Parameter Estimates	See Table 17 and Table 18 or univariate explanation of exposure results (ORR), cox proportional hazards model (OS) results	Acceptable
Model Evaluation	Not applicable	
Covariates and Clinical Relevance	There was no significant relationship between dordaviprone exposure and ORR in the primary efficacy analysis set.	Acceptable
Simulation for Specific Population	Not applicable	
Visualization of E-R relationships	Not applicable.	
Overall Clinical Relevance for ER	There was no significant relationship between dordaviprone exposure and ORR in the primary efficacy analysis set.	The results of E-R analysis for ORR are inconclusive due to the limited numbers of subjects in the analysis
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Not applicable	

Note, pediatric age and weight summarization presented in the ER (efficacy) Assessment Summary General Information Table is different from the table presented above (Table 8 in the POPPK report) because the data was summarized differently in the POPPK report. In the ER (efficacy) Assessment Summary General Information Table the pediatric patient (N=1) from the ONC006 study is included in summarization and the patients in the ONC014 study that were >18 years old are excluded.

Table 19.4: Applicant – Univariate Evaluation of Exposure – ORR Relationship

Model	AIC	p-Value
RANO-HGG		
ORR – AUC_{0-168}	40.7	0.911
ORR – C_{max}	40.5	0.643
RANO-LGG		
ORR – AUC_{0-168}	40.2	0.077
ORR – C_{max}	40.8	0.379
RANO 2.0		
ORR – AUC_{0-168}	44.8	0.252
ORR – C_{max}	45.6	0.467

Abbreviations: AIC=Akaike information criterion; AUC_{0-168}=area under the concentration-time curve over a 168-hour dosing interval; C_{max}=maximum concentration; ORR=objective response rate
Source: CHIM-PMX-ONC201-2784_ER_Efficacy-20241007.Rmd; m5.3.3.5

Table 19.5: Applicant – Cox Proportional Hazards Model Results

Model	AIC	p-Value
Overall Analysis Population		
OS – C_{max}	1459.94	0.57
OS – AUC_{0-168}	1458.90	0.26
Recurrent, Non-DIPG Population		
OS – C_{max}	699.99	0.03
OS – AUC_{0-168}	701.79	0.068

Abbreviations: AIC=Akaike information criterion; AUC_{0-168}=area under the concentration-time curve over a 168-hour dosing interval; C_{max}=maximum concentration; DIPG=diffuse intrinsic pontine glioma; OS=overall survival
Source: CHIM-PMX-ONC201-2784_ER_Efficacy-20241007.Rmd; m5.3.3.5

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

Exposure-response analysis was performed by the applicant to characterize the relationship between dordaviprone exposures and selected safety endpoints including Grade ≥3 Any TEAE, Grade ≥3 neurological TEAE, Grade ≥3 TEAE of special interest (noninfectious encephalopathy/delirium, extrapyramidal syndrome, torsades de pointes/QT prolongation, or embolic and thrombotic events). Total of 264 subjects from Study ONC006, ONC013 and ONC014 were included in the E-R safety analysis and no clear E-R relationship were observed between dordaviprone exposures and the selected safety endpoints.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:

General Information			
Goal of ER analysis		To explore the relationship between dordaviprone exposure and safety in patients from ONC006, ONC013, and ONC014	
Study Included		ONC006, ONC013, ONC014. These patient studies collected the safety endpoints of interest and allowed for assessment of safety in adult and pediatric patients	
Population Included		ITT patients	
Endpoint		Any TEAE of Grade 3 or higher, neurological TEAE of Grade 3 or higher, TEAE of special interest (noninfectious encephalopathy/delirium, extrapyramidal syndrome, torsade de pointes/QT prolongation, or embolic and thrombotic events) of Grade 3 or higher	
No. of Patients (total, and with individual PK)		N=264	
Population Characteristics	General	Age: 21.0 years median (range: 3.0 to 80.0 years) Weight: 62.9 kg median (range: 11.8 to 158 kg) Sex: N=120 (45.5%) male Race: N=194 (73.5%) White, N= 22 (8.3%) Black or African American, N=11 (4.2%) Asian, N=1 (0.4%) American Indian/Alaska Native, N=2 (0.8%) Multiple, N= 34 (12.9%) Other/Unknown	
	Organ impairment	Refer to population PK analysis for the numbers of patients with organ impairment.	
	Pediatrics (if any)	N=116 (43.9%) Age: 8.0 years median (range: 3.0 to 17.0 years) Weight: 30.1 kg median (range: 11.8 to 115.6 kg)	
	Geriatrics (if any)	Not analyzed separately from the general population.	
Dose(s) Included		125 mg to 625 mg	
Exposure Metrics Explored (range)		$AUC_{0\text{-}168}$, C_{max}	
Covariates Evaluated		Age, body weight, sex, race, number of relapses, Karnofsky/Lansky Performance score at baseline, concomitant medication use, diagnosis status, DIPG status, H3 K27M mutation status	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Univariate logistic regression and graphical exploration	Acceptable
Model Parameter Estimates		See Table 19 for univariate logistic regression p-values	Acceptable
Model Evaluation		Not applicable	

Covariates and Clinical Relevance	Due to the absence of a relationship between dordaviprone exposure and safety, no covariate analysis was performed.	Acceptable
Simulation for Specific Population	Not applicable	
Visualization of E-R relationships	Not applicable	
Overall Clinical Relevance for ER	There was no relationship between dordaviprone exposure and the safety endpoints: any TEAEs of Grade 3 or higher, neurological TEAE of Grade 3 or higher, TEAE of special interest (noninfectious encephalopathy/ delirium, extrapyramidal syndrome, torsade de pointes/QT prolongation, or embolic and thrombotic events) of Grade 3 or higher.	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Not applicable	

Table 19.6: Applicant – Univariate Logistic Regression p-Value of Exposure-Safety Relationships

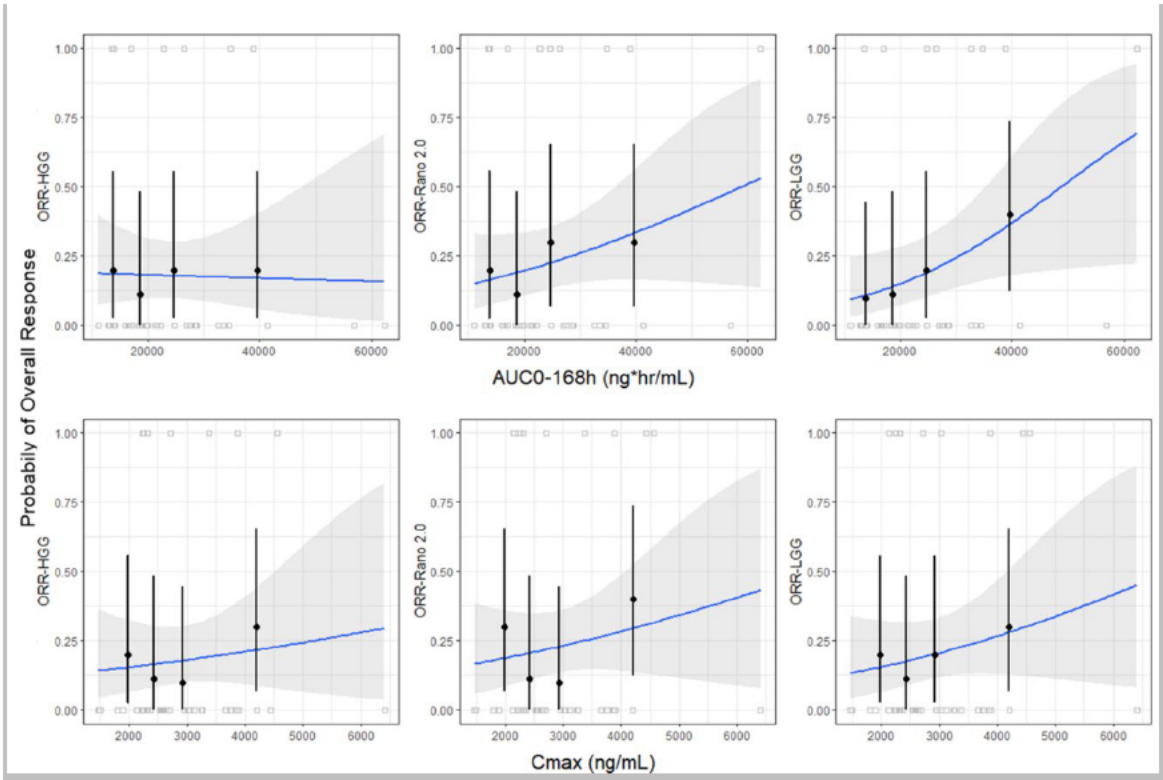
	Any TEAE	Neurological TEAE	TEAE of Special Interest
C_{max}	0.61	0.20	0.24
AUC_{0-168}	0.95	0.18	0.55

Abbreviations: AUC_{0-168}=area under the concentration-time curve over a 168-hour dosing interval; C_{max}=maximum concentration; TEAE=treatment-emergent adverse event.
Source: CHIM-PMX-ONC201-2784_ER_Safety.Rmd; m5.3.3.5

The FDA's Assessment:

The E-R efficacy analysis was checked by the reviewer. Although positive trends were observed for ORR-RANO 2.0, ORR-LGG with the exposures (AUC_{0-168h} and C_{max}) of dordaviprone, the relationships were not statistically significant (Figure 5). The results of E-R analysis are inconclusive due to the limited numbers of patients in the analysis.

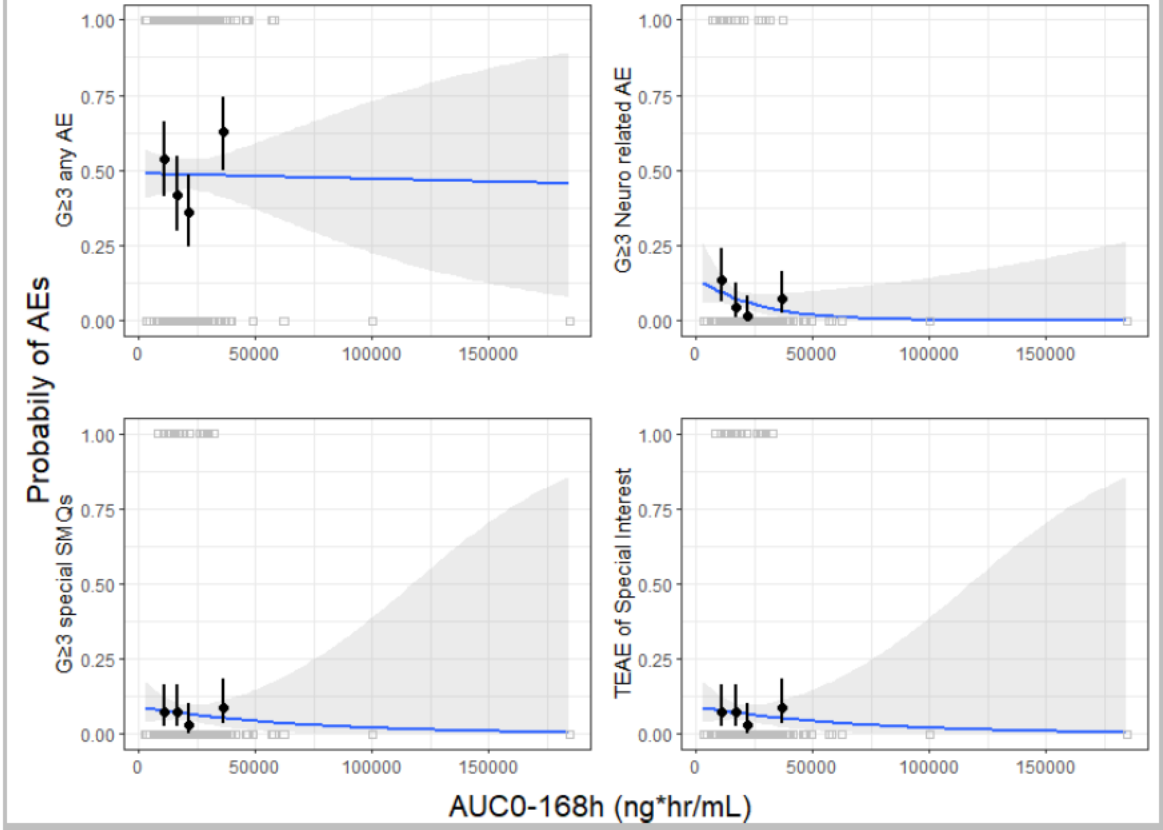
Figure 19.5. Logistic Regression for ORRs and dordaviprone exposures ($AUC_{0\text{-}168h}$ and C_{max})



Source: Reviewer's analysis.

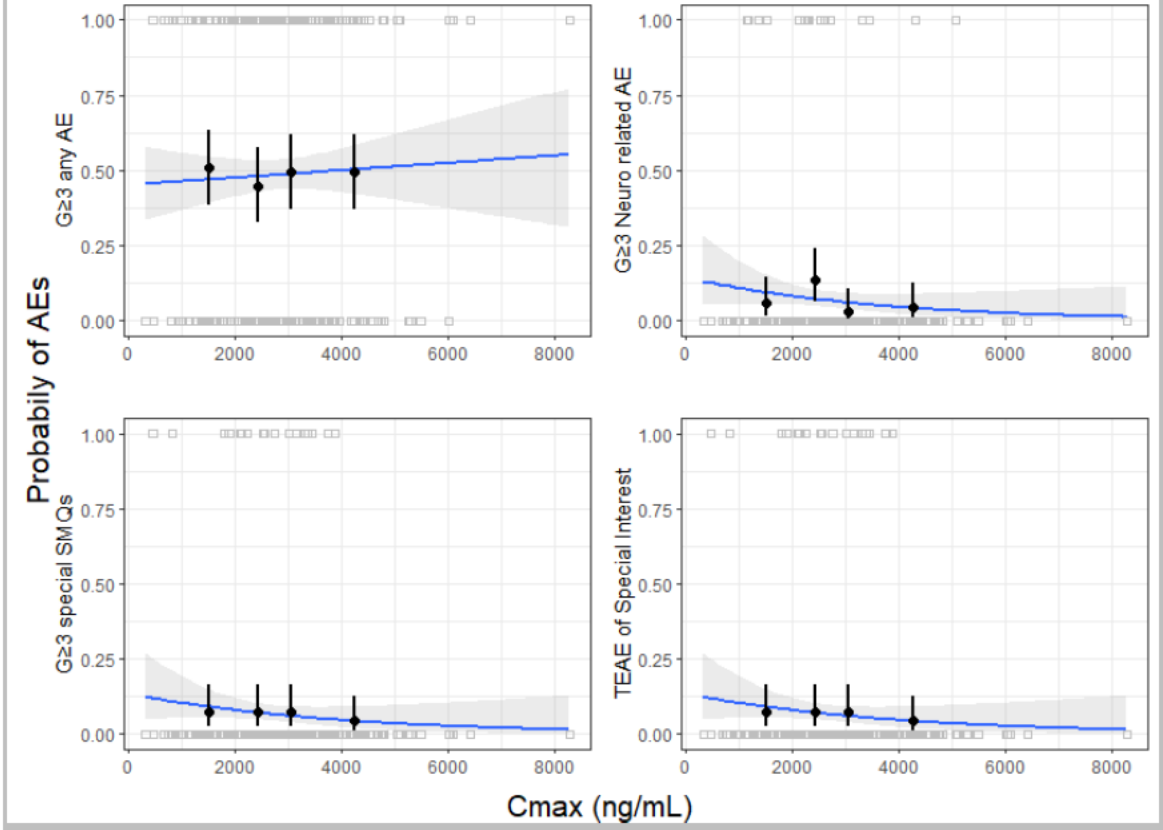
The E-R safety analysis was checked by the reviewer. No clear E-R trends were observed between dordaviprone exposures ($AUC_{0\text{-}168h}$, C_{max}) and selected safety endpoints including Grade ≥ 3 TEAE, Grade ≥ 3 neurological TEAE, Grade ≥ 3 for special SMQs, TEAE of special interest (noninfectious encephalopathy/delirium, extrapyramidal syndrome, torsades de pointes/QT prolongation, or embolic and thrombotic events) in Figure 6 and Figure 7.

Figure 19.6. Logistic Regression for Selected AEs and dordaviprone $AUC_{0\text{-}168h}$



Source: Reviewer's analysis

Figure 19.7. Logistic Regression for Selected AEs and dordaviprone C_{max}.



Source: Reviewer's analysis.

19.4.2.5. ER Review Issues

NA

19.4.2.6. Reviewer's Independent Analysis

NA

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The efficacy and safety analyses of dordaviprone in patients with recurrent H3 K27M-mutant diffuse glioma showed no significant relationship between drug exposure and ORR with no increased safety findings with higher exposures. This indicates minimal safety risk at the doses evaluated and supports the recommended dordaviprone dose of 625 mg, or the equivalent body

weight-adjusted pediatric dose, administered once weekly at least 1 hour before or 3 hours after a meal.

The FDA's Assessment:

Although E-R analysis for ORR was inconclusive due to the limited number patients in the analysis, positive trends were observed for ORR-RANO 2.0 and ORR-RANO LGG with exposures of dordaviprone. No clear relationships were observed for the selected safety endpoints in E-R safety analysis. Additional doses finding studies including higher doses or shorter dosing intervals should be conducted for dose optimization on efficacy and safety.

19.4.3. Physiologically based Pharmacokinetic Modeling

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to:

- Evaluate the drug-drug interaction (DDI) potential of dordaviprone as an object of CYP3A4 inhibitors and inducers.
- Evaluate the DDI potential of dordaviprone as a precipitant of substrates of CYP3A4, CYP2C8, CYP2D6, and P-gp.

FDA concluded the following:

- The PBPK analyses are adequate to predict the effects of CYP3A4 inhibitors on the exposure of dordaviprone. The moderate CYP3A4 inhibitors fluconazole and erythromycin were predicted to increase dordaviprone AUC up to 2.7-fold, and the weak CYP3A4 inhibitor cimetidine was predicted to increase dordaviprone AUC by approximately 1.7-fold.
- The PBPK analyses are adequate to predict the effects of CYP3A4 inducers on the exposure of dordaviprone. The strong CYP3A4 inducer rifampin was predicted to reduce dordaviprone AUC by 83%, and the moderate CYP3A4 inducer was predicted to reduce dordaviprone AUC by 65%.
- Dordaviprone was predicted to have negligible effects on the exposures of the CYP2D6 substrate desipramine, the P-gp substrate dabigatran etexilate, the OATP1B/BCRP substrate rosuvastatin, the CYP3A substrate midazolam, and the CYP2C8 substrate repaglinide following once weekly administration of 625 mg dordaviprone.

Background

Dordaviprone (also known as ONC201, ONC201•2HCl) is a small-molecule protease activator, which is being developed for the treatment of H3 K27M mutant diffuse glioma in adult and pediatric patients weighing at least 10 kg with progressive disease following prior therapy. The proposed dosage of dordaviprone is 625 mg (five 125 mg capsules) orally once weekly for adult and pediatric patients weighing at least 52.5 kg, and dose scaled by body weight, orally once weekly for pediatric patients weighing less than 52.5 kg. The available dosage strength is 125 mg capsules.

Dordaviprone plasma exposures (C_{max}, AUC_{last} and AUC_{inf}) increased approximately dose proportional over the range of 125 mg to 625 mg following oral administration of single doses of dordaviprone in healthy males based on the power model (Study ONC201-101, Part A). Following multiple doses of dordaviprone at the 375 and 625 mg QW dose in patients with advanced solid tumors, exposure increased with increasing dose and no accumulation was observed (Study ONC002). Compared to the fasted state, the median T_{max} was delayed by approximately 2 hours, AUC was unchanged and C_{max} decreased by approximately 40% in healthy adult subjects following a single oral dose of 625 mg dordaviprone after a standardized FDA high-fat meal (ONC201-101).

Dordaviprone is primarily metabolized by CYP3A4 in vitro, followed by CYP2D6 (ONC201-NCA-100). Contribution of CYP3A4 in dordaviprone metabolism was confirmed by a clinical DDI study with the strong CYP3A4 inhibitor itraconazole. Itraconazole 200 mg once daily increase dordaviprone AUC_{inf} and C_{max} by 4.48- and 1.93-fold, respectively when co-administered with a single 125 mg dordaviprone (Study ONC201-103). The human ADME study in healthy male adult patients (Study ONC201-106) following a single oral dose of 625 mg dordaviprone showed that approximately 91% of the dose administered orally was recovered, in which approximately 70% and 20% of the dose were recovered in the urine and the feces, respectively. Unchanged parent drug in feces represented less than 0.3% of the dose, indicating that dordaviprone was well absorbed. Less than 0.2% of the dose was excreted as unchanged drug in the urine, indicating that renal elimination of dordaviprone was minimal. The apparent oral clearance of dordaviprone was approximately 36 L/h.

Based on in vitro drug interaction studies, dordaviprone is determined to be a reversible inhibitor but not a time-dependent inhibitor of the CYP enzymes studied (Study I5678). Based on the hepatocyte induction study (15676-RPT03761), dordaviprone is an inducer of CYP1A2, CYP2B6, and CYP3A4 because, at 50 times of unbound plasma peak concentration (C_{max} = 14.4 mM), dordaviprone increased mRNA expression of CYP1A2, CYP2B6, and CYP3A4 greater than 2-fold in at least one donor, and a concentration-dependent increase was observed in CYP3A4 mRNA but not in CYP1A2 and CYP2B6 mRNA, likely due to decrease in hepatocyte viability at dordaviprone concentrations no less than 20 mM. Dordaviprone is not a substrate (Study C19207) but an inhibitor (Study I5679) of all the transporters tested (Table 19.7). Clinical drug interaction studies with dordaviprone as a precipitant have not been conducted. Refer to

clinical pharmacology section for detail information on dordaviprone regarding ADME properties, *in vitro* and clinical studies used in PBPK modeling.

Table 19.7 In vitro drug interaction potential of dordaviprone as an inhibitor of various transporters and enzymes

Transporters	Test system	Substrate	IC50 (uM)
P-gp / MDR1	MDCKII-MDR1	digoxin (1 µM)	53.7
BCRP	MDCKII-BCRP	prazosin (1 µM)	207.3
OATP1B1	HEK293-OATP1B1	Estradiol-17-glucuronide (1 µM)	52.3
OATP1B3	HEK293-OATP1B3	Cholecystokinine-8 (0.11 µM)	36.5
OAT1	CHO-OAT1	p-Aminohippurate (1 µM)	2.5
OAT3	MDCKII-OAT3	Estrone-3-Sulfate (1 µM)	3.8
MATE1	MDCKII-MATE1	Metformin (2 µM)	8.4
MATE2-K	MDCKII-MATE2-K	Metformin (10 µM)	75
OCT1	CHO-OCT1	Tetraethyl-ammonium (5 µM)	22.9
OCT2	CHO-OCT2	Tetraethyl-ammonium (5 µM)	28.8

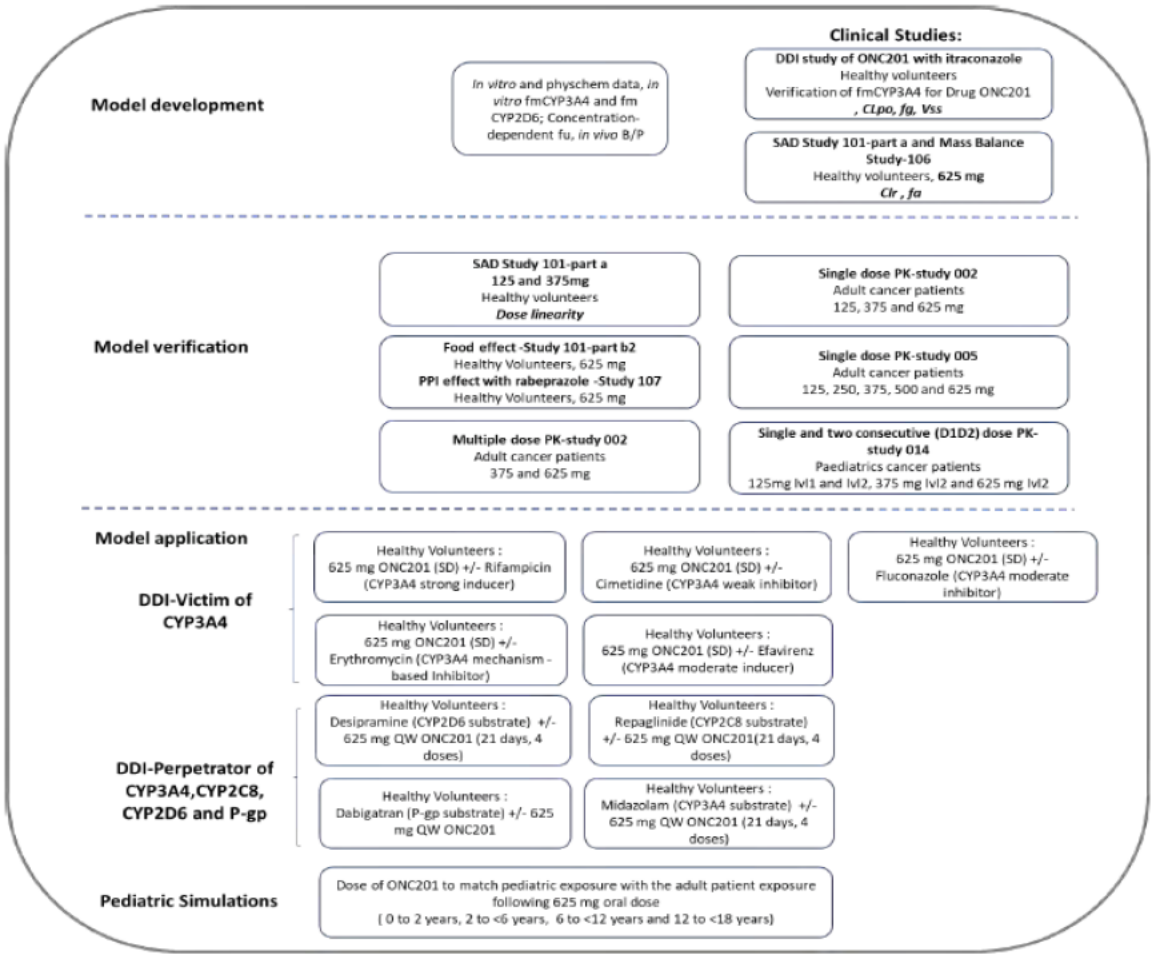
Test System: Human Liver Microsomes		Apparent K_i (µM)
Enzyme	Enzyme reaction	
CYP1A2	Phenacetin O-deethylation	NC
CYP2B6	Bupropion-hydroxylation	89.99
CYP2C8	Amodiaquine N-deethylation	31.20
CYP2C9	Diclofenac 4'-hydroxylation	61.75
CYP2C19	S-Mephenytoin 4'-hydroxylation	57.97
CYP2D6	Bufuralol 1'-hydroxylation	27.12
CYP3A4/5	Midazolam 1'-hydroxylation	54.60
CYP3A4/5	Testosterone 6β-hydroxylation	20.24

Source: Study I5678 and Study I5679

Methods

All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 21, Certara, Sheffield, UK), unless noted below. Simulations were performed using the default healthy subject population model. Age, sex, subject number, and dosing regimens were consistent with the actual trial design. Ten trials were simulated for each simulation scenario. Schemes of the PBPK modeling and simulation strategy are shown in Figure 19.8 Modeling and simulation strategy, which summarizes the studies used for dordaviprone model development and verification, and model applications in predicting DDI of dordaviprone as an object of CYP3A4 induction or inhibition and as a precipitant of various transports and enzymes. The final model input parameters are summarized in **Table 19.8** and **Figure 19.8**. All K_i values for the enzymes were half of the IC50 values generated experimentally. The dordaviprone PBPK models consist of an Advanced Dissolution, Absorption and Metabolism (ADAM) model for describing drug absorption in each gut segment, a minimal PBPK model with a single adjustable compartment for distribution, and an enzyme kinetics model for elimination. The Simcyp library files for the models of rifampin (SV-Rifampicin-MD), itraconazole, erythromycin, fluconazole, cimetidine, efavirenz, modafinil, repaglinide, desipramine, midazolam, and dabigatran were used without any modification, unless otherwise noted.

Figure 19.8 Modeling and simulation strategy



B/P: blood to plasma ratio; CL_{po}: oral clearance; CL_R: renal clearance; fa: fraction absorbed; F_G: intestinal availability; fu: fraction unbound; PPB: plasma protein binding; PPI: proton pump inhibitor; QW: once a week; SAD: single ascending dose; SD: single dose; V_{SS}: steady-state volume of distribution.

Source: Figure 1 in the PBPK report chmx3a-b

Table 19.8 Final input parameters in the PBPK model of dordaviprone

PARAMETER	Value	Reference
Physicochemical and Binding Parameters		
MW (g/mol)	386.49	Investigator's Brochure
Log P	3.09	Report 173047-PartA
Compound type	Diprotic Base	Investigator's Brochure
pKa	6.76, 4.99	Report 173047-PartA
B:P	0.778	Final Report ONC201-106
fu – 0.193 mg/L	0.0294	Report ONC201-NCA-106
fu – 0.386 mg/L	0.0303	
fu – 1.932 mg/L	0.0389	
fu – 3.865 mg/L	0.0412	
fu – 7.730 mg/L	0.0492	
Main binding protein	AAG	Report ONC201-NCA-101
Absorption Model – ADAM Model		
fu_{gut}	0.993	Retrograde model
Caco-2 P_{app} ($x10^{-6}$ cm/s)	27.01	Report C19208
Calibrator (Metoprolol) P_{app} ($x10^{-6}$ cm/s)	33.27	
$P_{eff,man}$ (pred) ($x10^{-4}$ cm/s)	3.74	Predicted
Formulation type	Immediate Release	Investigator's Brochure
Solubility data	User-defined pH-solubility profile	
Solubility (mg/mL) pH 1	62.2	Shake-flask Solubility Report
Solubility (mg/mL) pH 4	92.1	Shake-flask Solubility Report
Solubility (mg/mL) pH 4.5	98.6	Shake-flask Solubility Report
Solubility (mg/mL) pH 5	6.02	Shake-flask Solubility Report
Solubility (mg/mL) pH 6	0.26	Shake-flask Solubility Report
$K_{m:w,neutral}$	4.58	Simcyp predicted
$K_{m,w,Ion}$	2.58	Simcyp predicted
Precipitation Model	Model 2	
Precipitation Rate Constant (1/h)	4	Simcyp default
Critical Supersaturation Ratio	10	Simcyp default
Distribution Model – Minimal PBPK Model		
V_{SS} (L/kg)	1.11	Predicted (Method 3)
k_{in} (1/h)	0.11	Fitted parameters to recover observed plasma concentration *versus* time profiles in Clinical Study 101
k_{out} (1/h)	0.15	
V_{SAC} (L/kg)	6.60E-05	
Elimination Parameters		
CL/F (L/h)	29	Clinical Study 103
fm_{CYP3A4}	0.8	Adjusted fm inputs in retrograde calculations to recover Clinical Study 103 interaction results (AUC and C_{max} ratio in the presence and absence of itraconazole)
fm_{CYP2D6}	0.2	
CYP3A4 CL_{int} (µL/min/pmol)	1.17	Retrograde model; fmCYP3A4,0.8.
CYP2D6 CL_{int} (µL/min/pmol)	6.93	Retrograde model; fmCYP2D6,0.2.
CL_R (L/h)	0.00	Estimated as zero based on findings from Clinical Study 106
Interaction Parameters		
CYP3A4 K_i (µM)	20.24	Report RPT03773
CYP2C8 K_i (µM)	31.2	Report RPT03773
CYP2D6 K_i (µM)	27.12	Report RPT03773
fu_{mic}	0.93	Predicted
P-gp K_i (µM)	32.2	Report RPT03775

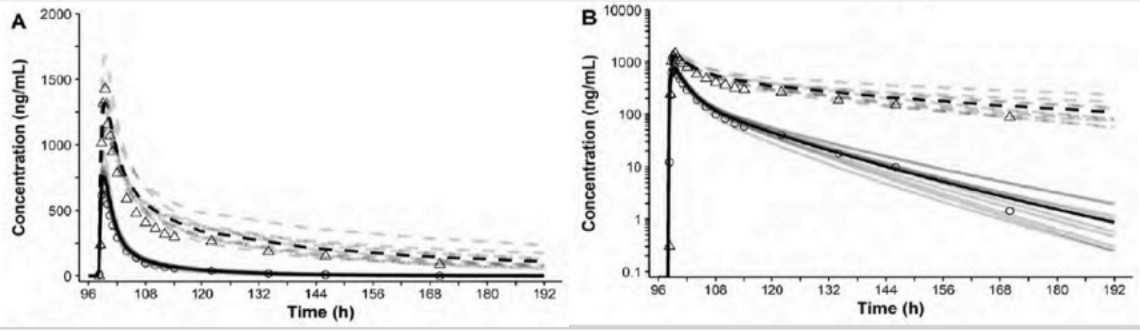
Source: Table 8 in the PBPK report chmx3a-b

Results

Can the PBPK model adequately describe the PK profiles of dordaviprone?

Yes. The model was developed and optimized using the data from the itraconazole DDI study (**Figure 19.9** and **Table 19.9**). Clinical PK data that had not been used in model development was used to verify the ability of the dordaviprone PBPK model to describe the PK profiles of dordaviprone. The model could reasonably describe the plasma concentration-time profiles of dordaviprone following single and multiple oral doses of dordaviprone in adult patients with cancer. Majority of the model-estimated AUC and C_{max} were within 2-fold of the observed values. This predictive performance was considered reasonable considering the high variability in dordaviprone PK (CV% >100%) reported in patients. Simulated and observed dordaviprone PK profiles and parameters are summarized in **Figure 19.10** and **Table 19.10**.

Figure 19.9 Simulated and observed mean plasma concentrations of dordaviprone in the absence and presence of itraconazole 200 mg once daily following a single 125 mg dordaviprone in healthy subjects



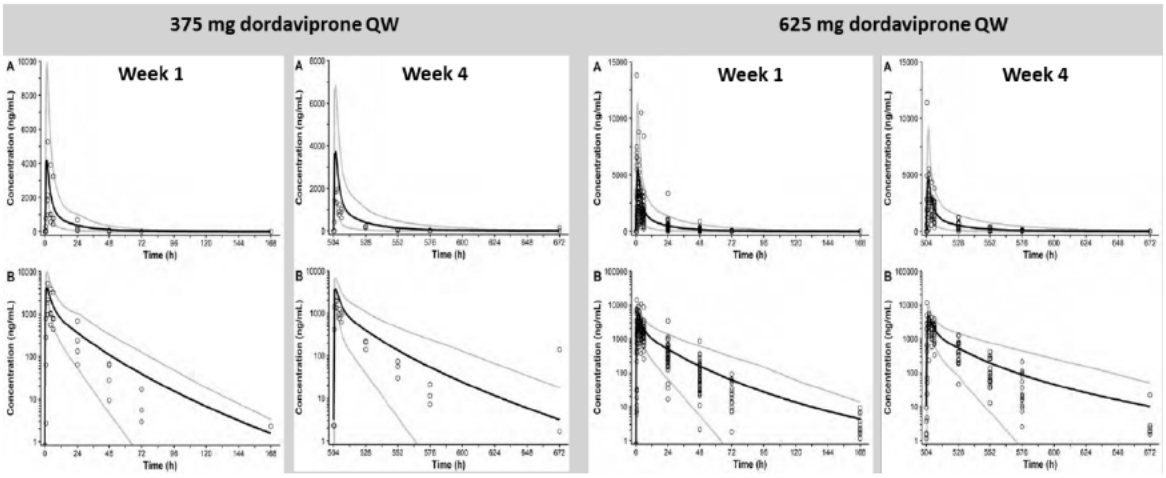
Depicted are observed (triangles, (ONC201 in the presence of itraconazole); circles, (ONC201 in the absence of itraconazole) arithmetic mean of n = 18 individuals; Clinical Study 103) plasma concentration-time profiles of ONC201 following a single dose of ONC201 in the absence of itraconazole (solid line) and on the 5th day of 8 days of dosing of itraconazole (dashed line). The grey lines represent arithmetic mean values of simulated individual trials and the black lines portray the arithmetic mean data of the simulated population (n = 180). A. Linear scale; B. Log-linear scale.
Source: Figure 10 in the PBPK report (chmx3a-b)

Table 19.9 Simulated and observed mean PK parameters of dordaviprone in the absence and presence of itraconazole 200 mg once daily following a single 125 mg dordaviprone in healthy subjects

	ONC201		ONC201 + Itraconazole		GMR	
	AUC_{0-t} (h.ng/mL)	C_{max} (ng/mL)	AUC_{0-t} (h.ng/mL)	C_{max} (ng/mL)	AUC_{0-t}	C_{max}
Simulated	4185	695	19356	1191	4.62	1.71
Observed	4119	763	17663	1475	4.46	1.93
S/O	1.02	0.91	1.10	0.81	1.04	0.89

Geometric means. S/O: Simulated/Observed. Observed data: Clinical Study 103; n = 18 individuals;
Source: Table 12 in the PBPK report (chmx3a-b)

Figure 19.10 Simulated and observed plasma concentration-time profiles following single and multiple oral doses of dordaviprone once weekly in adults with advanced solid tumors



Depicted are simulated (lines) and observed data (circles,375 mg: *n = 3; 625 mg: n=18, Clinical Study 002*). The grey lines represent the mean values of simulated individual trials, the dashed grey lines represent the 5th and 95th percentiles and the solid black line the mean data for the simulated population (n = 30 or 180). QW, once weekly
Source: Figures 25 -28 in the PBPK report (chmx3a-b)

Table 19.10 Simulated and observed PK parameters following single and multiple oral doses of dordaviprone in adults with advance solid tumors

	375 mg						625 mg					
	Week 1 (QW + Q3W) (n=4)			Week 4 (QW) (n=3)			Week 1 (QW + Q3W) (n=43)			Week 4 (QW) (n=16)		
	$AUC_{0\text{-}inf}$ (h.ng/mL)	C_{max} (ng/mL)	t_{max}* (h)	AUC_{tau} (h.ng/mL)	C_{max} (ng/mL)	t_{max}* (h)	$AUC_{0\text{-}inf}$ (h.ng/mL)	C_{max} (ng/mL)	t_{max}* (h)	AUC_{tau} (h.ng/mL)	C_{max} (ng/mL)	t_{max}* (h)
Simulated	30062	3758	1.25	29257	3501	1.25	40840	5014	1.35	40620	4431	1.35
CV%	64.8	51.6		85.4	55.8		66.8	54.9		71.4	49.8	
90% CI – Lower	25675	3302	0.900	23258	2979	0.950	38914	4814	0.700	37529	4181	0.700
90% CI – Upper	35198	4278	1.95	36805	4114	1.80	42861	5223	2.95	43965	4696	2.55
Observed	18313	2109	2.08	19797	1688	1.97	29710	3075	1.92	31823	3045	1.86
CV%	109	110		100	103		106	107		107	108	
S/O	1.64	1.78	0.601	1.48	2.07	0.635	1.37	1.63	0.703	1.28	1.46	0.726

* Median values were reported for T_{max}, others are geometric means. S/O: Simulated/Observed
Source: Tables 23 -24 in the PBPK report (chmx3a-b)

Can PBPK analyses predict the effects of CYP3A4 precipitants on the PK of dordaviprone?

Yes. The dordaviprone PBPK model could be used to predict the effects of CYP3A4 inhibitors or inducers. The moderate CYP3A4 inhibitors fluconazole and erythromycin were predicted to increase dordaviprone AUC up to 2.7-fold, and the weak CYP3A4 inhibitor cimetidine was predicted to increase dordaviprone AUC by approximately 1.7-fold The strong CYP3A4 inducer rifampin, the moderate CYP3A4 inducer efavirenz, and the weak CYP3A inducer modafinil were predicted to reduce dordaviprone AUC by 83%, 65%, and 22%, respectively **(Table 19.11).**

Table 19.11 Predicted effects of CYP3A4 inhibitors and inducers on dordaviprone exposure in healthy subjects following co-administration with a single dose of 625 mg dordaviprone

Categories	Perpetrator	AUC Ratio	C_{max} Ratio	Study Type
Strong CYP3A4 inhibitor	Itraconazole 200 mg QD	4.48	1.93	Observed
		4.62	1.71	Simulated
		1.03	0.90	Sim/Obs
Moderate CYP3A inhibitor	Fluconazole 200 mg QD	2.48	1.50	Simulated
	Erythromycin 500 mg TID	2.68	1.51	
Weak CYP3A4 inhibitor	Cimetidine 400 mg TID*	1.68	1.43	
Strong CYP3A4 inducer	Rifampin 600 mg QD	0.17	0.33	
Moderate CYP3A4 inducer	Efavirenz 600 mg QD	0.35	0.57	
Weak CYP3A4 inducer	Modafinil 200 mg QD *	0.78	0.90	

Source: Table 4 in the PBPK report (chmx3a-b) and reviewer's analyses (*)

***Reviewer's comments*:**

- To accurately predict the effects of CYP3A4 inhibitors and inducers on dordaviprone PK, the fraction metabolized by CYP3A4 ($f_{m,CYP3A}$) is one of key parameters that need to be verified in the dordaviprone PBPK model. The $f_{m,CYP3A}$ value in the dordaviprone model was optimized to be 80% based on its ability to reproduce the inhibitory effects of itraconazole on dordaviprone (Table 19.11).This value aligns closely with the 87% calculated from the reaction phenotyping study using recombinant CYP enzymes (ONC201-NCA-100).
- For the weak CYP3A4 inhibitor cimetidine, its PBPK model to predict inhibitory effects of cimetidine on CYP3A4 substrates was inadequately verified. As shown in Table 19.12, the observed inhibitory effects of cimetidine on the exposure of CYP3A4 substrates were not predicted in around 50-60% of the clinical DDI studies evaluated, even though predicted ratios of C_{max} and AUC were within 0.8-1.25-fold of the observed values. For those studies that cimetidine was predicted to have inhibitory effects (AUC ratio >1.25-fold), its effects were generally underpredicted. To address this issue, model evaluation was conducted by reducing CYP3A4 K_i value from 25 μM to 11 μM. Using the lower K_i value improved the predictions, except for two studies (Table 19.12). This updated cimetidine model with a CYP3A4 K_i value of 11 μM was used to predict the interaction of cimetidine with dordaviprone (Table 19.11).

Table 19.12 Verification of the cimetidine PBPK model to predict its interactions with CYP3A4 substrates

Cimetidine Dosing Regimens	Dosing Regimens of CYP3A Substrates	Observed		Predicted (K_I = 25 μM)		Predicted (K_I = 11 μM)	
		$C_{max}R$	AUCR	$C_{max}R$	AUCR	$C_{max}R$	AUCR
400 mg cimetidine BID (3 doses)	Midazolam 15 mg SD (D2) (30 min	NA	1.35	1.33	1.4	1.63	1.82
400mg cimetidine SD	Midazolam 15mg SD (2 hrs after	1.37	1.37	1.23	1.26	1.46	1.55
Cimetidine 200 mg TID with 400 mg pm on D1. 200 mg on D2	Midazolam 15 mg SD (D2) 2.5h after	2.38	2.02	1.1	1.11	1.21	1.24
Cimetidine 300 mg QID for 2 days	Triazolam 0.5 mg SD (D2)	1.39	1.32	1.18	1.21	1.34	1.43
Cimetidine 200 mg TID with 400 mg pm for 9 days	Triazolam 0.5 mg QD at night for 7 days	1.51	2.2	1.25	1.3	1.45	1.6
Cimetidine 300 mg QID (4 doses)	Triazolam 0.5mg SD (1 hr after 3rd cimetidine dose)	1.35	1.55	1.18	1.22	1.35	1.46
Cimetidine 200 mg TID with 400 mg pm for 9 days	Alprazolam 0.5mg TID for 7 days and morning dose on D8	1.82	1.64	1.06	1.08	1.13	1.17
Cimetidine 800 mg QD for 5 days	Nifedipine 10 mg TID for 4 Ds, 1 dose D5	2.3	2	1.41	1.64	1.55	2.04
Cimetidine 200 mg TID with 400 mg pm for 7 days	Nifedipine 10 mg QID for 6 Ds, 1 dose D7	2.02	1.6	1.13	1.23	1.28	1.53
Cimetidine 200 mg TID with 400mg pm for 3 days	Nifedipine 20 mg SD D2 (1 hr after first cimetidine dose)	NA	1.31	1.17	1.23	1.35	1.51
Cimetidine 300 mg QID for 7 days	Nifedipine 20 mg SD D7	1.4	1.52	1.21	1.33	1.43	1.72
Cimetidine 800 mg QD for 5 days	Nifedipine 20 mg SD D5 (1hr after cimetidine)	1.65	1.77	1.56	1.74	1.96	2.42
Cimetidine 300 mg QID for 7 days	Quinidine 330 mg (free base) SD on D6	1.2	1.57	1.07	1.16	1.13	1.32
Cimetidine 300mg QID for 3 days, a.m. dose day 4	Quinidine 330 mg (free base) SD on D4	1	1.27	1.07	1.1	1.13	1.2
Cimetidine 800 mg QD for 4 days	Sildenafil 50 mg SD D3 (2 hrs after)	1.54	1.56	1.36	1.41	1.65	1.78

SD, single dose; BID, twice daily; QD, once daily; TID, 3 times a day; D, day; am, in the morning; pm, at the night

Source: sv-cimetidinesummary-V21-kiupdated (NDA219685 seq0023)

Can PBPK analyses be used to estimate the effects of dordaviprone on substrates of various cytochrome P450 enzymes and transporters?

Effects of dordaviprone on midazolam:

Dordaviprone is expected to have a minimal effect on CYP3A4 substrates following once weekly dosing of 625 mg dordaviprone. Details are discussed as follows:

Dordaviprone 625 mg once weekly was predicted to have no inhibitory effect on the exposure of the CYP3A4 substrate midazolam. However, the hepatocyte induction study showed that dordaviprone increased CYP3A4 mRNA expression by 2- to 8-fold in all three donors at 2 and 20 μM of dordaviprone, which are below or close to 50 times of its unbound plasma peak concentration (C_{max}, 14.4 μM). The increase in expression was concentration-dependent despite approximately 50% decrease in hepatocyte viability and 80% reduction in 18s ribosomal RNA expression compared to the vehicle control at dordaviprone concentrations ≥ 20 μM). Therefore, potential CYP3A4 induction in vivo by dordaviprone cannot be ruled out.

Assuming that dordaviprone functions as a clinical inducer, the potential effect on CYP3A substrates under weekly dosing regimens was evaluated by (1) simulating midazolam interactions with rifampin ($t_{1/2}$= 3.5 h) and rifabutin ($t_{1/2}$= 38 h), a moderate CYP3A inducer, under various scenarios, and (2) collecting clinical DDI data involving rifapentine ($t_{1/2}$=14 -18 h), a strong CYP3A inducer, and rifabutin under twice-weekly dosing regimens. For comparison, the effects of these inducers following once daily dosing were included. The results in Table 19.13 indicated that, once weekly rifampin dosing had a minimal effect on midazolam exposure; and twice weekly administration, particularly with two consecutive doses, could result in moderate or weak induction effects on CYP3A substrates. Therefore, even if dordaviprone is a strong CYP3A inducer, its effect on the exposure of a CYP3A substrate is expected to be negligible under once-weekly dosing.

Table 19.13 Effects of CYP3A inducers on the exposure of CYP3A substrates following various dosing regimens

CYP3A inducers	CYP3A substrates	AUCinf ratio	Cmax ratio	Sources
Rifampin 600 mg twice weekly 16d*	Midazolam SD D16	0.25	0.34	PBPK simulations by reivewer
Rifampin 600 mg twice weekly 15d**	Midazolam SD D15	0.6	0.77	
Rifampin 600 mg once weekly 15d	Midazolam SD D15	0.9	1.08	
Rifampin 600 mg SD	Midazolam SD D1	1.05	1.22	
Rifampin 600 mg once daily 15d	Midazolam SD D15	0.09	0.15	
Rifampin **1200 mg** SD	nifedipine 10 mg SD	0.358	0.668	PubMed 9226591
Rifampin 600 mg once daily >10d	Midazolam SD	0.08 -0.15	0.12 -0.21	Multiple
Rifapentine 600 mg twice weekly 14d**	indinavir 800 mg tid 28d	0.3	0.45	Product label
Rifapentine 5 -20 mg/kg once daily	Midazolam SD	0.07 -0.1	0.11 - 0.2	Multiple
Rifabutin 150 mg twice weekly 15d**	ritonavir 100 mg qd	0.672†	0.66†	PubMed 21712242
Rifabutin **300 mg once daily**	Midazolam SD	0.316	0.47	PubMed 29569712
Rifabutin 150 mg twice weekly 16d*	Midazolam SD D16	0.69	0.74	PBPK simulations by reivewer
Rifabutin 150 mg twice weekly 15d**	Midazolam SD D15	0.77	0.81	
* two consecutive doses; ** 1st dose on the 1st day and 2nd dose on the 4th day of the week				
† compared to historical controls				

Effects of dordaviprone on CYP2D6 substrates desipramine

Dordaviprone is expected to have no effect on the exposure of the CYP2D6 substrate desipramine.

The Applicant assessed the inhibition potential of dordaviprone on CYP2D6 by applying the in vitro IC50 value generated using bufuralol as a CYP2D6 substrate (15678-RPT03773). Because in vitro substrate-dependent inhibition of CYP2D6 has been reported (PMID21976621), the predicted drug interactions of dordaviprone with desipramine need to be interpretated with caution.

The verification of the desipramine model has been previously evaluated (refer to NDA218197 PBPK review for further details). It was noted that the in vitro CYP2D6 $K_{i,u}$ value of an inhibitor needed to be reduced by 2- to 40-fold to reproduce the observed effects of this inhibitor on the exposure of CYP2D6 substrates. In the current analysis, reducing the in vitro CYP2D6 $K_{i,u}$ of dordaviprone by 40-fold, dordaviprone was predicted to have no effect on desipramine PK.

Effects of dordaviprone on the CYP2C8 repaglinide

Dordaviprone 625 mg once weekly was predicted to have no effect on the exposure of the CYP2C8 substrate repaglinide.

Effects of dordaviprone on the P-gp substrate dabigatran etexilate

Dordaviprone was predicted to have no effect on the P-gp substrate dabigatran etexilate. The potential of dordaviprone to clinically inhibit P-gp is likely low.

Dabigatran etexilate is a P-gp substrate. Dabigatran is a metabolite of dabigatran etexilate and is not a P-gp substrate. The effects of P-gp inhibitors on dabigatran etexilate are assessed by

changes in dabigatran plasma exposure. The ability of the PBPK models of dabigatran etexilate and dabigatran to predict P-gp interaction was assessed using clinical DDIs of dabigatran with verapamil, clarithromycin, quinidine, and ketoconazole (Dabigatran Simcyp summary report). Large range of IC50 values of these inhibitors are reported in literature (Certara DDI Database). The difference in IC50 between minimum and maximum values of each inhibitor ranges from 22- to 7450-fold if all the results were considered, and 1- to 100-fold if only experiments conducted in the condition similar to that of dordaviprone (e.g. MDCK-transfected cells and digoxin as a probe substrate) were considered. In addition, the reviewer also simulated the interaction effects of rifampin and belumosudil on dabigatran (PMID: 32705692 and NDA214783). The observed effects on dabigatran exposure by rifampin or belumosudil could only be reproduced when the IC50 values generated from the cell-based assays were reduced by 40- or 1000-fold, respectively (data not shown). In the current analysis by the reviewer, reducing the in vitro P-gp $K_{i,u}$ of dordaviprone by 1000-fold, dordaviprone predicted to have no effect on dabigatran PK. Therefore, the potential of dordaviprone to inhibit P-gp is likely low.

Effects of dordaviprone on the BCRP/OATP1B substrate rosuvastatin

The potential of dordaviprone to inhibit OATP1B and BCRP is low.

The effect of dordaviprone on rosuvastatin (Simcyp V22) was assessed following 625 mg dordaviprone once weekly for 4 weeks, with a single dose of 20 mg rosuvastatin co-administered on Day 1 of Week 4. Dordaviprone was predicted to have no effect on rosuvastatin, even when the in vitro determined inhibition parameters of OATP1Bs and BCRP in the dordaviprone model were reduced to 1/100 and 1/200 of their original values, respectively. Notably, OATP1B inhibition parameters were generated following 30-minute preincubation. While the BCRP inhibition parameter was assessed in a MDCK-BCRP cell monolayer system, the membrane vesicles system would produce a similar result due to the high permeability of dordaviprone. Taken together, these findings suggest that the potential of dordaviprone to clinically inhibit OATP1B and BCRP is likely low.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Not applicable

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROV	AUTHORED/ APPROVED
Clinical Reviewer	Elizabeth Duke, MD	CDER/OOD/DO2	Sections: 1-4, 7-13	**Select one:** _X__ Authored ___ Approved
	Signature: ELIZABETH S. DUKE -S Digitally signed by ELIZABETH S. DUKE -S Date: 2025.07.31 19:45:39 -04'00'			
Statistical Reviewer	Arup Sinha, PhD	CDER/OTS/DBV	Sections: 1, 8	**Select one:** _x__ Authored ___ Approved
	Signature: Arup K. Sinha -S Digitally signed by Arup K. Sinha -S Date: 2025.07.31 09:04:20 -04'00'			
Statistical Team Leader	Xiaxoue Li, PhD	CDER/OTS/DBV	Sections: 1, 8	**Select one:** _x__ Authored _x__ Approved
	Signature: Xiaoxue Li -S Digitally signed by Xiaoxue Li -S Date: 2025.07.31 09:56:31 -04'00'			
Division Director (OB/DBV)	Shenghui Tang, PhD	CDER/OTS/DBV	Sections: 1, 8	**Select one:** ___ Authored _x__ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2025.07.31 09:51:19 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHOR	AUTHORED/ APPROVED
Nonclinical Reviewer	Stephanie Aungst, PhD	CDER/OND/OOD /DHOT	Sections: 5, 19.1	**Select one:** _X_ Authored _X__ Approved
	Signature: Claudia Miller, PhD as proxy for Stephanie Aungst CLAUDIA MILLER -S Digitally signed by CLAUDIA MILLER -S Date: 2025.07.30 08:41:51 -04'00'			
Nonclinical Reviewer	Moran Choe, PhD	CDER/OND/OOD /DHOT	Sections: 5.5.4	**Select one:** _X_ Authored _X__ Approved
	Signature: Brenda Gehrke, PhD as proxy for Moran Choe Brenda Gehrke -S Digitally signed by Brenda Gehrke -S Date: 2025.07.30 08:55:01 -04'00'			
Nonclinical Team Leader	Claudia Miller, PhD	CDER/OND/OOD /DHOT	Sections: 5, 19.1	**Select one:** _X__Authored _X__ Approved
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Nonclinical Division Director	Haleh Saber, PhD	CDER/OND/OOD /DHOT	Sections: 5, 19.1	**Select one:** ___ Authored X_Approved
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Clinical Pharmacology Reviewer	Suryatheja Ananthula, PhD	CDER/OTS/OCP/ DCPII	Sections: 6	**Select one:** x Authored ___Approved
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Pharmacometrics Reviewer	Yangbing Li, PhD	CDER/OTS/OCP/ DPM	Sections: 6, 19.4	**Select one:** x Authored ___Approved
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Pharmacometrics Secondary Reviewer	Ye Xiong, PhD	CDER/OTS/OCP/ DPM	Sections: 6, 19.4	**Select one:** x Authored xApproved
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Physiologically-based pharmacokinetic (PBPK) modeling Reviewer	Ying-Hong Wang, PhD	CDER/OTS/OCP/ DPM	Sections: 6, 19.4	**Select one:** _x__ Authored ___Approved
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Physiologically-based pharmacokinetic (PBPK) modeling Secondary Reviewer	Manuela Grimstein, Ph.D	CDER/OTS/OCP/ DPM	Sections: 6, 19.4	**Select one:** x__ Authored xApproved
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Clinical Pharmacology Secondary Reviewer	Stacy Shord, PharmD	CDER/OTS/OCP/ DCPII	Sections: 6, 19.4	**Select one:** x Authored x_Approved
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Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	CDER/OTS/OCP/ DCPII	Sections: 6, 19.4	**Select one:** ___ Authored x Approved
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Associate Director for Labeling (ADL)	Barbara Scepura, MSN, CRNP	CDER/OND/OOD/ DOII	Section: 11	**Select one:** _xAuthored ___ Approved
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Cross-Disciplinary Team Leader (CDTL)	Diana Bradford, MD	CDER/OOD/DO2	Sections: All	Select one: __x__Authored __x__Approved
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Deputy Division Director (Signatory)	Nicole Drezner, M.D.	CDER/OOD/DO2	Sections: All	**Select one:** X__ Authored _X__Approved
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