

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219876Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 136090

MEETING PRELIMINARY COMMENTS

Chimerix, Inc.
Attention: Stacy Jasper, R.Ph., R.A.C.
Director, Regulatory Strategy
2505 Meridian Parkway, Suite 100
Durham, NC 27713

Dear Stacy Jasper:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dordaviprone.

We also refer to your August 16, 2024, correspondence, received August 16, 2024, requesting a virtual Pre-NDA meeting for dordaviprone for the treatment of recurrent H3 K27M-mutant diffuse glioma.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

If you have any questions, call me at 240-402-4558 or email
opeyemi.udoka@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Opeyemi Udoka DPT, CSM
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic
Diseases for Division of Oncology 2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Preliminary Comments



PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: November 1, 2024; 10:00AM – 11:00AM
Meeting Location: Video Conference
Application Number: 136090
Product Name: Dordaviprone
Indication: For the treatment of recurrent H3 K27M-mutant diffuse glioma.
Sponsor Name: Chimerix, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Martha Donoghue, M.D., Acting Associate Director for Pediatric Oncology, Office of Oncologic Diseases (OOD)
Nicole Drezner, M.D., Deputy Division Director, Division of Oncology 2 (DO2)
Diana Bradford, M.D., Cross Disciplinary Team Leader, DO2
Elizabeth Duke, M.D., Clinical Reviewer, DO2
Xiaoxue Li, Ph.D., Biostatistics Team Leader, DBV
Arup Sinha, Ph.D., Biostatistics Reviewer, DBV
Ankit Shah, Ph.D., Clinical Pharmacology Team Leader, Division of Cancer Pharmacology I (DCPI)
Vicky Hsu, Ph.D., Clinical Pharmacology Reviewer, DCPI
Emily Wearne, Ph.D., Acting Nonclinical Team Leader, Division of Hematology Oncology Toxicology (DHOT)
Amy Skinner, Ph.D., Nonclinical Reviewer, DHOT
Opeyemi Udoka, D.P.T., Senior Regulatory Health Project Manager, Division of Regulatory Operations for Oncologic Diseases (DRO-OD)

SPONSOR ATTENDEES

Joshua Allen, Ph.D., Chief Technology Officer
Mike Andriole, Chief Executive Officer
Tom Brundage, M.S. Vice President, Biostatistics
Heidi Colton, M.S. Executive Director, Translational Medicine & Head of Early Clinical Strategy Planning
Stacy Jasper Director, Clinical Research & Regulatory Strategy
Christopher Jordan, M.S.H.S., Vice President, Regulatory Affairs
Allen Melemed, M.D., Chief Medical Officer
Marion Morrison, M.D., Senior Executive Medical Director
Odin Naderer, Pharm.D., Vice President, Clinical Pharmacology and Translational Medicine

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 1, 2024; 10:00AM – 1:00AM between Chimerix, Inc., and the Division of Oncology 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

On August 15, 2024, Chimerix, Inc., (Chimerix) submitted a meeting request 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. Chimerix is working toward a submission by the end of the year. The meeting package was received on September 27, 2024.

Regulatory

On August 31, 2017, the IND-opening protocol for ONC201 in adults with recurrent high-grade glioma was deemed safe to proceed.

Oncoceutics, Inc. was granted Orphan Drug Designation, Fast Track Designation, and Rare Pediatric Disease Designation for ONC201.

On July 8, 2019, and May 12, 2020, Type C meetings were held to discuss the early efficacy results for ONC201 in patients with glioma. FDA stated that a sufficiently homogenous patient population should be identified to allow for an accurate interpretation of efficacy results, and that confirmed durable overall response rate (ORR) has previously supported accelerated approvals in patients with solid tumors, however, the response rate should be of a clinically meaningful magnitude, sufficient in duration, and likely to predict an improvement in survival and other clinical benefit. FDA stated that Oncoceutics will need to clearly demonstrate that responses are due to treatment with ONC201 and not possibly related to other treatment modalities (e.g., prior radiation).

On September 11, 2020, and January 11, 2021, meetings were held to discuss the nonclinical and CMC development programs, respectively.

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On March 11, 2021, INDs for ONC201 were transferred from Oncoceutics to Chimerix.

On June 8, 2021, a Type C meeting was held to discuss the clinical pharmacology development program and FDA conveyed concerns regarding the lack of completed clinical pharmacology studies as well as inadequate dose-finding to support the dose of ONC201 selected for clinical efficacy studies.

On March 31, 2022, November 28, 2022, and July 17, 2024, Type C meetings were held to discuss the clinical development program for ONC201 for the treatment of patients with recurrent H3 K27M-mutant glioma. FDA expressed concern regarding the uncertainty related to the determination of whether the estimated treatment effect observed in the proposed pooled efficacy population is due to dordaviprone. Given the inherent uncertainties in the determination of a treatment effect based on imaging-based responses in this disease setting, FDA requested additional information to support the evaluation of effectiveness of dordaviprone (e.g., additional response rate and durability data from patients beyond the previously identified efficacy population; additional evidence to support the observed treatment effect is due to dordaviprone rather than a delayed treatment effect of prior radiation therapy; data from patients with non-H3 K27M-mutant gliomas treated with dordaviprone). Refer to the Meeting Minutes dated July 30, 2024 for additional details.

A CMC-only pre-NDA meeting is scheduled for October 30, 2024.

Nonclinical

Dordaviprone is a small molecule antagonist of the G-protein coupled receptor dopamine receptor D2 (DRD2) and D3 (DRD3). Chimerix states that dordaviprone activates the integrated stress response (ISR), the same signaling pathway activated by ER stress-inducing compounds such as proteasome inhibitors, and cites data describing a role for dordaviprone in activation of the caseinolytic protease P (ClpP). ClpP is a serine protease located in the mitochondrial matrix that plays a role in mitochondrial protein quality control by degrading misfolded proteins. Additionally, per Chimerix, DRD2 antagonism downregulates Akt and ERK, causing the translocation of Foxo3a into the nucleus, where it binds to the TRAIL promoter to induce expression of apoptotic genes independent from p53 signaling.

To support a potential marketing application, Chimerix completed three primary pharmacology studies; safety pharmacology and pharmacokinetic studies; an in vitro phototoxicity study; GLP-compliant oral repeat-dose toxicology studies up to 13-weeks duration in rats and dogs including toxicokinetic assessments; and pilot embryo-fetal development (EFD) studies in rats and rabbits. Following preliminary evaluation of the pilot EFD studies, FDA previously conveyed to Chimerix (IR sent on April 1, 2021) that full-GLP compliant EFD studies do not appear warranted to support a marketing

application. Finally, Chimerix completed a battery of genotoxicity assays, including in vitro and in vivo studies.

Chimerix states a plan to obtain right of reference for published data demonstrating in vivo efficacy in two H3 K27M-mutant glioma disease models, as well as reversal of H3 K27me3-loss in tumor samples obtained from patients with H3 K27M-mutant glioma who received dordaviprone, with references to other published literature included in the NDA.

Clinical Pharmacology

The proposed dosage of dordaviprone is 625 mg (5 x 125 mg capsules) orally once weekly, with the dose scaled by body weight for patients who weigh < 52.5 kg.

The recommended dosage was selected based on an evaluation of safety and efficacy at variable doses (i.e., 125 mg, 250 mg, 375 mg, 500 mg, and 625 mg) and dosing frequencies (i.e., once every 3 weeks, once weekly, 2 consecutive days of the week, once daily). Nine clinical pharmacology studies are completed or ongoing. Chimerix submitted a high-level summary of the clinical pharmacology package in this meeting package and states a plan to include exposure-response modeling results in the NDA submission.

In the clinical studies from which results will be included in the planned NDA, patients received an “Early Phase” capsule formulation of dordaviprone which is no longer being administered. The bioequivalence of the “Early Phase” capsule formulation and the “Late Phase” (to-be-marketed) capsule formulation were evaluated in Study ONC201-103. In addition, Chimerix cites challenges related to taste-masking the drug substance and predicts a delayed timeline for developing an age-appropriate pediatric formulation.

Clinical

Dordaviprone is being developed for the proposed indication of the treatment of recurrent H3 K27M-mutant diffuse glioma, including in the following seven clinical studies:

- ONC-006 (NCT02525692): “Oral ONC201 in Recurrent GBM, H3 K27M Glioma and Midline Glioma” (Experimental Arm E)
- ONC-013 (NCT03295396): “ONC201 in Adults with Recurrent H3 K27M-mutant Glioma” (Experimental Arm B)
- ONC-014 (NCT03416530): “ONC201 in Pediatric H3 K27M Gliomas”
- ONC-016, ONC-018 and ONC-028: Expanded Access Protocols for ONC201
- ONC-201-108 (NCT05580562): “ONC201 for the Treatment of Newly Diagnosed H3 K27M-mutant Diffuse Glioma Following Completion of Radiotherapy: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study”

As defined in the 2021 WHO Classification of Tumors of the Central Nervous System, “diffuse midline glioma (DMG), H3 K27-altered”, is a pediatric-type diffuse high-grade glioma which primarily occurs in children but may also occur in adults (Louis et al, 2021). Originally classified as a unique tumor type in 2016, DMG includes tumors previously referred to as diffuse intrinsic pontine glioma (DIPG) (Louis et al, 2016).

In pediatric patients with DMG, the reported median overall survival is approximately 11 months from the time of diagnosis and 4-5 months after radiologic progression with few children surviving past 2 years from diagnosis (Coleman et al, 2023). The prognosis in adults is less well-characterized, with median overall survival ranging from 9 to 28 months (Meyronet et al, 2017; Daoud et al, 2018; Schreck et al, 2019; Schulte et al, 2020; Zheng et al, 2022; Vuong et al, 2022; Gong et al, 2023). These tumors may occur in anatomic structures along the midline, including brainstem, thalamus, cerebellum and spinal cord; it is not clear whether prognosis varies by anatomic location or other clinical characteristics such as primary tumor size, specific H3 mutation, status of ATRX expression, and Ki-67 index.

Available therapy for adult and pediatric patients with DMG includes radiotherapy; responses to chemotherapy and targeted agents evaluated in clinical trials have been limited. H3 K27M-mutant diffuse midline glioma is a serious and life-threatening condition with significant unmet medical need.

Efficacy Results

Chimerix proposes to submit an NDA by the end of December 2024 for accelerated approval of dordaviprone for the treatment of patients with recurrent H3 K27M-mutant diffuse glioma based on an integrated efficacy population across three single-arm trials (ONC006, ONC013, ONC014) and two expanded access protocols (ONC016, ONC018).

The proposed primary efficacy population includes 50 patients ages 8 to 70 years with recurrent or progressive H3 K27M-mutant DMG (excluding DIPG and primary spinal tumors) with measurable disease on contrast-enhanced brain MRI who received dordaviprone monotherapy at the dose 625 mg (or a dose scaled by body weight) once weekly. Prior therapy included at least radiotherapy (minimum 90 days prior to first dose of study treatment) and all patients were enrolled before February 26, 2020. As of July 31, 2024, none of these patients remain on treatment or in follow-up.

Demographic characteristics for the primary efficacy population include: 46% female with median age of 30 years (4 patients <18 years; 32 patients 18 to < 40 years; 14 patients ≥ 40 years); 78% were White; 66% had primary thalamic tumors and 34% had non-thalamic midline tumors; 72% had a baseline performance score (KPS/LPS) of at least 80.

As of the data cut-off date of May 31, 2021, with median follow-up of 18.8 months, the overall response rate (ORR) based on Response Assessment in Neuro-Oncology

criteria for high-grade glioma (RANO-HGG) as assessed by blinded independent central review (BICR) was 20% (95% CI: 10, 34) (Table 1). The median duration of response was 11.2 months (95% CI: 3.8, not reached). The ORR, defined as complete and partial responses, based on RANO 2.0 and RANO-LGG criteria as assessed by BICR were 20% (95% CI: 10, 34) and 12% (95% CI: 5, 24), respectively.

Table 1: BICR-Assessed Response Data for Primary Efficacy Population (Source: Meeting Background Package, page 43)

	Primary Efficacy Analysis Set N=50		
	RANO 2.0	RANO-HGG	RANO-LGG
Overall response rate (CR+PR [+MR^a]), % (n) [95% CI]	28% (14) [16, 42]	20% (10) [10, 34]	26% (13) [15, 40]
Complete response (CR)	2% (1)	2% (1)	0
Partial response (PR)	18% (9)	18% (9)	12% (6)
Minor response (MR)	8% (4)	Not applicable	14% (7)
Stable disease (SD)	12% (6) ^e	20% (10)	16% (8)
Not evaluable	22% (11)	16% (8) ^b	22% (11) ^c
Progressive disease (PD)	30% (15)	36% (18)	28% (14)
Not applicable ^d	8% (4)	8% (4)	8% (4)
Disease control rate (CR+PR+SD [+MR^a]), n (%) [95% CI]	40% (20) [26-55]	40% (20) [26-55]	42% (21) [28-57]
Duration of response, median (95% CI)	10.4 months (7.4-15.4)	11.2 months (3.8-NR)	10.4 months (3.6-12.7)
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)
Progression-free survival, % (95% CI)			
6 months	32% (19-47)	35% (21-49)	39% (24-54)
12 months	27% (15-41)	30% (17-44)	30% (17-45)

In addition to ORR and DOR data for the primary efficacy population, Chimerix stated a plan to include the following supplementary information in the NDA submission:

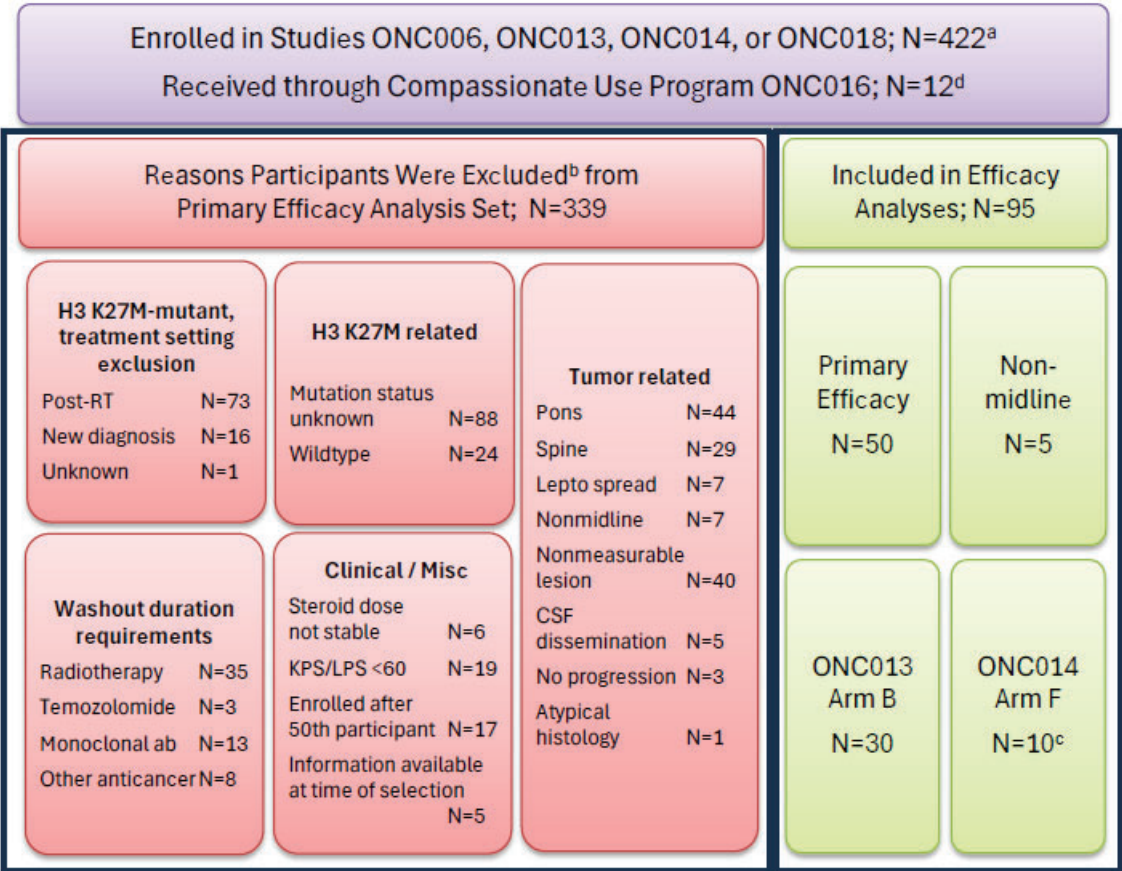
- Additional data for the primary efficacy population, including narratives describing clinical benefit and “flipbooks” of sequential MR images of the target tumor in 14 of 16 patients with at least a minor response (MR) by any response criteria;

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evidence to support true progressive disease as opposed to pseudoprogression at baseline in 15 responders (e.g., pathological confirmation of progressive disease, increased perfusion or restricted diffusion imaging, confirmation of progressive disease on multiple MRIs, incidence of new lesions)

- Investigator-assessed objective response data for 41 patients with recurrent H3 K27M-mutant glioma enrolled in Clinical Studies ONC013 Arm B (N=30 adult patients) and ONC014 Arm F (N=11 pediatric/young adult patients), including narratives describing clinical benefit in 6 of 6 responders
- Investigator-assessed objective response data for 5 patients with non-midline gliomas, including 2 responder narratives
- Investigator-assessed objective response data for 20 patients with non-H3 K27M-mutated glioma who received ONC201 (no responders)
- A tabular summary of all patients enrolled in company-sponsored clinical studies for glioma and rationale for exclusion from the primary efficacy population, as appropriate (e.g., unknown or wildtype H3K27M status, absence of progressive or measurable disease, primary tumor location in pons or spine, inadequate radiation washout; Figure 1)
- Clinical pharmacology data suggesting reversal of H3 K27me3-loss (“disease driver”) in patient tumor samples and reduction of H3 K27M in circulating tumor DNA

Figure 1: Efficacy Analysis Sets and Reasons for Exclusion from the Primary Integrated Efficacy Analysis Set (Source: Meeting Background Package, page 40)



^a All participants enrolled in Studies ONC006, ONC013, and ONC014, and expanded access protocol ONC018 are included in the integrated safety analysis set (N=422).
^b Participants may have been excluded for more than one reason.
^c One additional participant in Study ONC014 Arm F is counted with the non-midline tumor group.
^d Reasons for exclusion of compassionate use participants from the primary efficacy analysis set have been consolidated with the larger population in this figure.

Ongoing Randomized Trial

The safety and efficacy of dordaviprone for the treatment of patients with H3 K27M-mutant glioma are being evaluated in an ongoing trial (ONC201-108), a multi-regional, double-blind, randomized (1:1:1) controlled trial of 450 patients with H3 K27M-mutant DMG as determined by local CLIA-certified laboratory testing randomized 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 years vs. ≥ 21 years) and higher risk vs. lower risk features (higher risk category includes enhancing tumor size ≥10 cm², multifocal lesions, and/or brainstem location).

The dual primary endpoints are overall survival (OS) and progression-free survival (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. Chimerix states that as of July 31, 2024, 143 of the planned 450 patients (32%) were randomized.

Safety Results

The integrated safety population includes 422 patients with glioma ages 3 to 80 years who received dordaviprone in clinical studies ONC006, ONC013, ONC014, and ONC018 (data cut-off date: July 31, 2024). The most common adverse events (>20%) were fatigue (33%), headache (32%), vomiting (25%), and nausea (24%). The most common laboratory abnormalities (>10%) were decreased lymphocyte count (15%), hyperglycemia (12%), and increased alanine aminotransferase (11%).

Forty-nine percent (49%) of patients had a Grade 3 or higher AE; those that occurred in >3% included hydrocephalus (5.9%), gait disturbance (4.3%), hemiparesis (4.3%), muscular weakness (4.0%), headache (3.8%), and decreased lymphocyte count (3.6%). Serious adverse events occurred in 34% of patients and dosage modifications in 8%. Fatal AEs occurred in 9% of patients, none were attributed as treatment related.

In the proposed NDA, supportive safety information will include data from the ongoing clinical pharmacology studies, the ongoing expanded access study ONC028, company-sponsored studies in other indications, and the ongoing randomized trial ONC201-108 (blinded data).

SPONSOR QUESTIONS AND FDA RESPONSES

Preamble: We acknowledge the high unmet need for patients with H3 K27M-mutant diffuse midline glioma (DMG) and the additional data provided in the meeting background package in response to concerns conveyed by FDA in prior meetings. However, we have remaining concerns regarding our ability to contextualize the observed treatment effect of dordaviprone in the proposed primary population given the lack of information available for the additional >300 patients treated across the development program. It is critical for us to understand the overall population of patients with diffuse glioma who received dordaviprone, as well as justification for their inclusion in or exclusion from the primary efficacy population, supported by scientific rationale. Although we have agreed that use of a pooled efficacy population may be acceptable in the context of a rare disease with a high unmet medical need, an inappropriate pooling approach or an approach that cannot be replicated may be a filing issue.

Prior to NDA submission, provide a more detailed flow chart of all patients enrolled in company-sponsored studies of dordaviprone and each selection criterion that ultimately led to the primary efficacy population of 50 patients. The diagram should reflect the exact process of patient selection (e.g., which factor was considered first and how many

patients were excluded due to that factor, which factor was considered second, etc.). Please also refer to Question 3 and Additional Comments 11-15.

Content and Organization

1. Does the Agency agree that the content of the proposed table of contents and organization of the NDA are acceptable for filing?

FDA Response: FDA generally agrees with the proposed table of contents and organization of the proposed NDA as described in the meeting background package. The final clinical study reports for Studies ONC006, ONC013, ONC014, ONC016, and ONC018 will be essential for our determination of substantial evidence of effectiveness of dordaviprone. In the proposed NDA, include a summary of ORR and DOR data for these studies in the Summary of Clinical Efficacy and Integrated Summary of Effectiveness. In addition, see FDA Response to Question 4 regarding pharmacology studies.

Clinical Safety

2. Does the Agency agree with the proposed safety analyses to support the NDA, as well as the plan to provide the integrated summary of safety discussion within the Summary of Clinical Safety (m2.7.4) in lieu of a separate Integrated Summary of Safety document?

FDA Response: No. FDA regulations for NDA submissions (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)), state that an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) are required in all applications submitted to the FDA. Therefore, ensure an ISE and ISS are included in the eCTD. These integrated summaries may be very brief and can cross-reference other sections of the application (e.g., Clinical Overview, Clinical Study Reports) as appropriate.

Clinical Efficacy

3. Does the Agency agree that the efficacy data package is sufficient to support submission of the proposed NDA for accelerated approval?

FDA Response: Although the proposed content may be sufficient to support the submission of an NDA for dordaviprone for the treatment of patients with recurrent H3 K27M-mutant diffuse glioma, refer to Preamble.

Whether the data are adequate to support filing, or to support approval, will be determined at the time of review. We continue to have the following concerns regarding the determination of the substantial evidence of effectiveness of dordaviprone for the proposed patient population and these will be review issues:

- Whether the available data are sufficient to provide substantial evidence that the observed treatment effect is due to dordaviprone and not due to other factors, particularly prior radiotherapy.
- Whether the supportive nonclinical data and clinical data in patients outside of the primary efficacy population are sufficient to provide confirmatory evidence, in the context of one clinical trial and confirmatory evidence paradigm for establishing substantial evidence of effectiveness for accelerated approval.
- Whether the proposed indication is appropriate given the WHO Classification of Tumors of the Central Nervous System includes the term “midline” as part of the tumor type definition (i.e., “diffuse midline glioma, H3 K27-mutant” [2016], “diffuse midline glioma, H3 K27-altered” [2021]).
- Whether the safety and efficacy of dordaviprone have been established in patients of all ages with recurrent H3 K27M-mutant diffuse glioma given the limited number of pediatric patients with available efficacy data.
- The appropriate response criteria to be used for this patient population, including whether the inclusion of minor responses is appropriate in this disease setting. The RANO 2.0 response criteria have not previously been used to support an approval. We recommend that the submitted CSR include efficacy data by each of the response criteria (RANO-HGG, RANO-LGG, and RANO 2.0) and narratives which provide evidence of clinical benefit, including in patients with minor responses.
- The progress of the ongoing randomized trial, ONC201-108. The proposed NDA should include an updated timeline for study ONC201-108, including the expected timing of the interim analysis for efficacy as well as study completion. Provide an assessment of any ongoing plans to mitigate bias in this trial (e.g., monitoring for evidence of early crossover or unintentional unblinding due to side effects or other factors).

Regulatory Pathway

4. Does the Agency agree that a 505(b)(1) submission would be the appropriate pathway for the NDA?

FDA Response: Based on information provided in the meeting package, you expect to obtain right of reference to the Venneti 2023 publication evaluating the in vivo activity of dordaviprone in H3 K27M-mutant glioma disease models; however, it is unclear whether you have right of reference to literature articles demonstrating that dordaviprone is an antagonist of DRD2/DRD3. Conduct in vitro pharmacology studies or obtain right of reference for data supporting any mechanism of action claims you intend to make for dordaviprone.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, your application will be considered a 505(b)(2). Please indicate in your NDA submission whether you have the right

to reference published articles necessary for approval (i.e., nonclinical data). In addition, you must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. If your application will be considered a 505(b)(2), see 505(b)(2) Regulatory Pathway Information below.

We will make a final determination of the nonclinical data that is critical for approval during review of the original NDA submission.

Clinical Pharmacology

5. Does the Agency agree that the clinical pharmacology package is sufficient to support submission of the proposed NDA?

FDA Response:

We agree that your proposed clinical pharmacology package appears sufficient to support an NDA submission. Whether additional clinical pharmacology studies or analyses may be needed in the future will be a review issue.

Refer to additional clinical pharmacology comments below regarding our general expectations for an NDA submission.

Pediatric Study Plan

6. An initial Pediatric Study Plan for dordaviprone has been agreed with the Agency. Pediatric formulation development began as planned; however, challenges related to taste-masking the drug substance have delayed development timelines. Does FDA agree that an updated timeline for developing a pediatric formulation may be agreed upon during the review cycle of the NDA?

FDA Response: A revised iPSP may not be necessary. Clarify the duration of the expected delay for the age-appropriate formulation development, and whether you anticipate that this delay will result in a change to the timelines for study completion dates and report submission dates as currently outlined in the agreed iPSP.

You note that you have conducted a relative BA study comparing administration of dordaviprone dissolved in Gatorade vs. intact capsules. In a future NDA submission, provide justification that dordaviprone may also be dissolved in Powerade, apple juice, lemonade, or water as described in the meeting background package.

Safety Update Report

7. Given the high unmet need in H3 K27M-mutant diffuse glioma, Chimerix intends to request Priority Review for this NDA. Does the Agency agree with the proposed data cutoff and timing for a 90-day Safety Update report?

FDA Response: The proposed data cutoff and timing of a 90-day safety update appear reasonable.

Regarding Priority Review, a determination will be made at the time of NDA filling. Refer to “FDA Guidance for Industry: Expedited Programs for Serious Conditions” for additional information (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics>).

Administrative/Technical

8. Does the Agency agree with the proposals for study data standardization, inclusion of CRFs, and content for BIMO listings?

FDA Response: We generally agree with the proposed plan. In the ADaM pooled datasets for safety and efficacy, provide flags for each of the following: patients included in the primary efficacy population, patients included in the primary safety population, patients with H3 K27M-mutant diffuse glioma who received the proposed dose, patients with all solid tumors who received the proposed dose, and any other populations you deem relevant to the review of the application. FDA may have additional requests during the review period upon review of the data.

In addition, Appendix E of the meeting background package does not include Study ONC-201-108. However, the meeting background package states a plan to include blinded safety data from this study in the application. Confirm whether you plan to include safety datasets from Study ONC-201-108 in the proposed NDA.

Assessment Aid

9. Does the Agency agree that an Assessment Aid may be submitted within 30 days after the initial NDA submission?

FDA Response: We agree.

Complete Application

10. Considering all available information to be included in the proposed NDA, does the Agency agree that this would be a complete application to accept for review for accelerated approval of dordaviprone for the treatment of recurrent H3 K27M-mutant diffuse glioma?

FDA Response: Refer to Preamble and Question 3. The proposed content appears acceptable, and a final determination will be made upon review of the submitted application.

Additional FDA Comments

11. In order to contextualize the observed treatment effect in the proposed primary efficacy population, your summary of ORR and DOR across all company-sponsor studies for patients with glioma provided prior to submission of an application, and in the NDA, should include but not be limited to a tabular summary of ORR and DOR by study for patients with H3 K27M-mutant tumors vs. H3 K27M-wildtype tumors, as shown in the table below.

Additional summaries should provide more detailed granularity, including subgroups by age, tumor location (e.g., midline vs. non-midline; specific anatomic location), H3 K27M mutation status (e.g., mutant vs. wildtype vs. unknown), and any other relevant clinical characteristics that may impact outcome.

<i>Study</i>	ONC006 (Total N)		ONC013 (Total N)		ONC014 (Total N)		ONC016/ONC018 (Total N)	
<i>Population</i>	H3K27M-mutant, N	H3K27M-wildtype, N	H3K27M-mutant, N	H3K27M-wildtype, N	H3K27M-mutant, N	H3K27M-wildtype, N	H3K27M-mutant, N	H3K27M-wildtype, N
ORR, N (95% CI)								
Observed DOR, median (range)								

12. The proposed primary efficacy cohort includes the ‘first’ 50 patients who met the selection criteria. It is unclear how these first 50 patients were selected both with respect to exclusion criteria (e.g., 17 patients enrolled after the 50th participant excluded in the red box of Figure 3 of the meeting background package) as well as with respect to the broader “Efficacy Analysis” population (i.e., 30 patients from ONC013 Arm B and 10 patients from ONC014 Arm F in the green box of Figure 3). Clarify whether these patients were selected chronologically within each study or across all studies, and the exact process and rationale for inclusion or exclusion. Additionally, clarify whether those patients excluded from the first

- 50 patients (57 patients described in the parentheses above) have radiologic scans available from each study that may be used for BICR assessment of tumor response.
13. Provide additional details regarding the 17 patients enrolled after the 50th participant who were excluded from eligibility for the primary analysis population. In particular, provide the response rate in these patients as well as the rationale for excluding these patients from the eligible efficacy population.
 14. Provide the overall response rate in the 10 patients with midline tumors from ONC014 Arm F who are considered eligible for the efficacy population (i.e., those the green box in Figure 3 of the meeting background package).
 15. Provide rationale for the exclusion of seven patients with non-midline tumors in the red box of Figure 3 of the meeting background package vs. inclusion of five patients with non-midline tumors in the green box of Figure 3.
 16. Clarify whether any neurologic assessments were captured systematically in the study CRFs for patients in the primary efficacy population.
 17. Provide any updates on the H3 K27M local laboratory performance data and sample availability data discussed at the meeting held on June 26, 2023 for Q-Submission Q230873.

Clinical Pharmacology

Regarding the preparation of an NDA for dordaviprone:

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, [Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format](#).

Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

18. What is the basis for selecting the recommended dosage used in the trials intended to support your marketing application? Include a description of the translational evidence, pharmacokinetics, safety, efficacy, dose-response/exposure-response and other information used to support dosage selection as described in the [Oncology Dosing Tool Kit](#).

- Include the dose-finding approach (e.g., dose escalation, modeling and simulations, based on adult recommended dosage).
 - Provide the rationale for the dosing approach (body weight, body surface area, or tiered based on body size or age).
 - Include relevant information on the ontogeny of metabolizing enzymes, transporters, and renal function that may affect drug exposures and require a different dosage in pediatric patients.
 - Identify participants who required dosage modifications and provide time to the first dose modification and reasons for the dosage modifications.
19. How does the PK of dordaviprone in relevant pediatric age groups (such as <2 years, 2 to <6 years, 6 to <12 years, and 12 to <17 years) compare to that of adults? Calculate PK parameters (e.g., clearance, volume of distribution) relative to body size to facilitate comparison across age groups.
20. What is the effect of dordaviprone on the QT/QTc interval?
21. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
22. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
23. What is the relative bioavailability of the age-appropriate formulation(s) used in clinical trials to that of the commercial formulation? What is the effect of food on the bioavailability of the age-appropriate formulation? If the drug is proposed to be administered with soft foods as a vehicle, what is the effect of soft foods on the bioavailability of the age-appropriate formulation?
24. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, body size, and organ dysfunctions) influence exposure, efficacy, or safety? What dosage modifications are recommended?

Apply the following advice in preparing the clinical pharmacology sections of the submission:

25. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
26. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data with central tendency and intersubject/patient variability or median with maximum and minimum as appropriate.

27. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
- Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Identify individual subjects with dosage modifications; the time to the first and subsequent dose reduction, interruption or discontinuation; and the reasons for dosage modifications in the datasets.
28. Submit the following for the population pharmacokinetic analysis reports:
- Standard model diagnostic plots
 - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
 - Model parameter names and units in tables.
 - Summary of the report describing the clinical application of modeling results.
 - Refer to the following [pharmacometric data and models submission guidelines](#).
29. Submit the following information and data to support the population pharmacokinetic analysis:
- SAS transport files (*.xpt) for all datasets used for model development and validation
 - A description of each data item provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)
30. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers, safety and tolerability) relationships in the targeted patient population. Refer to Guidance for Industry for [population PK](#), [exposure-response relationships](#), and [pharmacometric data and models submission guidelines](#).
31. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of

intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

32. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct

(including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).²

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to [FDA.gov](https://www.fda.gov).³

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit [FDA.gov](http://www.fda.gov).⁶

⁶ <http://www.fda.gov/ectd>

U.S. Food and Drug Administration
Silver Spring, MD 20993
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The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁷

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.⁸

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

⁸ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

U.S. Food and Drug Administration

Silver Spring, MD 20993

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Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁹ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*¹⁰. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations, including 21 CFR 314.50(i) and 314.54, the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), and the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed

⁹ <https://www.fda.gov/media/84223/download>

¹⁰ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

To demonstrate that reliance on a listed drug is scientifically justified, you should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each relied-upon listed drug approved under section 505(c) of the FD&C Act. You should use the relied-upon listed drug(s) approved under section 505(c) in your study (or studies) intended to establish the scientific bridge. If you propose to use a product other than the relied-upon listed drug(s), such as a non-US-approved drug product or a generic drug product approved under section 505(j), to justify reliance on the relied-upon listed drug, you should consult the review division prior to conducting the study (or studies).

If you intend to rely on published literature for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the published literature is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., by trade name(s)). If you intend to rely on published literature describing a listed drug(s) approved under section 505(c), your reliance on the published literature is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s), and the regulatory requirements for reliance on the listed drug(s) (including, but not limited to, an appropriate patent certification or statement) would apply.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a “bridge” to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA’s finding of safety and/or effectiveness for a listed

drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication A</i>
<i>(3) Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>(4)</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and*

BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.¹¹

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR¹²: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹³

SPLIT REAL TIME APPLICATION REVIEW (STAR) PILOT PROGRAM

The FDA is conducting a pilot program, the Split Real Time Application Review (STAR).

¹¹ <https://www.fda.gov/media/85061/download>

¹² <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹³ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

STAR is a pilot review process allowing earlier patient access to therapies that address an unmet medical need via interactive engagement with the application so that review and analysis of data may commence prior to full supplemental new drug application (sNDA)/supplemental biologics license application (sBLA) submission. An applicant can communicate interest in participating in this pilot program to the FDA review division by submitting a STAR Entry Request if the applicant believes a proposed efficacy supplement fulfills the conditions outlined in the eligibility criteria. Those applicants who do not wish to participate in the pilot program will follow the usual submission process with no impact on review timelines. More information on this pilot program, including eligibility criteria and timelines, can be found at the FDA website for STAR.¹⁴

¹⁴ <https://www.fda.gov/drugs/development-resources/split-real-time-application-review-star>

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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/

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