

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219876Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: July 24, 2025

To: Opeyemi Udoka, Senior Regulatory Project Manager, Division of Oncology 2 (DO2)

Barbara Scepura, Associate Director for Labeling, (DO2)

From: Mispa Ajua-Alemanji, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for MODEYSO™ (dordaviprone) capsules, for oral use

NDA/BLA: 219876

Background:

In response to DO2's consult request dated January 29, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original NDA 219876 submission for MODEYSO™ (dordaviprone) capsules, for oral use.

PI/PPI/IFU:

OPDP's comments on the proposed labeling are based on the draft PI, PPI and IFU received by electronic mail from DO2 on July 11, 2025, and revised labeling downloaded from SharePoint on July 24, 2025, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed and comments on the proposed PPI and IFU were sent under separate cover on July 21, 2025.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling received by electronic mail from DO2 on July 17, 2025, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Mispa Ajua-Alemanji at Mispa.Ajua-Alemanji@fda.hhs.gov.

PI:

<u>Section</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comment</u>
HIGHLIGHTS OF PRESCRIBING INFORMATION: DRUG INTERACTIONS 5 WARNINGS AND PRECAUTIONS: 5:2 QTc Interval Prolongation. 7 DRUG INTERACTIONS: 7.2 Table 7 Products that Prolong QTc Interval	• “Avoid concomitant use of MODEYSO with products known to prolong the QT interval. If concomitant use cannot be avoided, separate administration of MODEYSO and the QT-prolonging product. (5.2, 7.2, 12.2)	The current recommendation to "separate administration of MODEYSO and QT-prolonging products" is vague and may not provide sufficient guidance for healthcare professionals in clinical practice. While Table 3 includes dosage modification recommendations for adverse reactions including QTc interval prolongation management, it would be beneficial to include more detailed instructions for the dosage separation guidance. We recommend providing specific timing recommendations for separating MODEYSO administration from other QT-prolonging products (e.g., minimum time intervals between doses) if available. This information could be helpful to providers as it pertains to the appropriate dosing of MODEYSO.

Carton and container labeling:

<u>Section</u>	<u>Statement from Draft Labeling (if applicable)</u>	<u>OPDP Comment</u>
Principal display panel including front, back and side panels.	"MODEYSO™ (dordaviprone) capsules"	OPDP recommends revising the established name on the proposed carton and container labeling to be in accordance with 21CFR 201.10(g)(2) which states that, '[t]he established name shall be at least half as large as the letters comprising the proprietary name or designation.' Specifically, we note that the font size of the established name in relation to the proprietary name does not meet regulatory requirements. We recommend increasing the font size of the established name so that it is at least half as large as the letters comprising the proprietary name, as required by 21 CFR 201.10 (g)(2)).

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MISPA L AJUA-ALEMANJI
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OPEYEMI O UDOKA
08/11/2025 09:37:08 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 21, 2025

To: Opeyemi Udoka DPT, CSM
Senior Regulatory Health Project Manager
Division of Oncology II (DO2)

Through: Barbara Fuller, MSN, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Laurie Buonaccorsi, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Mispa Ajua-Alemanji, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (established name): MODEYSO (dordaviprone)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 219876

Applicant: Chimerix, Inc.

1 INTRODUCTION

- 2 On December 18, 2024, Chimerix, Inc. submitted for the Agency's review an original New Drug Application (NDA) 219876 for MODEYSO (dordaviprone). The Applicant proposes an indication (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on January 29, 2025, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for MODEYSO (dordaviprone). On February 19, 2025, DO2 requested that the Applicant submit a detailed Instructions for Use (IFU) for MODEYSO (dordaviprone) for use by patients who are unable to swallow capsules.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on May 23, 2025.

3 MATERIAL REVIEWED

- Draft MODEYSO (dordaviprone) PPI received on February 14, 2025, revised throughout the review cycle, and received by DMPP and OPDP on July 11, 2025.
- Draft MODEYSO (dordaviprone) IFU received on April 24, 2025, revised throughout the review cycle, and received by DMPP and OPDP on July 11, 2025.
- Draft MODEYSO (dordaviprone) Prescribing Information (PI) received on December 18, 2024, revised throughout the review cycle, and received by DMPP and OPDP on July 11, 2025.
- Approved OJEMDA (tovorafenib) NDA 218033, TAFINLAR (dabrafenib mesylate) NDA 217514, and ROZLYTREK (entrectinib) NDA 212725 comparator labeling dated June 26, 2024, April 7, 2025, and October 20, 2023, respectively.

4 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable

5 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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LAURIE J BUONACCORSI
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MISPA L AJUA-ALEMANJI
07/21/2025 11:03:47 AM

BARBARA A FULLER
07/21/2025 11:27:40 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 10, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219876
Product Name, Dosage Form, and Strength:	Modeyso (dordaviprone) Capsules, 125 mg
Applicant Name:	Chimerix Inc.
FDA Received Date:	July 8, 2025
TTT ID #:	2025-12356-2
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

Chimerix Inc. submitted revised container label and carton labeling received on July 8, 2025 for Modeyso. The Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Modeyso (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Chimerix Inc. implemented all our recommendations and we have no additional recommendations at this time.

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Stewart, J. Label and Labeling Review for Modeyso Capsules (NDA 219876). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 JUN 27. TTT ID: 2025-12356-1.

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JANINE A STEWART
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Clinical Inspection Summary

Date	July 1 st , 2025
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Elizabeth Duke, Medical Officer Diana Bradford, Cross-disciplinary Team Leader Nicole Drezner, Deputy Division Director Division of Oncology 2 (DO2), Office of Oncology Products
NDA #	NDA 219876
Applicant	Chimerix, Inc.
Drug	Dordaviprone (ONC201)
NME (Yes/No)	Yes
Therapeutic Classification	Oncology - small molecule imipridone
Proposed Indication(s)	(b) (4)
Consultation Request Date	February 7, 2025
Summary Goal Date	July 7, 2025
Action Goal Date	August 6, 2025
PDUFA Date	August 18, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from five single-arm, open-label clinical studies (ONC006, ONC013, ONC014, ONC016, and ONC018) were submitted to the Agency in support of New Drug Application (NDA) 219876 for dordaviprone (b) (4)

Three clinical investigators, Drs. Isabel Arrillaga-Romany (Site MGH), Nazanin Majd (Site MDACC), and Marissa Barbaro (Site NYU), as well as the Sponsor, Chimerix Inc. were inspected. A remote regulatory assessment (RRA) of the imaging Contract Research Organization (CRO), (b) (4) was conducted.

Inspections of Drs. Arrillaga-Romany (Study ONC006), Majd (Studies ONC013 and ONC018), and Barbaro (Study ONC013), the Sponsor Chimerix and the RRA of imaging CRO, (b) (4) 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.

II. BACKGROUND

Chimerix Inc. submitted NDA 219876 seeking approval for dordaviprone (ONC201) (b) (4)

Dordaviprone is a new molecular entity (NME), small molecule imipridone that acts as a mitochondrial caseinolytic protease P (ClpP) agonist and a dopamine receptor D2 (DRD2) antagonist. Dordaviprone exhibited antitumor activity in cell-based and in vivo models of H3 K27M-mutant diffuse glioma.

Safety data from a total of 422 subjects with gliomas and glioblastomas and efficacy data from 50 subjects with H3 K27M-mutant diffuse glioma enrolled in five single arm studies were submitted to support the NDA (see Table below).

Study	Design	Population	Safety Pop. (N)	Efficacy Pop. (N)
ONC006	Phase 2	Glioblastoma H3 K27M-mutant glioma, and diffuse midline glioma	84	10
ONC013	Phase 2	H3 K27M-mutant glioma	73	29
ONC014	Phase 1	Pontine Glioma and H3 K27M Gliomas	134	2
ONC016	Compassionate Use	H3 K27M Gliomas	0	1
ONC018	Expanded Access	H3 K27M-mutant and/or Midline High Grade Gliomas	131	8
Total			422	50

A programmatic selection was performed for screening to identify appropriate participants to be included in the efficacy population, based on available case report form data from the 5 studies.

The final primary efficacy population consists of a subgroup of 50 subjects enrolled across ONC006, ONC013, ONC014, ONC016, or ONC018 trials and who fulfilled the following predefined key eligibility criteria:

- Were ≥ 2 years of age.
- Had a diffuse glioma with a known H3 K27M mutation.
- Had involvement of a midline structure of the brain (e.g., thalamus, hypothalamus, basal ganglia, brainstem (non-DIPG), cerebellum, cerebellar peduncle, midline

- cortex, corpus callosum, pineal region, optic tract, or optic chiasm).
- Received prior therapy, with at least radiation therapy.
- Participants with diffuse intrinsic pontine glioma (DIPG), primary spinal tumors, atypical and non-astrocytic histology, leptomeningeal spread, or evidence of cerebrospinal fluid dissemination were excluded.
- Weight ≥ 10 kg

Eligible patients must have received single agent dordaviprone in one of the five studies at a dose of 625 mg orally once weekly (or an equivalent body weight-adjusted dose for pediatric patients weighing less than 52.2kg) in 3-week cycles. Dordaviprone was to continue until evidence of disease progression, intolerable adverse event, or patient withdrawal.

The primary efficacy endpoint to support the proposed indication is overall response rate (ORR) per Response Assessment in Neuro-Oncology (RANO) criteria as assessed by blinded independent central review (BICR) at (b) (4) the CRO responsible for central review of radiographic images.

Subjects underwent clinical evaluation after each 3-week or 4-week cycle. Neuroimaging studies with contrast-enhanced brain MRI or CT were performed at baseline, at 8 weeks from treatment initiation, and then every 8 weeks thereafter in Studies ONC006, ONC013, or per standard of care (generally every 2 or more cycles of therapy) in Studies ONC014, ONC016, and ONC018,

III. RESULTS (by site)

1. Dr. Isabel Arrillaga-Romany (Site MGH) 101 Merrimac St, 4th Floor Boston, MA 02114-4724

Inspection dates: March 25 – 31, 2025

Dr. Arrillaga-Romany was inspected as a BIMO review-based inspection for Study ONC006. This was the first inspection for this investigator.

The site enrolled 27 subjects in Study ONC006 across 5 cohorts: 7 in Cohort A, 9 in Cohort B, 2 in Cohort C, 8 in Cohort D, and 1 subject in Cohort F.

Selected source records from 10 subjects (ID (b) (6)), enrolled at the site were reviewed. Records reviewed included, but were not limited to informed consent forms, eligibility criteria, investigational drug administration, adverse event reporting, protocol deviations, and concomitant medications. There were no significant discrepancies when compared to the data submitted to the NDA.

Additional records reviewed during the inspection included, but were not limited to, financial disclosure forms, staff training information, communication with the sponsor, monitoring activities, and IRB correspondence. No issues were observed.

Notwithstanding the unreported concomitant medication, the data generated by Dr. Arrillaga-Romany appear to be acceptable in support of the NDA.

2. Dr. Nazanin Majd (Site MDACC)

1515 Holcombe Blvd
Houston, TX 77030

Inspection dates: April 9 – 15, 2025

Dr. Majd was inspected as a BIMO review-based inspection for Study ONC013 and Study ONC018. This was the first FDA inspection for this investigator.

The site screened 13 and enrolled 9 subjects in Study ONC013. All subjects had completed study treatment at the time of the inspection. For Study ONC018, the site screened 5 and enrolled 4 subjects, of whom, all 4 had completed treatment

Source records for all 9 subjects enrolled in Study ONC013 and 4 enrolled in ONC018 were reviewed and compared with the data listings submitted to the NDA. Records reviewed included, but were not limited to, informed consent forms, eligibility criteria, investigational drug accountability, adverse event reporting, and protocol deviations. All subjects met eligibility criteria. No significant discrepancies were observed.

The inspection verified that the radiographic scans to assess primary and secondary efficacy endpoints were obtained according to protocol specified time points and were consistent with the data submitted for central assessment.

Additional records reviewed during the inspection included, but were not limited to, protocols and amendments, signed investigator statements, staff training, adherence to the study protocol, IRB documentation, financial disclosures, and study monitoring records. No issues were observed.

Based on the inspection, the data generated at Dr. Majd's site appear acceptable in support of the proposed indication in the NDA.

3. Dr. Marissa Barbaro (Site NYU)

240 East 38th Street, 19th Fl
New York, NY 10016

Inspection dates: April 1 – 4, 2025

Dr. Barbaro was inspected as a BIMO review-based inspection for Study ONC013. This was the first FDA inspection for this investigator.

At the time of the inspection, the site had screened 24 subjects and enrolled 19 in the study. The study was closed, with no active subjects. Nineteen subjects completed treatment, with five of the 19 subjects who were dosed being lost to follow-up.

Source records for all 19 subjects enrolled at the site were reviewed and compared with the data listings submitted to the NDA. Records reviewed included, but were not limited to, informed consent forms, subject eligibility, protocol deviations, and adverse event reporting. All subjects met eligibility requirements. There was no significant underreporting of AEs.

The inspection verified that radiographic scans to evaluate the efficacy endpoint were performed as specified in the protocol and scans were submitted for central review.

Additional records reviewed during the inspection included, but were not limited to, staff training records, investigational drug accountability, IRB approval and correspondence, financial disclosure forms, electronic records, and site monitoring activities,

Based on the results of the inspection, the data generated at Dr. Barbaro's site appear acceptable in support of the proposed indication in the NDA.

4. Chimerix, Inc.

2505 Meridian Parkway, Suite 100
Durham, NC 27713

Inspection dates: March 10 - 14, 2025.

This inspection assessed Chimerix's oversight responsibilities for Studies ONC006, ONC013, ONC014, ONC016, and ONC018. This was the first inspection for this sponsor.

The inspection included review of the study master file, standard operating procedures (SOPs) related to the study, site monitoring practices, handling of adverse events, data collection, determining whether the sponsor discovered any non-compliant sites, and processes to bring non-compliant sites into compliance. The inspection also obtained information related to procedures for selection of clinical investigators, monitors, monitoring procedures, safety monitoring, selection of the blinded independent central reader (BICR), contract services used, and other sponsor/monitor related activities. There were no significant objectionable conditions or practices.

Monitoring files for three clinical sites were reviewed in depth for compliance and clinical monitoring: MGH (ONC006), NYU (ONC013), and MDACC (ONC013 and ONC018). Site monitoring records for two additional sites, that enrolled only pediatric

subjects for Study ONC014 (site CHOA, Children's Hospital of Atlanta, and SCH, Seattle Children's Hospital) were also reviewed. No issues were observed.

No issues related to safety/adverse event handling or reporting were observed during the inspection for Studies ONC006, ONC013, ONC014, ONC016, and ONC018.

Based on the inspection findings, Chimerix's overall oversight of the studies and monitoring of the clinical investigators appear adequate.

5.

(b) (4)

Inspection dates: (b) (4)

This RRA reviewed (b) (4) responsibilities to perform an independent central imaging review for subjects enrolled in studies ONC006, ONC013, ONC014, ONC016, and ONC018 who were included in the efficacy population for NDA 219876. The firm was last inspected (b) (4)

Records reviewed included the firm's data collection, analysis, and transfer procedures, quality assurance processes, electronic records and systems utilized in analyzing and marking the scans and the imaging review charter. The source records were compared with the data listings submitted to the NDA. The review found the processes adequate.

The RRA verified response data for 14 subjects reported as having achieved an objective tumor response by the sponsor. Source data was compared to the efficacy line listing submitted to the NDA. No discrepancies were observed. The IDs of these subjects are as follows:

SUBJECT ID			
ONC006	(b) (6)	ONC013-	(b) (6)
ONC006		ONC013-	
ONC006		ONC013-	
ONC013		ONC014-	
ONC013		ONC016-	
ONC013		ONC018-	
ONC013		ONC018-	
ONC013		ONC018-	

Based on the RRA, the imaging review data generated by (b) (4) and submitted by the sponsor appear acceptable in support of the proposed indication in the NDA.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigation

CC:
Review Division /Project Manager/Opeyemi Udoka
OSI/DCCE/GCPAB/Program Analyst/ Yolanda Patague

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MICHELE B FEDOWITZ
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JENN W SELLERS
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 27, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219876
Product Name, Dosage Form, and Strength:	Modeyso (dordaviprone) Capsules, 125 mg
Applicant Name:	Chimerix Inc.
FDA Received Date:	June 25, 2025
TTT ID #:	2025-12356-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

Chimerix Inc. submitted revised container label and carton labeling received on June 25, 2025 for Modeyso. The Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Modeyso (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The container label and carton labeling unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Chimerix Inc. in Section 3.

3 RECOMMENDATIONS FOR CHIMERIX INC.

Container Label

1. We recommend presenting important product information in a customary format as follows:
 - a. Relocate the strength statement to appear immediately below the established name.
 - b. Relocate the net quantity statement to appear on the principal display panel, but away from the strength statement. We recommend placing the net quantity statement at the top left side of the PDP with prominence similar to that of the NDC number.

Carton Labeling

1. As proposed, the strength statement appears where the net quantity statement customarily appears. Therefore, we recommend the following revisions to present important product information in a customary format:
 - a. Relocate the strength statement to appear immediately below the established name.
 - a. Relocate the net quantity statement to appear below the statement that reads "Dispense the enclosed...".

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

^a Stewart, J. Label and Labeling Review for Dordaviprone Capsules (NDA 219876). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 MAY 23. TTT ID: 2025-12356.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 22, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219876
Product Name, Dosage Form, and Strength:	Dordaviprone ^a Capsules, 125 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Chimerix Inc.
FDA Received Date:	December 18, 2024, March 14, 2025, and April 24, 2025
TTT ID #:	2025-12356
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

^a The proposed proprietary name, Modeyso, was found unacceptable by DMEPA (OSE # 2024-1044725969 and 2024-1044726173). A new name was submitted and is currently under review. Therefore, the established name dordaviprone is used throughout this review.

1 INTRODUCTION

As part of the approval process for Dordaviprone Capsules, the Division of Oncology 2 (DO2) requested that we review the proposed Dordaviprone Prescribing Information (PI), Patient Package Insert (PPI), container label(s), carton labeling, and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

We evaluated the proposed Dordaviprone Patient Package Insert (PPI) determined that it is acceptable from a medication error perspective.

However, the proposed Dordaviprone Prescribing Information (PI), container label(s), carton labeling, and Instructions for Use may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 2 (DO2) in Section 4 and for Chimerix Inc. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Section 2 Dosage and Administration

- In the second column of Table 1: Recommended Weight-Based Dosage in Pediatric Patients, remove the dash that appears between the numerical portion (125) and the units (mg) of the capsule strength.

2. Section 3 Dosage Forms and Strengths

- Revise the Dosage Forms and Strengths information for improved clarity to read as follows:

Capsules: 125 mg, white, opaque, hard capsules printed with “DDP” and “125” on the body and “CMRX” on the cap of the capsule. Each capsule contains 125 mg dordaviprone (b) (4)

3. Section 16 How Supplied/Storage and Handling

- Revise the How Supplied/Storage and Handling information for improved clarity and readability as follows:

How Supplied

Strength	Description	Capsules per Bottle	NDC Number
125 mg	White, opaque, hard capsules printed with “DDP” and “125” on the body and “CMRX” on the cap of the capsule. (b) (4)	10	XXXX-XXXX-XX

Storage (b) (4)

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

B. Instructions for Use

1. In Step 5, we recommend adding the word “liquid” at the end so that the instructional statement reads “Use a tablespoon ((b) (4) 15 mL) to measure liquid.”
2. In Step 7, we acknowledge that the clock image contains the text “within 2 hours”. However, we also recommend shading the “two hours” mark in the clock image to clearly illustrate two hours. An example image is provided below to demonstrate our recommendation only, and is not intended to be true to size, scale, color, etc.



5 RECOMMENDATIONS FOR CHIMERIX INC.

A. General Comments (Container Label(s) and Carton Labeling)

1. Remove the (b) (4) statement as it is not necessary (b) (4) (b) (4) to appear on the container labels and carton labeling for oral dosage form products.
2. We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

3. As proposed, the strength statement (125 mg) lacks prominence compared to the net quantity statement (10 CAPSULES). Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Consider all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement).
4. As presented, the net quantity statement is in close proximity to the strength statement on the principal display panel (PDP). From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength. We recommend relocating the net quantity statement away from and with less prominence than the product strength, such as to the bottom of the principal display panel. *See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*
5. As currently presented, the format for the expiration date is not defined (e.g., XXXX-XXX-XX). To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends use of a hyphen or forward slash to separate the portions of the expiration date. *See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*

B. Container label

1. We note the NDC number placeholder is located on (b) (4) the principal display panel. The human-readable NDC is often used for product verification and identification prior to dispensing or administering a drug. It is an important safety feature that is recommended to be prominently displayed on the principal display panel of the container label and carton labeling. We request that you include the NDC number or placeholder on the top of principal display panel of the carton labeling.

C. Carton Labeling

1. Consider replacing the statement on the principal display panel (PDP) that reads (b) (4) with a statement that

directs pharmacists to dispense the Patient Information labeling which provides important product information for patients and caregivers (e.g., preparing an oral solution for patients who cannot swallow capsules). For example: “See Enclosed Patient Information for administration instructions” or “Dispense the enclosed Patient Information to each patient” or similar statement displayed prominently on the PDP.

2. We note the NDC number placeholder is located on the (b) (4) panel. The human-readable NDC is often used for product verification and identification prior to dispensing or administering a drug. It is an important safety feature that is recommended to be prominently displayed on the principal display panel of the container label and carton labeling. We request that you include the NDC number or placeholder on the top of principal display panel of the carton labeling.
3. For consistency with the language used in the PI, revise the statement on the side panel that reads (b) (4) to read “Recommended Dosage: See Prescribing Information”.
4. As proposed, the storage statement is inconsistent with the storage information in Section 16 of the Prescribing Information. Revise the storage temperature statement for consistency and accuracy across all labeling components. Include the numerical temperature range for proper storage as appropriate.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Dordaviprone received on March 14, 2025 from Chimerix Inc.

Table 2. Relevant Product Information for Dordaviprone	
Initial Approval Date	N/A
Active Ingredient	dordaviprone
Indication	(b) (4)
Dosage Form	Capsules
Strength	125 mg
Route of Administration	Oral
Dose and Frequency	(b) (4)
How Supplied	Supplied as 10-count bottles in cartons
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure	High-density polyethylene white opaque bottles with desiccant, closed with an induction seal, and capped with a child-resistant, white-ribbed (b) (4) cap.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Dordaviprone labels and labeling submitted by Chimerix Inc.

- Prescribing Information received on March 14, 2025, available from <\\CDSESUB1\EVSPROD\nda219876\0013\m1\us\114-labeling\draft\labeling\draft-uspi-us-prescribing-information.docx>
- Patient Package Insert received on April 24, 2025 available from <\\CDSESUB1\EVSPROD\nda219876\0025\m1\us\114-labeling\draft\labeling\patient-package-insert-dordaviprone-word.docx>
- Instructions for Use received on April 24, 2025 available from <\\CDSESUB1\EVSPROD\nda219876\0025\m1\us\114-labeling\draft\labeling\instructions-for-use-dordaviprone-word.docx>
- Container label(s) received on December 18, 2024
- Carton labeling received on December 18, 2024

B.2 Container Label(s) and Carton Labeling Images

Container Label(s):



1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANINE A STEWART
05/23/2025 01:27:43 PM

TINGTING GAO
05/23/2025 08:34:54 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 219876
Submission Number	1
Submission Date	12/18/2024
Date Consult Received	1/29/2025
Drug Name	dordaviprone
Indication	(b) (4)
Therapeutic Dose	625 mg QW
Clinical Division	DO2
Protocol Review	04/18/2022

Note: Any text in the review with a light background should be considered to be copied from the Applicant's document.

This review responds to your consult dated 1/29/2025 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Previous IRT review dated [05/20/2021](#) and [04/18/2022](#) in DARRTS;
- Proposed label (NDA 219876 / SN0001; [link](#));
- Cardiac safety report (NDA 219876 / SN0001; [link](#));
- Clinical Information Amendment/Response to Information Request (NDA 219876 / SDN017; [link](#));
- Clinical study report (NDA 219876 / SN0001; [link](#)); and
- QT evaluation checklist and highlights of clinical pharmacology and cardiac safety (NDA 219876 / SN0005; [link](#)).

1 SUMMARY

Concentration-dependent prolongation of the QTc interval was observed for dordaviprone and its major metabolite (ONC207) in a thorough QTc (TQT) study, as detailed in Table 1. At the maximum recommended dosing regimen, the predicted increase in the mean QTc (90% CI) is 11 (10 – 13) msec.

The TQT study (Study ONC201-102) was designed as a single-dose, placebo and positive-controlled, 3-period, 6-sequence crossover study to assess the QTc effects of the maximum tolerated dose of dordaviprone. The mean maximal concentration (C_{max}) of the maximum tolerated dose (750 mg) encompasses the therapeutic C_{max} and the increased C_{max} for dordaviprone and ONC207 resulting from strong CYP3A4 inhibition and severe renal impairment, respectively.

Uncertainty exists regarding QTc prolongation when co-administered with a CYP3A4 inducer. This is because an increase in Cmax of ONC207 is expected and the Applicant's worst-case prediction is 1200 ng/mL for the 625 mg dose, which exceeds the Cmax at the maximum tolerated dose the TQT study (797 ng/mL). Additionally, uncertainty exists regarding QTc prolongation in severe hepatic impairment, as the impact on dordaviprone pharmacokinetics has not been evaluated in this population.

Data from the TQT study were analyzed using exposure-response analysis as the primary analysis, indicating that dordaviprone and ONC207 prolong the QTc interval in a concentration-dependent manner (section 4.5). The primary analysis findings are corroborated by by-time analysis (section 4.3). The positive findings are consistent with the low hERG safety margin of both dordaviprone (4x) and ONC207 ($\geq 83x$), though there is uncertainty in the hERG safety margin for ONC207 as the protein binding has not been reported (section 3.1.2).

Further safety evaluation of dordaviprone treatment was conducted in 422 adult and pediatric patients with glioma across four open-label clinical studies (ONC006, ONC013, ONC014, and ONC018). Electrocardiograms (ECGs) were collected at screening in studies ONC013 (n = 73), ONC014 (n = 134), and ONC018 (n = 131). In study ONC006 (n = 84), ECGs were collected on Day 1 of each cycle (pre-dose for most subjects). One subject exhibited a QTcF >500 msec (508 msec, baseline: 394 msec) at a follow-up visit in study ONC006. All other QTcF values for this subject from Cycle 2 to Cycle 11 (excluding Cycles 6 and 10) were below 450 msec. Five subjects demonstrated a change from baseline QTcF >60 msec, with two of these subjects exhibiting a maximum QTcF >480 msec (495 msec and 508 msec).

In the four open-label studies, 13 patients (3%) experienced treatment-emergent adverse events (TEAEs) of torsade de pointes/QT prolongation (broad Standardized MedDRA Query), with preferred terms of syncope (6 patients, 1.4%), cardiac arrest (4 patients, 0.9%), and electrocardiogram QT prolonged (3 patients, 0.7%). All electrocardiogram QT prolonged adverse events were Grade 1 with QTcF <460 msec (maximum QTcF: 455 msec), and no actions regarding the investigational product were taken due to these events. Three patients experienced Grade 3 syncope events, none of whom had post-dose ECG data. All four cardiac arrest events were fatal. . Two deaths were directly attributed to the cardiac arrest events. None of the four patients had post-dose ECG data available.

Table 1. Summary of findings

QT assessment pathway	☒ <i>Thorough QT study</i> ☐ <i>Substitute for thorough QT study (5.1)</i> ☐ <i>Alternative QT study when a thorough QT study is not feasible (6.1)</i>
Clinical QT study findings	The maximum dose utilized in the QTc assessment encompasses the maximum plasma concentration (Cmax) for dordaviprone and ONC207 under two specific scenarios: 1) administration of 375 mg dordaviprone with a strong CYP3A4 inhibitor, and 2) administration of 625 mg dordaviprone in patients with severe renal impairment. (section 3.1)

	Uncertainty exists regarding the extent of QTc prolongation in two situations: 1) concomitant administration of dordaviprone with a CYP3A4 inducer, and 2) administration of dordaviprone in patients with severe hepatic impairment. (section 3.1)				
	ECG parameter	Treatment	Concentration	ΔΔQTcF (msec)	90% CI (msec)
	ΔΔQTcF	Highest therapeutic or clinical trial dosing regimen (625 mg QW)	Dordaviprone: 3830.0 ng/mL ONC207: 729.0 ng/mL	11.4	(9.6 to 13.2)
	ΔΔQTcF	375 mg dordaviprone co-administered with strong CYP3A inhibitor	Dordaviprone: 4425 ng/mL ONC207: 137 ng/mL	11.1	(4.7 to 17.5)
	ΔΔQTcF	Administration of 625 mg dordaviprone in severe renal impairment	Dordaviprone: 4173 ng/mL ONC207: 845 ng/mL	11.8	(9.5, 14.0)
	ΔΔQTcF	Dordaviprone 750 mg (At ONC207's T _{max})	Dordaviprone: 2376.0 ng/mL ONC207: 797.1 ng/mL	11.1	(9.6 to 12.6)
	ΔΔQTcF	Dordaviprone 750 mg (At dordaviprone's T _{max})	Dordaviprone: 4223.1 ng/mL ONC207: 748.8 ng/mL	11.6	(9.6 to 13.6)
In vitro findings	- hERG safety margin to clinical C_{max} is 4x for dordaviprone. The corresponding hERG safety margin for the major metabolite, ONC207, is ≥83x depending on protein binding, which was not reported. - Limited information provided for QTc assessment in in vivo tox study report.				
In vivo findings					

2 RECOMMENDATIONS

2.1 PROPOSED LABEL

We defer final labeling decisions to the respective Division, as labeling practices may vary across different FDA Divisions. This deferral is particularly important because we are not fully aware of the benefit-risk profile of dordaviprone in the specific patient

population, nor are we familiar with the details of risk management strategies employed in the clinical trials. Different Divisions may have varying approaches to presenting this information in the label, based on their expertise in the therapeutic area and established precedents.

Below are proposed edits to the label submitted to SN 0001 ([link](#)) based on the draft labeling guidance for QT. Our changes are highlighted ([addition](#), ~~deletion~~). Each section is followed by a rationale for the changes made.

2. ^{(b) (4)} Recommended Testing Before ^{(b) (4)} TRADENAME ^{(b) (4)} • Monitor electrocardiograms (ECG) and electrolytes before initiating and periodically during treatment, as clinically indicated [see Warnings and Precautions (5 ^{(b) (4)}) and Drug Interactions (7.2)].
<i>Reviewer's comment: No changes were made in this section.</i>
5.4 QT Interval Prolongation ^{(b) (4)} TRADENAME causes a concentration-dependent QTc interval prolongation [see Clinical Pharmacology (12.2)]. Monitor ECGs and electrolytes before initiating and periodically during treatment, as clinically indicated. ^{(b) (4)} ^{(b) (4)} Increase the frequency of ECG and/or electrolyte monitoring when administering TRADENAME to patients with congenital long QT syndrome, existing QTc prolongation, a history of ventricular arrhythmias, electrolyte abnormalities, heart failure, or those who are taking ^{(b) (4)} strong/moderate CYP3A4 inhibitors. ^{(b) (4)} ^{(b) (4)} Coadministration with other QTc-prolonging products may increase the risk of QTc-associated arrhythmias. ^{(b) (4)} ^{(b) (4)} Withhold or discontinue TRADENAME in patients who develop QTc prolongation with signs of life-threatening arrhythmias. <i>Reviewer's comment: Insufficient ECGs were collected in patient studies to provide useful information ^{(b) (4)} and we did therefore not include information ^{(b) (4)} in the label. ^{(b) (4)}</i> <i>In section 2, monitoring of ECG and electrolytes are recommended in all patients, instead of patients who are at increased risk of QTc prolongation. We moved the language to reduce ambiguity.</i>

We recommend using more specific language, such as “increase monitoring”, instead of (b) (4) (b) (4) when describing steps to prevent or mitigate the risk of QTc prolongation.

We recommend increasing monitoring for patients receiving concomitant CYP3A4 inhibitors, to be consistent with section 7.1.

We recommend withholding TRADENAME in all patients who develop QTc prolongation with signs of life-threatening arrhythmias, (b) (4) (b) (4)

(b) (4) We moved the sentence to reduce ambiguity.

7.1 Effect of Other Drugs on TRADENAME

Table (b) (4) Effect of Other Drugs on TRADENAME

(b) (4)

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Strong or Moderate CYP3A4 Inducers

(b) (4)	• (b) (4)
	• <u>Coadministration of strong or moderate CYP3A4 inducers may increase the exposure of the major metabolite ONC207, which may increase the incidence and severity of QTc interval prolongation [see Warnings and Precautions (5.4)].</u>

Prevention or Management	• (b) (4)
Reviewer's comment: We added information of (b) (4) prevention/management of co-administration of moderate/strong CYP3A4 inhibitors/inducers on QTc prolongation.	
7.2 Drugs Known to Prolong QTc Interval	
Table (b) (4) Products that Prolong QTc Interval	
Products that Prolong QTc Interval	
Clinical Impact	(b) (4) • (b) (4) with other QTc-prolonging products may increase the risk of QTc-associated arrhythmias [see Warnings and Precautions (b) (4)]
Prevention or Management	• Increase frequency of ECG and/or electrolyte monitoring (b) (4) (b) (4) (b) (4)
Reviewer's comment: The results of the TQT study do not support (b) (4) and we therefore propose to remove that statement. If the recommendation (b) (4) is consistent with the clinical trial conduct, then it is reasonable to maintain this recommendation. Otherwise, we recommend that the Division omits statements (b) (4) in this section and other sections. We have also proposed changes consistent with recommendations in section 5.	
12.2 Pharmacodynamics	
<u>Cardiac Electrophysiology</u> (b) (4)	

participants. The primary concentration-QTc analysis indicated that dordaviprone caused QTc

(b) (4)

The increase in the QTc interval was dependent on dordaviprone concentrations and the major metabolite ONC207 [see Warnings and Precautions (5.4)].

(b) (4)

Reviewer's comment: We have proposed revisions to simplify the description of the key findings of the TQT study. The results of our analysis and the Applicant's analysis are similar and we therefore propose (b) (4) significant digit. Considering that the results of the by-time and concentration-response, the primary endpoint, are similar we suggest only reporting the findings from one of the two analyses. We recommend reporting the findings by-time and include information about the timing of the maximal increase and separately state that the increase in QTc was concentration-dependent.

As stated in our comments to section 7, we disagree with the inclusion of a statement (b) (4) as we don't agree that the data supports the proposed statement.

We also disagree with the inclusion of the statement (b) (4)

Lastly, (b) (4)

(b) (4) we do not consider (b) (4) to be sufficient to support statements (b) (4).

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

Dordaviprone (ONC201, immediate release oral capsules, MW: 386.49 g/mol, free base) is an imipridone (b) (4)

The recommended dose is 625 mg orally once weekly (QW) for adult and pediatric patients weighing at least 52.5 kg. Dose is scaled by body weight QW for pediatric patients weighing less than 52.5 kg. Dordaviprone should be taken on an empty stomach, at least 1 hour prior to or 3 hours after a meal.

The CS-IRT reviewed the protocol of the thorough QT (TQT) study ONC201-102 previously (DARRTS [04/18/2022](#)) and found the proposed study design and analysis plan acceptable to characterize the effects of dordaviprone on the QTc interval. We also recommended ICH E14 Q&A 6.1 if the selected dose failed to cover high clinical exposures.

Study ONC201-102 was composed of two parts. Part 1 was an open-label lead-in study to select a safe dose for Part 2 with comparable exposures observed in patients. Six healthy

subjects were randomized 1:1 to receive one of two treatments: the first treatment was a single dose of 750 mg; the second treatment was two doses of 625 mg separated by 4-hours. Based on Part 1, 750 mg single dose was selected as the dose in Part 2. Part 2 was a single dose, placebo and positive controlled, 3-period (750 mg dordaviprone, placebo, and moxifloxacin [unblinded]), 6-sequence crossover TQT study of 30 healthy subjects. Washout was 7 days between periods. C-QTc based on Part 2 was the primary analysis using both the parent and metabolite concentration. See the Appendix of our previous review ([04/18/2022](#)) for details.

The following deviations were noted in the Applicant's C-QTc analysis compared to their initial analysis plan:

- i. Although the Applicant planned to use the average of pre-dose ECGs for individual baseline ECGs, their C-QTc analysis however used a centered baseline. The centered baseline was calculated as the population mean baseline ECGs for all participants in each study period.
- ii. The C-QTc analysis excluded one subject during active treatment period because of high pre-dose concentrations of both parent and metabolite. However, the subject's data during placebo and moxifloxacin treatment periods were included in the analysis.

The Applicant's use of a centered baseline in the calculation of QTcF change from baseline is acceptable. Findings by Huang D et al (2021)¹ indicated no significant difference between an averaged baseline and a time-matched baseline in the parameters of a C-QTc model for a crossover study design.

Excluding subjects from C-QTc analysis due to missing data is acceptable. This was also done in the Agency's independent analyses in section 4.

3.1.1 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety.

The primary route of elimination was metabolism via CYP3A4. Following administration of ¹⁴C-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.

Metabolic profiling of dordaviprone in human hepatocytes identified ONC207 as the only metabolite present at >10% of total radioactivity, accounting for approximately 20% of dordaviprone plasma C_{max}.

T_{max} (range) was 0.5 to 5.6 hours in patients and 0.5 to 2.0 hours in healthy subjects for parent. T_{max} was 0.5 to 8.0 hours in healthy subjects for ONC207. Terminal half-life was 11 hours in adult patients for parent and was 27 hours for ONC207 in healthy subjects. There's no accumulation for weekly dosing.

¹ Huang, D. (Patrick), Chen, J., & Tsong, Y. (2020). Baseline selection in concentration-QTc modeling: impact on assay sensitivity. *Journal of Biopharmaceutical Statistics*, 31(2), 168–179. <https://doi.org/10.1080/10543406.2020.1814797>

Analysis in healthy adults demonstrated dose proportionality across the range of 125 mg to 750 mg.

No clinically significant differences in the pharmacokinetics of dordaviprone were observed based on age, sex, or race. Severe renal impairment increased dordaviprone C_{max} by 13%. No dose adjustment 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 and there is no dosing recommendation in label.

Moderate hepatic impairment increased dordaviprone C_{max} by approximately 20%. No dose adjustment 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 and there is no dosing recommendation in label.

In pediatric patients, the maximum C_{max} was 3070 ng/mL in patients with weight ≥ 27.5 kg and < 42.5 kg following 375 mg QW.

Coadministration of dordaviprone and itraconazole resulted in a 2-fold increase in C_{max} . Dose is reduced to 375 mg QW for adult and pediatric patients who weigh at least 52.5 kg.

Pharmacokinetic simulations predict that coadministration of strong (rifampin) and moderate (efavirenz) CYP3A4 inducers reduce dordaviprone C_{max} by 68% and 44%, respectively.

A high-fat meal decreased the rate of absorption (C_{max}) of dordaviprone.

Table 2. Summary of Dose and Exposure Assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	625 mg QW, oral capsules, in adult patients	Parent: 3830 ng/mL ($C_{max,ss}$) ONC207: 729 ng/mL ($C_{max,ss}$)
Applicant's High clinical exposure scenario	For parent: 375 mg dordaviprone co-administered with strong CYP3A inhibitor.	Parent: 4425 ng/mL ¹ ONC207: 137 ng/mL ¹
	For ONC207: Administration of 625 mg dordaviprone in severe renal impairment	Parent: 4173 ng/mL ¹ ONC207: 845 ¹ ng/mL
Highest dose in QT assessment	750 mg single dose, oral capsules, in healthy subjects	Parent: 4223 ng/mL ONC207: 797 ng/mL
C_{max} Ratio	Parent: 1.1-fold over clinical; 0.9-fold over high clinical ONC207: 1.1-fold over clinical;	

¹From Applicant's response to IR. The Applicant recommends to avoid coadministration of strong and moderate CYP3A4 inducers with dordaviprone, and considers severe renal impairment is the high clinical exposure scenario for ONC207; [link](#)

3.1.2 Nonclinical Safety Pharmacology Assessments

The Applicant evaluated the effects of dordaviprone on hERG current in the study report (190924.POC, [link](#)). The hERG current was assessed at near physiological temperature

(33 to 35°C) using a manual patch clamp assay with a voltage protocol that is similar to the recommended hERG protocol by the FDA.

The hERG IC₅₀ was 2.4 µM (Hill coefficient = 1), which corresponds to a hERG safety margin of 4-fold (MW: 386.49 g/mol; PB: 95%) using the high clinical exposure scenario (4596 ng/mL, see CP Table 2).

The Applicant also evaluated the effects of the metabolite (ONC207) on hERG current (Study ID: CHI-24-01, [link](#)). The hERG current was assessed at near physiological temperature using a voltage protocol that is the same with the recommended hERG protocol by the FDA.

ONC207 inhibited the hERG currents by 4.1%, 8.3%, 14.6% and 29.7% at 0.1, 1, 10 and 30 µM, respectively. The estimated IC₅₀ of ONC207 on hERG current is 205 µM, which provide a hERG safety margin of >83-fold (MW: 296 g/mol; PB: unavailable, assuming 0% as the worst-case scenario) using the anticipated clinical exposure (729 ng/mL).

Reviewer's comment: *Both hERG assays met the best practice recommendations according to the ICH S7B Q&A 2.1 except a lack of proper positive control (only one concentration of terfenadine was tested in study 190924.POC). The results showed that the parent drug dordaviprone has a hERG safety margin of 4x and the metabolite has a safety margin of >83x at the anticipated clinical exposures, suggesting that parent drug has a risk for QTc prolongation by direct inhibition of the hERG current at the high clinical exposure.*

The in vivo toxicity study (ONC201-TX-101, [link](#)) assessed the effects of dordaviprone on ECG following weekly oral dosing to male dogs for three months. ECGs were taken prior to treatment initiation and on the final day of dosing (Week 13) pre-dose and 30 to 60 minutes post-dose. The free C_{max} of the highest dose (60 mg/kg, C_{max} 9907 ng/mL, PB in dogs 90%) in the study is 4.7-fold the free C_{max} of the high clinical exposure scenario (4223 ng/mL, PB 95%). The analysis of ECG parameters, such as heart rate, QT, QRS, or PR intervals, are not included in the study report. The Applicant stated that the ECG changes were “within normal limit” after drug exposure for all dogs.

Reviewer's comment: *The study report provided limited information on ECG parameter or QTc changes after drug exposure in the in vivo tox study.*

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

The Applicant conducted IUT by-time analysis based on MMRM model.

The analysis assessing the effect of dordaviprone on $\Delta\Delta\text{QTcF}$ demonstrated a maximum $\Delta\Delta\text{QTcF}$ LS mean increase of 13.8 ms (90% CI: 11.15 to 16.48) at 5 hours postdose.

The primary analysis for dordaviprone was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *The reviewer applied the same MMRM model and got the similar results and the Applicant's. Please see Section 4.3 for more details.*

3.2.1.1 Assay Sensitivity

The Applicant conducted concentration-QTc analysis for moxifloxacin as a primary analysis for assay sensitivity. The results of the Applicant's analysis show that the study demonstrated assay sensitivity as the slope (4.4 msec/ μ g/mL) and intercept (1.59 msec) were significantly higher than zero and the model predicted mean (90%CI) $\Delta\Delta$ QTcF was 9.34 msec (8.09, 10.58) at geometric mean C_{max} of 1771.8 ng/mL (lower bound at the geometric mean C_{max} is >5 msec).

Reviewer's comment: *The findings from the Applicant's assay sensitivity analysis are like those obtained by the reviewers, see Section 4.5.1.1.*

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the Applicant.

3.2.2 Categorical Analysis

There were no significant outliers per the Applicant's analysis for QTc (i.e., >480 msec or >60 msec over baseline), HR (<50 or >100 beats/min and 25% over baseline), PR (>200 msec and 25% over baseline), and QRS (>100 msec and 25% over baseline).

Reviewer's comment: *The reviewer's analysis has slightly different threshold for HR (>100 beats/min), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline). The analysis also shows no significant outliers for QTc, HR, PR and QRS intervals. Please see Section 4.4 for more details.*

3.2.3 Exposure-Response Analysis

The Applicant applied three models, 1) including parent and metabolite, 2) parent only and 3) metabolite only. Based on AIC, the Applicant used the model that included dordaviprone and its metabolite ONC207, but without interaction term between the parent and metabolite. Also, the Applicant used a population mean baseline in each period for calculation of QTcF the change from baseline. The results of the Applicant's analysis show that dordaviprone is associated with significant QTc prolonging effect.

Reviewer's comment: *The reviewer used the model recommended in the white paper including parent and metabolite. The reviewer used individual averaged pre-dose baselines for calculation of QTcF change from baseline and included an interaction term between dordaviprone and ONC207. Despite the differences, the results of the Applicant's analysis are consistent with those of the reviewer's analysis. See Section 4.5 for details.*

3.2.4 Safety Analysis

The integrated safety analysis set is comprised of 422 patients with glioma who were enrolled in 4 open-label studies ONC006, ONC013, ONC014, and ONC018.

Doses of dordaviprone varied across studies: 89.1% of patients received 625 mg once weekly, 8.1% received <625 mg once weekly, and 2.8% received 625 mg twice weekly. Pediatric patients weighing less than 52.5 kg received an equivalent body weight-adjusted dose. 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. The median patient age was 21.5 years (range: 3 to 80).

QT prolongation was reported in 3 participants (0.7%) in the integrated safety analysis set; 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 Applicant considered the events unlikely related because these events occurred at least 6 days following dordaviprone dosing.

Reviewer's comment: See Section 4.6 for reviewer's safety analysis.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., $|\text{mean}| > 10$ beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to the study treatment. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

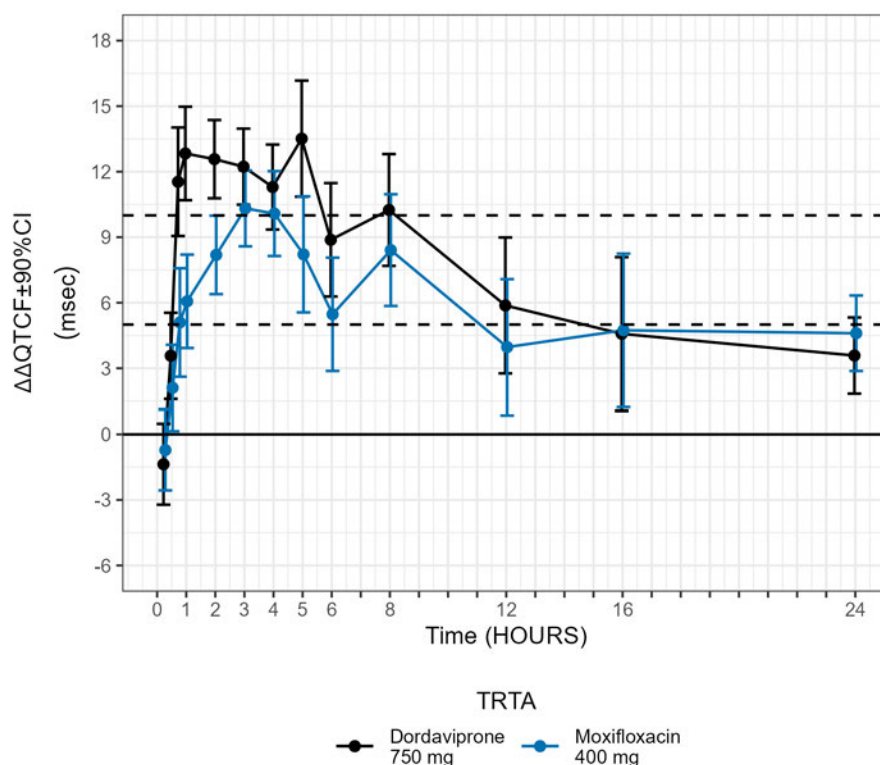
Data for subject (b) (6) during the ONC201 treatment period were excluded for the analysis due to a pre-dose concentration being $> 5\%$ of the participants' C_{max} .

The reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF , ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups.

Figure 1. Mean and 90% CI of $\Delta\Delta\text{QTcF}$ Time-Course (Unadjusted CIs)



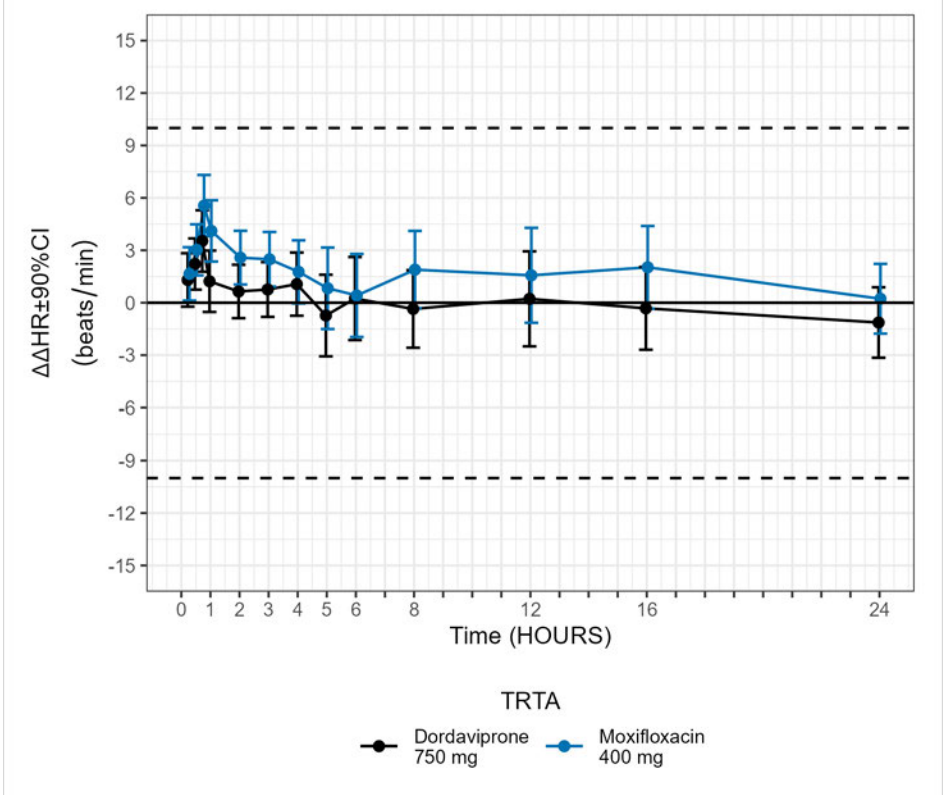
4.3.1.1 Assay Sensitivity

The primary method for establishing assay sensitivity for this study was based on exposure-response analysis—see section 4.5.1.1 for details.

4.3.2 HR

Figure 2 displays the time profile of $\Delta\Delta\text{HR}$ for different treatment groups.

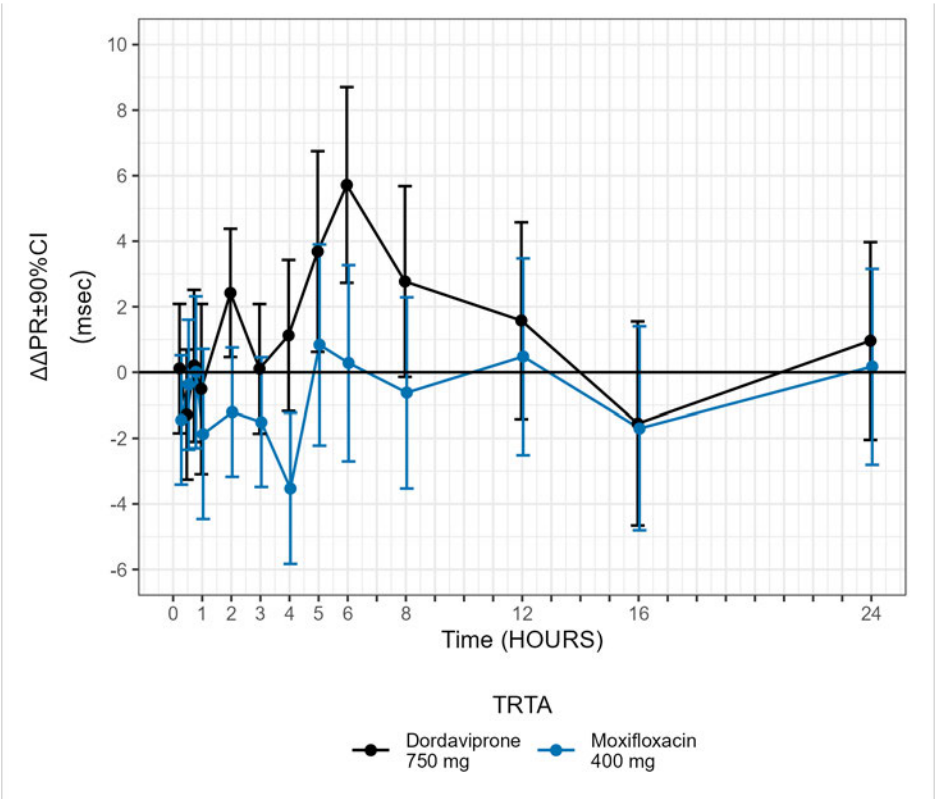
Figure 2. Mean and 90% CI of $\Delta\Delta HR$ Time-Course



4.3.3 PR

Figure 3 displays the time profile of $\Delta\Delta PR$ for different treatment groups.

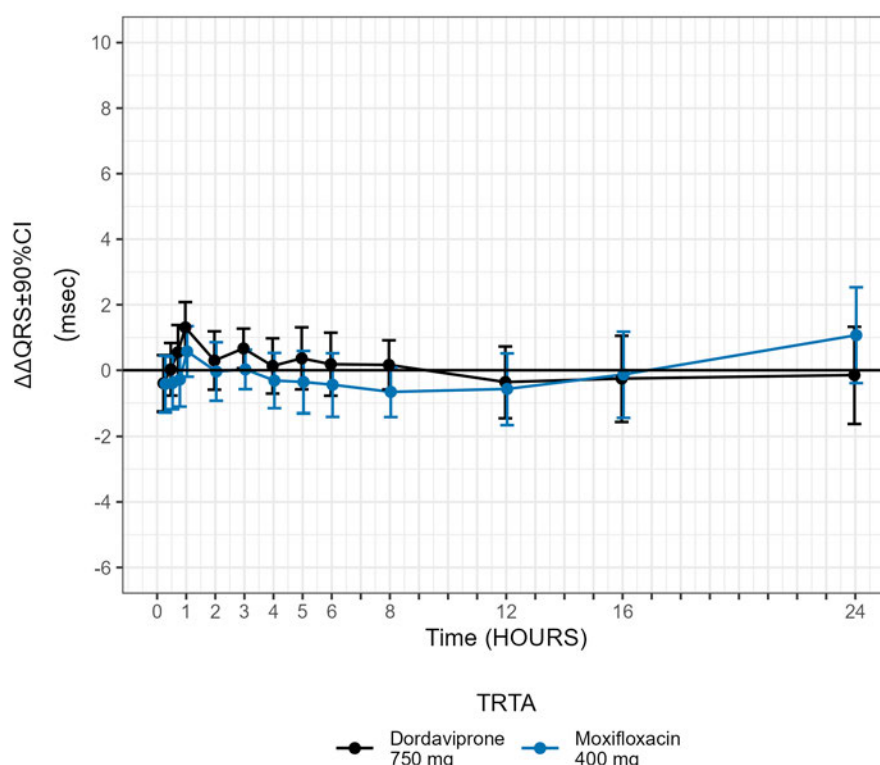
Figure 3. Mean and 90% CI of $\Delta\Delta PR$ Time-Course



4.3.4 QRS

Figure 4 displays the time profile of $\Delta\Delta QRS$ for different treatment groups.

Figure 4. Mean and 90% CI of $\Delta\Delta$ QRS Time-Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects had QTcF >480 msec. None of the subjects had Δ QTcF >60 msec.

4.4.2 HR

None of the subjects had HR >100 beats/min.

4.4.3 PR

None of the subjects had PR >220 msec.

4.4.4 QRS

None of the subjects had QRS >120 msec with 25% increase over baseline.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects receiving dordaviprone 750 mg (n = 29) or placebo (n = 27) or moxifloxacin 400 mg (n = 29) who had baseline and at least one post-baseline ECG, with time-matched PK. However, data from one subject

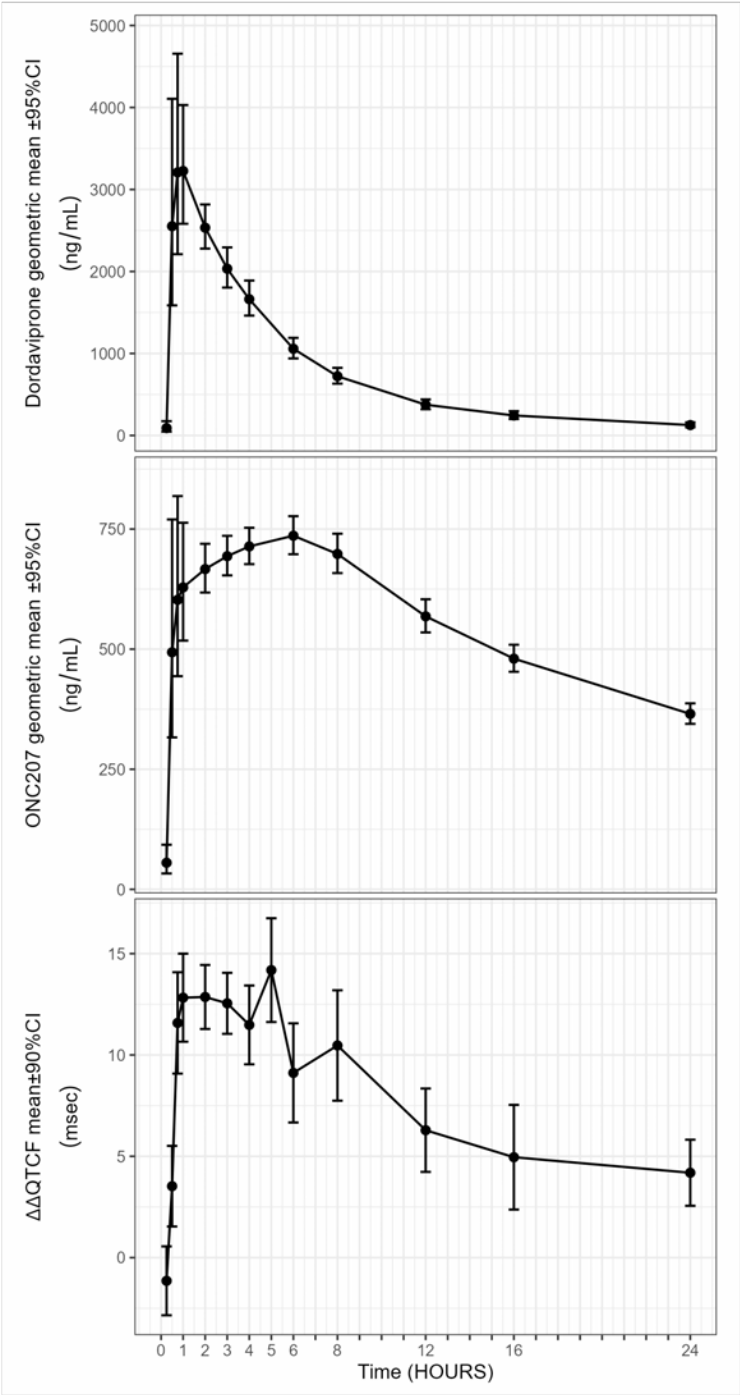
with unexplained high pre-dose concentrations of dordaviprone and ONC207 during dordaviprone treatment period were excluded for the analysis as they were >5% of the participants' C_{max} .

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and $\Delta\Delta QTcF$; and 3) absence of a nonlinear relationship.

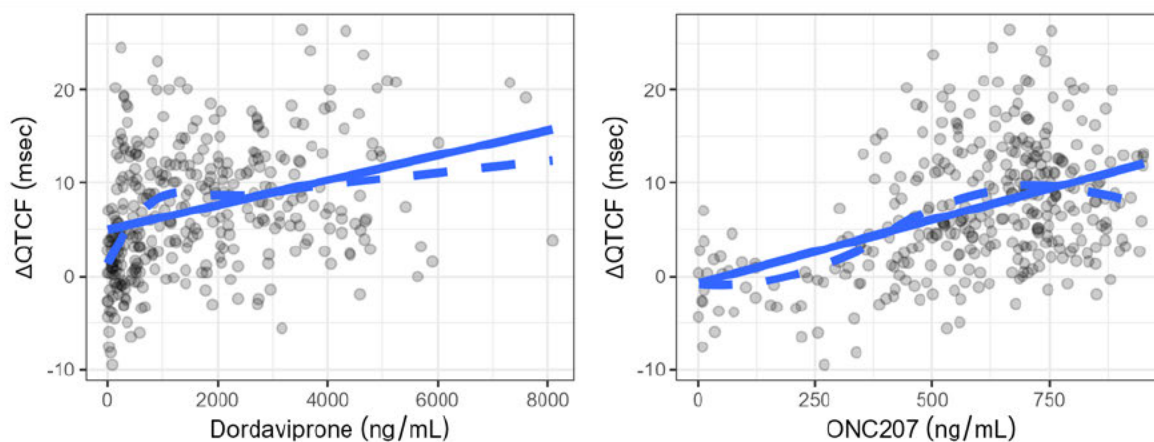
Figure 2 shows the time-course of $\Delta\Delta HR$, with an absence of significant $\Delta\Delta HR$ changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and $\Delta\Delta QTcF$. A significant QTc prolongation is observed at the peak dordaviprone concentration. QTc prolongation continues after T_{max} of dordaviprone to reach mean maximal $\Delta\Delta QTcF$ at about the peak of ONC207. Therefore, although hysteresis exists between $\Delta\Delta QTcF$ and dordaviprone concentration, peak $\Delta\Delta QTcF$ nearly coincides with the peak of ONC207, thus explaining the hysteresis and supporting a multivariate model with both dordaviprone and ONC207 as predictors of $\Delta\Delta QTcF$. In addition, the Applicant estimated a Pearson correlation coefficient of about 0.53 between dordaviprone and ONC207 concentration indicating non-collinearity and further supporting the multivariate model. Figure 6 shows the relationship between drug concentration and $\Delta QTcF$ and supports the use of a linear model. The inclusion of dordaviprone and ONC207 in the C-QTc analysis is also supported by the nonclinical findings (section 3.1.2).

Figure 5. Time-Course of Drug Concentration (Top) and QTcF (Bottom)²



² $\Delta\Delta QTcF$ shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6. Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data. Predictions from the concentration-QTcF model are provided in Table 3.

Table 3. Predictions From Concentration-QTcF Model

Actual Treatment	Dordaviprone (ng/mL)	ONC207 (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Dordaviprone 750 mg (at ONC207's T _{max})	2,376.0	797.1	11.1	(9.6 to 12.6)
Dordaviprone 750 mg (at dordaviprone's T _{max})	4,223.1	748.8	11.6	(9.6 to 13.6)
375 mg dordaviprone co-administered with strong CYP3A inhibitor (High clinical exposure scenario at dordaviprone's T _{max})	4,425.0	137.0	11.1	(4.7 to 17.5)
Administration of 625 mg dordaviprone in severe renal impairment (High clinical exposure scenario at ONC207's T _{max})	4,173.0	845.0	11.8	(9.5 to 14.0)
Highest therapeutic or clinical trial dosing regimen	3,830.0	729.0	11.4	(9.6 to 13.2)

4.5.1.1 Assay Sensitivity

The time course of moxifloxacin concentration and $\Delta\Delta\text{QTcF}$ is shown in Figure 8. When the same linear mixed effect model is applied, the goodness-of-fit plot for moxifloxacin is shown in Figure 8, and the predicted QTcF at the geometric mean C_{max} is listed in Table 4. Assay sensitivity was established by concentration-QTc analysis for moxifloxacin as a primary analysis for assay sensitivity.

Figure 7. Time-Course of Moxifloxacin Concentration (Top) and QTcF (Bottom)

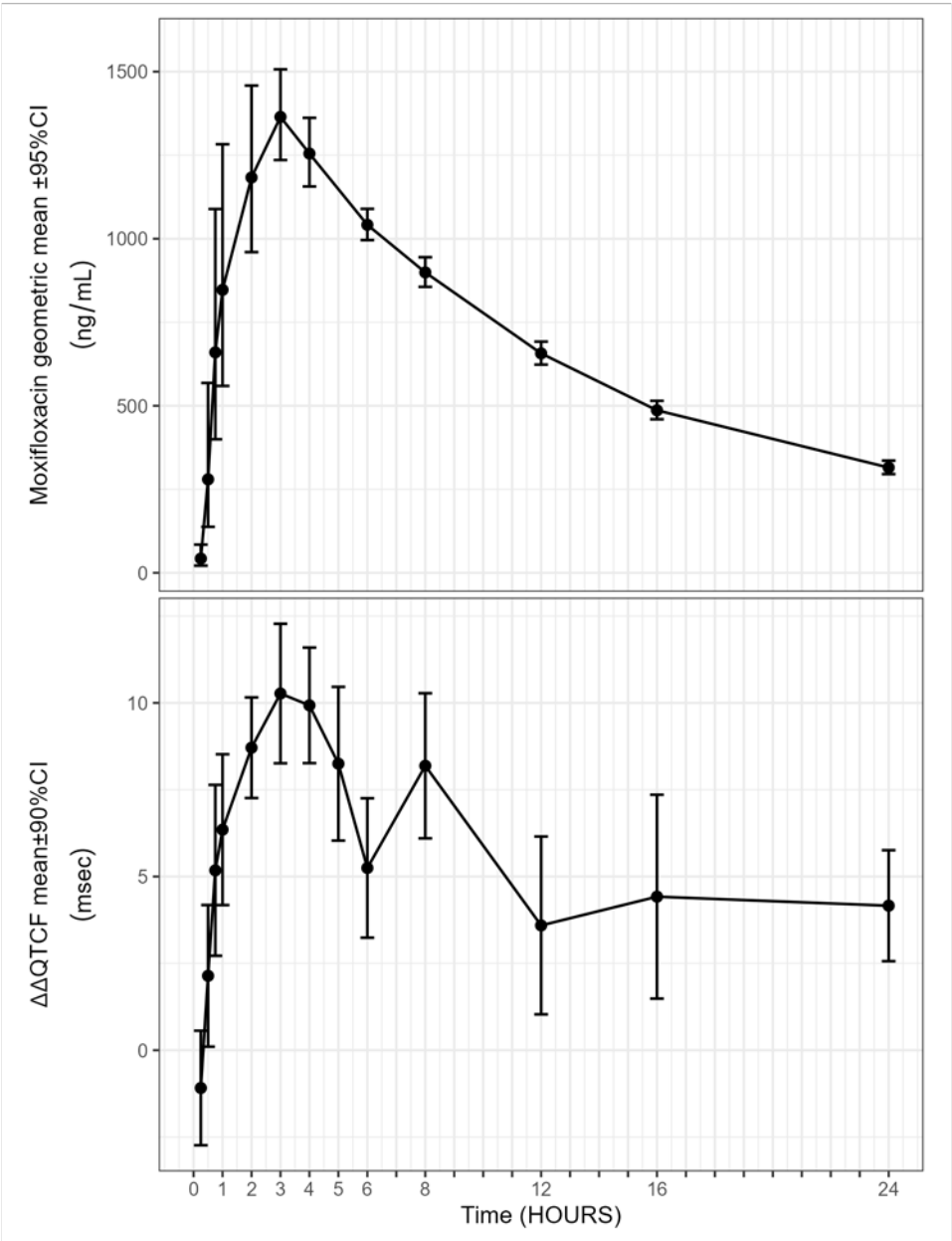


Figure 8. Goodness-of-Fit Plot of $\Delta\Delta\text{QTcF}$ for Moxifloxacin

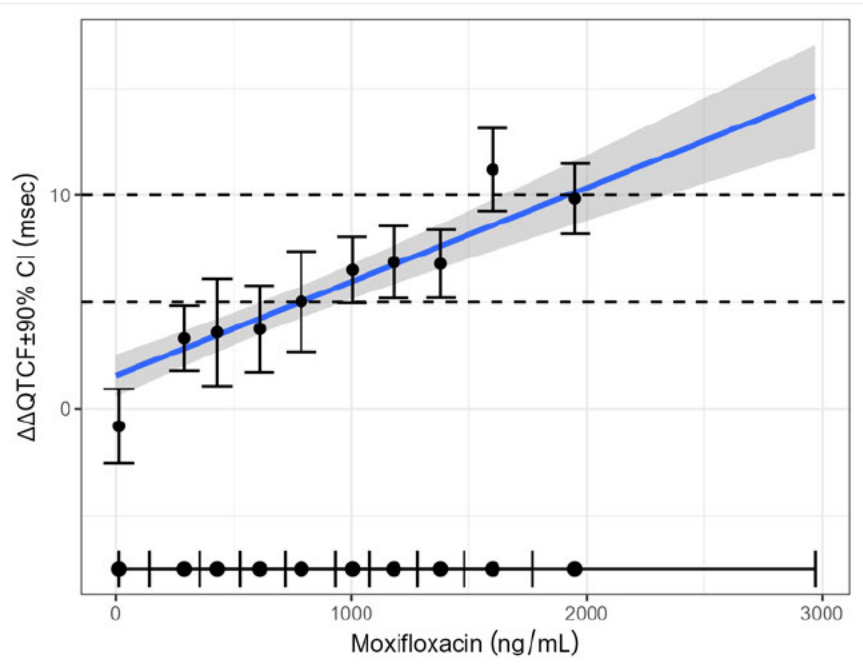


Table 4. Predictions From Concentration-QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	1,774.4	9.4	(8.0 to 10.7)

4.6 SAFETY ASSESSMENTS

The reviewer's analysis focused on the integrated safety analysis set of 422 patients with glioma who were enrolled in 4 open-label studies (ONC006, ONC013, ONC014, and ONC018). This is the same population described in the proposed label section 6.

ECGs were only collected at screening in studies ONC013 (n = 73), ONC014 (n = 134), and ONC018 (n = 131). ECGs were collected at each cycle on Day 1 in study ONC006 (n = 84).

In the integrated safety analysis set, one patient had QTcF >500 msec (508 msec, baseline: 394 msec), collected at a follow-up visit in study ONC006 (Day 296). All his other QTcF values collected from Cycle 2 to Cycle 11 (missing Cycle 6 and Cycle 10) were below 450 msec. Five patients had change from baseline QTcF >60 msec and two of them had maximum QTcF > 480 msec (495 msec and 508 msec).

In total 33 patients (7.5%) had TEAEs of seizure and 18 of them were SAEs. Seizures are common symptoms of glioma (brain tumor).

In total, 13 patients (3%) experienced TEAEs of torsade de pointes/QT prolongation (broad SMQ), with preferred terms of syncope (6 patients, 1.4%), cardiac arrest (4 patients, 0.9%), and electrocardiogram QT prolonged (3 patients, 0.7%). All electrocardiogram QT prolonged AEs were Grade 1 with QTcF <460 msec (maximum

QTcF: 455 msec). No actions were taken due to these events. Three patients had Grade 3 syncope events. None of them had post-dose ECG data. All four cardiac arrest events were SAEs and all four patients died. Two were due to the cardiac arrest events (subject ID: ONC018- (b) (6) and ONC018 (b) (6)). None of the four patients had post-dose ECG data.

Patient ONC014- (b) (6) was a 15-year-old African American female who was enrolled in Arm D of Study ONC014 for the treatment of glioma in pediatrics. The patient's glioma was diagnosed on (b) (6) and was considered to be recurrent (first recurrence) at the time of study enrollment. Dosing with dordaviprone 375 mg QW started on (b) (6) (Day 1). The patient's last dose was administered on (b) (6) (Day 15). On (b) (6) (Day 21), the patient experienced the SAEs of hypoxia, acute respiratory failure, cardiac arrest, and shock. It was reported that while she was in the backseat of her mother's car, she was unresponsive. The patient required seven minutes of resuscitations with cardiopulmonary resuscitation and two doses of epinephrine before return of spontaneous circulation. The patient was intubated and started on treatment with norepinephrine 0.12 mcg/kg/min and 3.5 L (approximately 100 mL/kg) nasal saline boluses heated for hypothermia. She was admitted and transferred to the intensive care unit. On (b) (6) (Day 28), the patient experienced the SAE of death (Grade 5) (narrative: [CSR](#) page 347).

Patient ONC018- (b) (6) was an African American 9-year-old male enrolled in the ONC018 study. The patient was diagnosed with a diffuse intrinsic pontine glioma on (b) (6). Initial treatment included photon radiation followed by a single dose of CED 1241-8H9 on (b) (6). On (b) (6) the patient started dordaviprone 625 mg QW. On (b) (6), the patient was seen at his local emergency department (ED) following an episode of dyspnea, which resolved. The patient was treated with oxygen and diazepam and discharged to home. On (b) (6) he presented for cycle 2 screening after tolerating cycle 1 treatment well. At this visit he had mostly stable neurological symptoms over the past month and was determined acceptable to start the next course of treatment. Last dose was administered on (b) (6). On (b) (6) patient presented with cardiac arrest and died following supportive care (narrative: [CSR](#) page 249).

Patient ONC018- (b) (6) was an 18-year-old White male who was enrolled in study ONC018 (Arm A) on 1 (b) (6). The patient's glioma was diagnosed on (b) (6) and was considered recurrent (first recurrence) at the time of study enrollment. Dosing with dordaviprone 625 mg QW began on (b) (6) (Day 1). On (b) (6) (Day 35), the patient started to receive bevacizumab IV. On (b) (6) (Day 99), the patient experienced the SAEs of respiratory failure, cardiac arrest, and aspiration. Prior to the onset of the SAE, dordaviprone was administered on (b) (6) (Day 93). It was reported that the patient and his family were on the way to the site in their car due to a one-day history of urinary retention. While on the route, the patient became apneic and cyanotic. The family performed rescue breathing EMS arrived. He was then transferred to the site's hospital where he was intubated due to altered mental status and hypoxia with oxygen saturation in the 80s. He was transferred to the intensive care unit (ICU) for invasive mechanical ventilation. On (b) (6) (Day 100), following the bronchoscopy, the patient became bradycardic and then developed a pulseless electrical activity (PEA)

arrest. The Return of Spontaneous Circulation (ROSC) was obtained after approximately 3 minutes of cardiopulmonary resuscitation (CPR) and 2 doses of epinephrine. Troponin-T done on the same date was 74 ng/L (rr: <18). Chest x-ray showed an interval increase of right lower lung opacities that may represent atelectasis, pneumonia, or aspiration. A small right pleural effusion was also noted. That same day, the event of cardiac arrest was considered resolved. On (b) (6) (Day 101), the patient was extubated. A CT chest showed extensive pneumomediastinum with subcutaneous emphysema extending into the neck. Pneumoperitoneum was also visible in the upper abdomen. There was debris seen within the bilateral pulmonary bronchi and atelectasis of the right middle, lower lobes, and the left lower lobe likely with superimposed bilateral aspiration material. No evidence of pulmonary embolism was noted. A small right pleural effusion was reported. On (b) (6) (Day 101), the event of respiratory failure was considered resolved. On (b) (6) (Day 106), the patient was discharged from the hospital on do not resuscitate (DNR)/ do not intubate (DNI) orders. On (b) (6) (Day 107), the event of aspiration was considered resolved. He had acute gastrointestinal (GI) bleeding with evidence of bright red blood from the orogastric tube (OGT), which was resolved. The patient met the criteria for a hospice bed, but he mentioned that he was not quite ready to transition to home hospice and deferred further decision-making until the next visit. On (b) (6) (Day 107), the patient passed away at home. Study treatment was interrupted due to the events. On an unknown date, dordaviprone was resumed. On (b) (6) (Day 105), the patient took his last dose of dordaviprone (narrative: [CSR](#) page 367).

Patient ONC018- (b) (6) was a 32-year-old Caucasian male enrolled in study ONC018. The patient's medical history included bradycardia. On (b) (6), the patient started dordaviprone 625 mg QW. The last dose was administered on an unknown date in (b) (6). On (b) (6) the patient experienced the serious adverse event of asystole (cardiac arrest), which resulted in death (narrative: [CSR](#) page 397).

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/s/

ELIFORD N KITABI
04/15/2025 09:57:59 AM
Hongfei Zhang drafted the initial review.

XUTONG ZHAO
04/15/2025 10:00:17 AM

YU-TING WENG
04/15/2025 11:15:58 AM

DONGLIN GUO
04/15/2025 11:51:59 AM

YANYAN JI
04/15/2025 12:58:27 PM

MICHAEL Y LI
04/15/2025 12:59:35 PM

DEVI KOZELI on behalf of LARS JOHANNESSEN
04/15/2025 01:12:41 PM
Lars is OOO

CHRISTINE E GARNETT
04/15/2025 01:16:42 PM

Consult Memorandum

Date: April 1, 2025

To: Elizabeth Duke, MD CDER/OND/OOD/DO2
Diana Bradford, MD CDER/OND/OOD/DO2

From: Caryl Giuliano, PhD CDRH/OPEQ/DMGP/MGB

Through: Zivana Tezak, PhD CDRH/OPEQ/DMGP/MGB
Soma Ghosh, PhD CDRH/OPEQ/DMGP
Reena Philip, PhD Associate Director of Biomarkers and Precision Oncology, OCE

Subject: NDA219876

Drug Name: Dordaviprone

Drug Sponsor: Chimerix

Biomarker(s): Gliomas harboring the H3 K27M mutation

Device Name: Immunohistochemistry (IHC)/Next Generation Sequencing (NGS)

Device Sponsor: Not Specified

CDRH Tracking: ICC2500164/ICCR01053251

Related Submissions: Q230873, ICC2200866, ICC2200275

I. BACKGROUND

Chimerix is developing dordaviprone for the treatment of H3 K27M-mutant diffuse glioma, a rare and life-threatening disease with an unmet medical need, as there are currently no pharmacologic agents approved specifically for the treatment of H3 K27M-mutant diffuse glioma. Dordaviprone is a novel, orally administered small molecule imipridone and dopamine receptor D2 (DRD2) antagonist with anticancer activity in gliomas harboring the H3 K27M mutation. CDER requested consult from CDRH to provide comment regarding our position on a companion diagnostic (CDx) for dordaviprone.

Submission History

The submission history was reviewed for prior feedback to Chimerix in regard to a potential CDx, as no updated CDx information was provided in the current NDA submission:

- **April 14, 2023:** Chimerix submitted Q230873 in regard to testing for the H3 K27M mutation
- **June 13, 2023:** Dr. Elizabeth Duke provided a CDER consult memo.
- **June 21, 2023:** Chimerix received written feedback from CDRH.
- **June 26, 2023:** An FDA/Chimerix virtual meeting was held.
- **July 11, 2023:** Meeting minutes were submitted to CDRH by Chimerix.

II. CLINICAL TRIAL ONC201-108 'ACTION' study

The safety, efficacy and clinical benefit of dordaviprone for the treatment of patients with H3 K27M-mutant diffuse glioma is being evaluated in an ongoing Phase 3 study (ONC201-108) entitled, "ONC201 for the Treatment of Newly Diagnosed H3 K27M-mutant Diffuse Glioma Following Completion of Radiotherapy: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study." The study will assess whether treatment with dordaviprone following frontline radiotherapy will extend overall survival and/or PFS in this population.

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Eligible participants will have histologically diagnosed H3 K27M-mutant diffuse glioma and have completed standard frontline radiotherapy. The primary endpoints are overall survival and PFS (based on RANO criteria). Approximately 450 participants will be randomized to have 327 deaths at the final analysis; interim analyses for overall survival are planned after 164 and 246 deaths have been reported. The final analysis for PFS will be completed when 286 PFS events have been observed. This will be both a confirmatory study for the initial accelerated approval in recurrent disease and the registration study for a full approval in the newly diagnosed, post-radiotherapy population.

III. USE OF DEVICE(S) IN THE TRIAL ONC201-108 'ACTION' Study

Below is a summary of the pertinent discussions and feedback provided to Chimerix in regard to use of standard of care testing for H3 K27M mutations in glioma, the challenges of obtaining sufficient tumor tissue for development of a CDx and CDRH recommendations.

Dr. Elizabeth Duke Memo 6.13.23 (Q230873)
The ongoing clinical trials of ONC201 which require an H3 K27M mutation for eligibility have enrolled patients based on local, standard of care laboratory testing for H3 K27M mutation status. Laboratory developed tests to identify the H3 K27M mutation in glioma tissue are used in current clinical practice and include either: • Immunohistochemistry (IHC) detection of mutant H3 protein • Next generation sequencing (NGS) of H3-encoding genes
The sponsor states that H3 K27M mutation testing occurs with reliable methods as standard of care testing for patients with newly diagnosed glioma, and the H3 K27M diagnostic status would already be known for patients under consideration for treatment with ONC201 based on Clinical Laboratory Improvement Amendment (CLIA)-certified institutional standard of care testing. Local testing is typically reliant on a limited amount of biopsy tissue that is often exhausted by the standard diagnostic workup. The sponsor states that a CDx would be redundant to testing already completed, add unnecessary turnaround time, and would not be feasible for many patients given insufficient remaining tissue after standard diagnostic testing. In addition, due to the midline anatomic location of most of these tumors, obtaining an additional sample to support central CDx testing would pose an additional risk to patients.
Standard of care treatment for newly diagnosed DMG is maximal safe surgical resection followed by radiation. Standard of care testing for newly diagnosed gliomas includes molecular profiling and notably, H3 K27M alteration is part of the WHO Classification definition of H3 K27M-altered tumors. Due to the midline location primarily including the thalamus, basal ganglia and brainstem, gross total resection is rarely feasible, and typically only biopsies are performed due to the critical structures in this anatomic area. While chemotherapeutic agents lomustine and carmustine are approved for brain tumors, studies have shown limited efficacy of chemotherapy for H3 K27M-altered DMG. Upon recurrence, some patients may undergo re-resection or re-irradiation, or enroll on a clinical trial.
Based on the data provided, DO2 agrees that a CDx is not needed for the safe and effective use of ONC201 for the treatment of patients with H3 K27M-mutant glioma. The disease entity is defined by the presence of the H3 K27M mutation, which is already determined prior to the initiation of systemic therapy. In addition, we agree that local laboratory testing is standard of care with IHC or NGS testing. The limited available tissue and risk of additional sampling due to tumor location would pose unnecessary risk to patients.

Sponsor TCON 6.26.23 Meeting Minutes

Given that H3 K27M is a clonal and genetic event retained throughout glioma disease progression and that H3 K27M mutation testing with reliable, robust, and concordant methods already occurs as standard of care testing for glioma patients in accordance with the 2021 World Health Organization (WHO) Classification and 2022 National Comprehensive Cancer Network (NCCN) guidelines, along with the infeasibility and associated challenges of development and implementing a centralized companion diagnostic (CDx) in vitro diagnostic (IVD) into this established standard of care testing process (e.g., sourcing H3 K27M-positive glioma samples for CDx analytical validation studies and executing CDx clinical bridging), does CDRH agree that a CDx IVD would not be required for identification of patients for treatment with ONC201?

The use of multiple approaches (i.e., immunohistochemistry [IHC] and sequencing) is not due to uncertainty; both testing methods are used when possible due to their distinct advantages. The Sponsor would like to provide further clarification on the diagnostic standard of care testing for H3 K27M-mutant glioma and clarify that there is unlikely to be additional sample remaining after this diagnostic testing to support additional centralized testing (i.e., a CDx IVD), and re-biopsy is not feasible.

Chimerix' external pathology expert, (b) (4) reviewed the standard of care diagnostic testing workflow. (b) (4) provided clarification that next-generation sequencing (NGS) testing is not needed to make a H3 K27M diagnosis and that a definitive diagnosis is usually made from IHC testing alone. He also clarified that testing by NGS is performed in addition to immunohistochemistry (IHC) testing only if sufficient tissue remains and because it provides complementary information on additional clinically relevant molecular alterations (e.g., IDH1, NTRK). NGS testing is not performed if there is no available tissue sample following the IHC and other initial standard testing, which can be an issue in this patient population.

Chimerix external pathology expert noted that IHC staining for the mutation is generally strongly uniformly positive in tumor nuclei since the mutation is generally clonal for the disease. The testing is also codified in WHO guidelines for diagnosis of the disease. Additionally, Chimerix' external pathology expert noted that in his experience, NGS testing is usually always concordant with IHC-positive staining.

There was further discussion on whether an IHC-based CDx testing would be feasible and Chimerix clarified that there is unlikely to be any tissue remaining for an additional post-diagnosis IHC test in the majority of the cases, not even 2 to 3 slides. The Sponsor noted that IHC H3 K27M positive tests almost always have positive NGS.

FDA stated that whether contemporaneous approval is required is made by CDER on a case-by-case basis and FDA stated that none of this discussion is intended to delay or prevent the ONC201 ongoing clinical development program, or the eventual submission and approval of an NDA.

IV. CDER Question to CDRH:

Please provide your position regarding a companion diagnostic (CDx) for NDA219876.

V. CDRH RESPONSE TO CDER:

We defer to CDER to make the determination as to whether a CDx is required for the safe and effective use of dordaviprone; however, if the drug indication indicates that patients with glioma with H3 K27M mutations will benefit from dordaviprone, then a CDx test will be needed for safe and effective use of the drug. We acknowledge prior discussions (Q230873) and recommendations (Dr. Elizabeth Duke consult memo 6.13.23); however, we recommend that a PMA for the CDx should be submitted as soon as possible

for CDRH review. CDRH additionally recommends that a post marketing commitment (PMC) should be agreed upon with the Sponsor to develop an analytically and clinically validated CDx that is adequate to support device and drug labeling.

CDRH defers to CDER to determine if a PMC for the CDx is justified and to determine if the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared in vitro diagnostic (IVD) companion diagnostic device. If CDER believes a PMC for the CDx is appropriate and justified, CDRH has the following recommended language for the PMC and Section 2.1 of the dordaviprone label.

CDRH recommendation for PMC to support a CDx for dordaviprone:

Commitment to support the availability of an in vitro diagnostic device that is essential to the safe and effective use of dordaviprone for patients with glioma with H3 K27M mutation through appropriate analytical and clinical validation using clinical trial data that is adequate to support labeling.

CDRH recommendation for Section 2.1 Patient Selection of the dordaviprone label:

Select patients for treatment with dordaviprone based on the *presence of a H3 K27M mutation* in tumor tissue specimens from patients with glioma [see Clinical Studies (14)]. An FDA-approved test for detection of H3 K27M mutation for selecting patients for treatment with dordaviprone is not currently available.

This consult review is limited to the information provided in NDA219876. If there are any questions regarding this review, please contact Caryl Giuliano by email at Caryl.Giuliano@fda.hhs.gov.

Caryl
Giuliano -S



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