

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215500Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

IND 144875

MEETING MINUTES

US WorldMeds, LLC (dba US WorldMeds)
Attention: Kristen Gullo
Vice President, Development and Regulatory Affairs
4441 Springdale Road
Louisville, KY 40241

Dear Ms. Gullo:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eflornithine (DFMO).

We also refer to the teleconference between representatives of your firm and the FDA on October 25, 2021. The purpose of the meeting was to discuss and reach agreement on the clinical, nonclinical, and clinical pharmacology aspects of the DFMO program in advance of a planned NDA. Additionally, you wish to formally request participation in the Real-Time Oncology Review (RTOR) pilot program.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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 301-796-9630.

Sincerely,

{See appended electronic signature page}

Ashley Lane, MS
Consumer Safety Officer
Office of Regulatory Operations
Division of Regulatory Operations – Oncologic
Diseases for DO2
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- NDA/BLA Multi-Disciplinary Review and Evaluation
- Instructions for Completing the NDA/BLA Multi-Disciplinary Review and Evaluation



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: October 25, 2021; 8:30 AM – 9:30 AM, EDT
Meeting Location: Teleconference

Application Number: IND 144875
Product Name: eflornithine (DFMO)
Indication: DFMO for treatment of pediatric patients with high-risk neuroblastoma with no evidence of disease or no active disease after first-line multiagent, multimodality therapy

Sponsor Name: US WorldMeds, LLC (dba US WorldMeds)
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Martha Donoghue, MD, Deputy Director, Division of Oncology 2 (DO2)
Diana Bradford, MD, Cross Disciplinary Team Leader, DO2
Claudia Miller, PhD, Nonclinical Team Leader (acting), Division of Hematology Oncology Toxicology (DHOT)
Anwar Goheer, PhD, Nonclinical Reviewer, DHOT
Xing Wang, PhD, Senior Pharmaceutical Quality Assessor, Division of New Drug Products I, (DNDPI)
Olen Stephens, PhD, Drug Product Reviewer, DNDPI
Shenghui Tang, PhD, Director, Division of Biometrics V (DB V)
Yuan-Li Shen, DrPH, Deputy Director, DB V
Pallavi Mishra-Kalyani, PhD, Statistics Team Leader, DB V
Arup Sinha, PhD, Statistics Reviewer, DB V
Hong Zhao, PhD, Clinical Pharmacology Team Leader, Division of Cancer Pharmacology II (DCPII)
Yi-Bo Wang, PhD, Clinical Pharmacology Reviewer, DCPII
Gregory Reaman, MD, Associate Director of Pediatric Oncology, Oncology Center of Excellence (OCE)
Donna Rivera, PharmD, MS, Associate Director of Pharmacoepidemiology, OCE
Banu Zolnik, PhD, Biopharmaceutics Team Leader, Division of Biopharmaceutics (DB)
Linyi Wei, PhD, Biopharmaceutics Reviewer, DB
Idara Udoh, MS, Chief, Project Management Staff, Division of Regulatory Operations (DRO)
Ashley Lane, MS, Consumer Safety Officer, DRO

SPONSOR ATTENDEES

Kristen Gullo, Vice President, Development & Regulatory Affairs, USWM, LLC
Giselle Saulnier Sholler, MD, Director, ISF Solid and Rare Tumor Program, Pediatric Oncology Chair, Beat Childhood Cancer Research Consortium, Levine Children's Hospital/Atrium Health

Thomas Clinch, Senior Director, Biometrics & Clinical Development, USWM, LLC

(b) (4) Consultant to USWM and BCC, (b) (4)
(b) (4), Consultant to USWM, LLC

Kim New, Senior Director, Clinical Research and Data Sciences, USWM, LLC

Randal Seburg, PhD, Director, CMC Product Development, USWM, LLC

Adam Reuther, Director, Regulatory Affairs, USWM, LLC

Lee Schmidt, PhD, Manager, Pharmacology and Toxicology, USWM, LLC

(b) (4) Consultant to USWM, LLC

Veronica Massey, PhD, Manager, Clinical Science, USWM, LLC

Henry van den Berg, Senior Vice President, USWM, LLC

(b) (4)

BACKGROUND

Meeting Purpose

On August 13, 2021, FDA received a Pre-New Drug Application (NDA) meeting request from US WorldMeds to discuss and reach agreement on the clinical, nonclinical, and clinical pharmacology aspects of the DFMO program in advance of a planned NDA. Additionally, the sponsor wishes to formally request participation in the Real-Time Oncology Review (RTOR) pilot program. FDA granted the meeting on August 20, 2021.

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

Regulatory

US WorldMeds is planning to submit a 505(b)(2) NDA (reference drug product (DP) is Ornidyl, NDA019879) for DFMO (192 mg immediate release [IR] tablets) for treatment of pediatric patients with high-risk neuroblastoma (HRNB) with no evidence of disease or no active disease (NED/NAD) after first-line multiagent, multimodality therapy.

FDA granted Orphan Drug Designation for DFMO for the treatment of neuroblastoma on November 22, 2017.

FDA granted Breakthrough Therapy Designation (BTD) for DFMO for the treatment of pediatric patients with high-risk neuroblastoma with NED/NAD after first-line multiagent, multimodality therapy on April 3, 2020.

Chemistry, Manufacturing and Controls

A Type B, CMC-only, Pre-NDA meeting was held on October 15, 2020. At the meeting, FDA and the sponsor reached agreements regarding the bridging data necessary between the clinical trial material and registration batches for NDA review. FDA stated that the shelf life for the commercial product would be determined during review on the basis of the bridging data and stability data available at the time of NDA review. US WorldMeds was reminded to submit Letters of Authorization in the NDA for any referenced DMFs. (b) (4)

(b) (4) Discussion at the meeting considered submitting both (b) (4) and Scinopharm as DS suppliers in the original NDA submission and the data package that would be necessary at the time of NDA submission. To facilitate review of the revised proposal, FDA requested detailed differences in the manufacturing processes between the two vendors. FDA stated that the revised proposal appeared reasonable provided the two sources could be deemed comparable. DS specifications were discussed, and the sponsor received feedback regarding controls that are expected in the NDA submission. FDA alerted the sponsor regarding additional data that is necessary to bridge differences in the formulation and manufacturing changes using alternative DS using in vitro release data instead of a bioequivalence pharmacokinetic (PK) study. DP specifications were also discussed, and no significant issues were raised.

Nonclinical

Difluoromethylornithine, (eflornithine or DFMO) is a small molecule irreversible inhibitor of ornithine decarboxylase (ODC), a transcriptional target of MYCN (n myc protooncogene protein) and the rate limiting enzyme in the polyamine synthesis pathway. The commercial sponsor plans to rely on literature, FDA's previous findings of safety, and pharmacology/toxicology data previously submitted to NDA 019879 to support an NDA submission for the proposed formulation of eflornithine in pediatric

patients with HRNB. Following the Type B meeting held on September 24, 2020, the commercial sponsor received Right of Reference from Sanofi, the current holder of NDA 019879.

Clinical Pharmacology

The proposed biopharmaceutics and clinical pharmacology package for the NDA includes:

- Analytical method validation reports for the two bioanalytical methods for analysis of clinical PK samples from Studies 3b and 14.
- Three-way crossover food effect study (USWM-FE1-1001).
- PK bridging study after a change in drug supply manufacturer.
- Referencing the Ornidyl NDA 019879 labeling, and/or submit source reports from the Ornidyl development program obtained by right of reference related to DFMO clinical pharmacology and ADME.
- A summary of relevant publications in the scientific literature describing the pharmacology, pharmacodynamics, and ADME attributes of DFMO.
- The PK characterization of DFMO in the intended patient population from Studies NMTRC003b (Study 3b) and NMTRC014 (Study 14).
- Study 14 PK/PD analyses including concentration-effect analyses on QTc and an assessment of the potential effect of renal and hepatic impairment on exposure.
- In vitro data from CYP450 drug interaction and transporter studies.

Clinical

US WorldMeds proposes to submit a 505(b)2 NDA with clinical data provided primarily from Study 3b. Study 3b was a single-arm study evaluating DFMO in patients with HRNB in remission who achieved NED/NAD after first-line treatment on Children's Oncology Group (COG) study ANBL0032. To support registration, US WorldMeds proposes a comparative analysis of event-free survival (EFS) patients enrolled in Study 3b and patients treated on ANBL0032 who were in remission and did not go on to receive additional therapy after completion of ANBL0032 (designated the NO DFMO group). The primary endpoint is EFS with a key secondary endpoint of overall survival (OS). Table 1 below is adapted from Table 8 in the briefing document (page 54) and describes the clinical studies supporting the NDA.

Table 1: Clinical Studies to be included in the NDA

Study Number	Title	Brief Eligibility Criteria	Treatment administered	Follow-up	Number of Patients Treated	Status
3b	A Phase II Preventative Trial of DFMO as a Single Agent in Patients with High-risk Neuroblastoma in Remission	Patients 0 – 21 years of age with HRNB that is in remission (Stratum 1: after first line therapy, Stratum 2 after therapy for R/R disease)	750 ± 250 mg/m ² BID DFMO (27 cycles of 28-day treatment periods) to total 2 years	Safety for 2 years of DFMO treatment • Efficacy (EFS and OS) for 7 years from start of DFMO treatment	Stratum 1: 106 Stratum 2: 35 Total: 141 (with 40 patients from BCC001) Direct enrollers on Study 3b: N=52	Enrollment closed. No patients remain in the on-therapy portion of the study.
BCC001	Retrospective chart review for High-Risk Neuroblastoma Patients Note: Subset of patients originally enrolled in Study 3 prior to change in manufacturer, did not transfer to Study 3b	Patients ages 0 – 21 years of age diagnosed with HRNB between 1/1/2003 and 1/1/2019	Retrospective review, not treatment protocol, but patients received same therapy as Study 3b	Date range for records reviewed: 01/01/2003 to 12/31/2020	N=40	Enrollment closed
ANBL0032	Phase III Randomized Study of Chimeric Antibody 14.18 (Ch14.18) in High- Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell Rescue	Patients with HRNB who were 0 – 30 years of age at diagnosis and have completed up-front therapy	Randomized portion of trial: • Strata 01-06 and 08-25: • Randomized to Treatment 01 (RA-only) or Treatment 02 (RA+anti-GD2 [ch14.18]) • Stratum 07: persistent disease after ASCT.	Long term EFS and OS follow up for 10 years	N=1440, includes patients randomized to cisRA only. 1328 patients were either randomized to ch14.18 or received as initial treatment in open label phase	Enrollment completed 2015, Long term follow up is ongoing
Study 14	NMTT Neuroblastoma Maintenance Therapy Trial Using DFMO	Patients with HR NBL in remission who are 0 – 30 years of age at diagnosis.	Strata 1, 2, 3 and 4: 750 ± 250 mg/m ² BID DFMO for 730 days • Stratum 1b: 2,500 mg/m ² BID	Safety for 2 years of DFMO treatment • Efficacy (EFS and OS) for 7 years from start of DFMO treatment	• Stratum 3: 30 • Stratum 4: 48 • Total: 280	Enrollment closed except Stratum 1b & Stratum 2. Treatment with DFMO ongoing

						with some patients in LTFU
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R/R: relapsed or refractory; LTFU: Long-term follow-up

Proposed NDA

The proposed clinical package for the NDA will include prospective analysis from Study 3b, comparisons of Study 3b to the ANBL0032 external control, independent central review of imaging studies, and supporting literature. The safety database will include 311 patients with HRNB, including relapsed/refractory patients, who received the recommended dose of oral DFMO of $750 \pm 250 \text{ mg/m}^2$ BID, as well as additional patients who received 2500 mg/m^2 in Study 14, and supportive literature.

Table 2 below (Table 9 in the meeting package, copied from page 63) provides a summary of the clinical information proposed to be included in the NDA.

Table 2: Supporting Elements for Clinical Studies and Integrated Safety Analyses

Supporting Element	Study 3b	BCC001	COG ANBL0032 Study	External Control Efficacy (3b vs. ANBL0032)	Study 14	Integrated Safety ^a
Report Type NDA Location	Full CSR 5.3.5.1	Publication 5.3.5.2	Publications 5.3.5.2	Efficacy Report 5.3.5.4	PK report only 5.3.5.2	2.7.4 only
SDTM Datasets	Yes	Raw data – legacy format	No	Raw data – legacy format	Yes	Yes
ADaM Datasets and Programming	Yes	Yes	No	Yes	Yes	Yes
TFLs NDA Location	Yes 5.3.5.1	No ^b	No ^b	Yes 5.3.5.4	No ^c	Yes 5.3.5.3
Financial Certification	Yes	No	No	NA	Yes	NA
Patient Narratives and Corresponding CRFs	Yes	No	No	NA	Yes	Yes
BIMO Dataset	Yes	No	No	NA	No	NA

NA: not applicable

^a Studies 3b and 14 presented at the study level and pooled

^b Efficacy output displayed in SCE tables only (external control comparisons include 3b vs. ANBL0032)

^c Study level data to be displayed in ISS tables

Notably, the data package supporting the NDA will include the following:

- A CSR will be provided for Study 3b; a separate report will present comparative analyses between Study 3b and ANBL0032.

- An efficacy summary is planned for Module 2.7.3 including findings from Study 3b and ANBL0032. A separate Integrated Summary of Efficacy (ISE) report is not planned for Module 5.
- Datasets:
 - SDTM datasets will be provided for Study 3b (safety, efficacy, and PK) and Study 14 (safety and PK).
 - The ADaM dataset for the Study 3b vs ANBL0032 external control will include data from Study 3b transfer and direct enrollers, BCC001 non-transfer patient data, and ANBL0032 external control data
 - The ISS Dataset will include Study 3b and Study 14 safety data

Proposed Efficacy Content

The SAP-defined primary analysis for the ANBL0032 external control comparison is an unadjusted Cox proportional hazards (CPH) model controlling only for treatment (DFMO versus NO DFMO) for the primary outcome, EFS, and key secondary outcome, OS. The primary analysis populations for the primary and key secondary endpoint analyses are the DFMO PER COG -Complete Case and the MATCHED population, derived from the NO DFMO-Complete Case population by the SAP-defined propensity score matching (PSM) algorithm. Table 3 (copied from page 81, Table 14 in the meeting package), provides the results of the SAP-defined primary endpoint.

Table 3: Primary Analysis for Event Free Survival in PS Matched DFMO PER COG and NO DFMO Populations

Parameter	Treated with DFMO (N = 92)	Not Treated with DFMO (N = 852)
Number of Complete Case Patients n (%)	91 (98.9)	516 (60.6)
Number of Patients in Overlapping PS Range n (%)	90 (97.8)	493 (57.9)
Number of Patients in Matched Samples n (%)	90 (97.8)	270 (31.7)
Censored n (%)	76 (84.4)	191 (70.7)
Events n (%)	14 (15.6)	79 (29.3)
Comparison of DFMO treated versus control from unstratified log-	p = 0.0096	
Hazard Ratio (95% CI)	0.479 (0.271, 0.847)	
Comparison of DFMO treated versus control from unadjusted CPH	p = 0.0113	

The key secondary analysis comparing OS between the DFMO PER COG and NO DFMO (Matched) groups demonstrated a HR of 0.355 (95%CI 0.161, 0.784), p=0.0104.

FDA previously advised that a blinded, independent central review be performed for the EFS assessment in Study 3b, and a blinded independent imaging assessment in a pre-specified number of patients in the NO DFMO group from ANBL0032; discordance above a stated threshold would trigger a full blinded independent review of all events. In the package, the sponsor argues that, given that bias would likely result in a more

favorable outcome in the control arm, and that events of relapse are unlikely to be equivocal, independent review is not necessary in the NO DFMO control group. The sponsor proposes that the central review charter will include independent blinded review with a single reader per patient. US WorldMeds is evaluating the feasibility of including a subset of the NO DFMO group in the independent central review. US WorldMeds notes that COG will not be able to provide a patient ID linker to the sponsor but would provide the ID linker to FDA if directly requested. US WorldMeds also notes that they lack authorization to view medical records for patients enrolled in ANBL0032 except if patients are a part of the BCC database, including databases for Study 3b, Study 14 and BCC001; US WorldMeds estimates up to 71 patients in the NO DFMO analysis population (8% of the NO DFMO cohort) may have records eligible for an independent review, and is evaluating availability of scans for these patients. US WorldMeds is working with COG and QARC/IROC to determine the availability of a data or report from the protocol-specified central imaging review for ANBL0032.

Proposed Safety Content

US WorldMeds proposes an ISS safety population comprised of direct enrollers on Study 3b for whom full safety information is available (n=52, includes 11 Stratum 2 patients) and Study 14 (n=259) who have received the recommended phase 2 dose (RP2D) (n=311). Results for patients in Study 14 who received a higher dose (2500 mg/m²/day BID) are reported separately. Safety reporting for these studies differed; Study 3b reported Grade 2 and higher events whereas Study 14 reported Grade 3 and higher events. Laboratory data was not captured in the database for Study 3b, and the ISS evaluation of laboratory data will include only data from Study 14. The most frequently occurring adverse events were hypoacusis (9.3%), alanine aminotransferase increased (7.5%), aspartate aminotransferase increased (5.4%) and pyrexia (5.1%).

Case Report Forms (CRFs) and narratives will be provided for all patients in Studies 3b and 14 who experience serious adverse events (SAEs), death, or discontinuation while on treatment with DFMO and up to 30 days following the last dose, as well as Grade 3 or higher events of hearing loss. US WorldMeds proposes to submit a 120-day safety update with any additional study visit data from Study 14 from the NDA data cut-off through the end of the 2-year treatment period.

Proposed Approval Pathway

In meeting minutes from the September 24, 2020 meeting, FDA stated that given the nature of the comparison between Study 3b and ANBL0032, a randomized controlled trial (e.g., NMTRC-012) would be necessary to confirm the clinical benefit observed in Study 3b. However, in the meeting package the sponsor proposes that the current submission meets the standard for regular approval rather than accelerated approval. NMTRC-012 is a randomized trial in patients with HRNB who will receive induction therapy with the addition of a targeted molecular agent (ceritinib, dasatinib, sorafenib, or vorinostat) followed by immunotherapy and then DFMO (1000 mg/m² BID) or the same therapy without DFMO. The primary endpoint is EFS.

SPONSOR QUESTIONS AND FDA RESPONSES

Nonclinical

1. Does the Agency agree with the Sponsor's submission plans for the nonclinical pharmacology and toxicology information in the NDA, including plans for submission of reports in Module 4 and the preparation of nonclinical written and tabulated summaries in the relevant subsections of Module 2.6?

FDA Response: Your proposed plan appears acceptable.

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor acknowledges the Agency's response.

Discussion During Meeting: Discussion did not occur during the meeting.

2. Does the Agency agree that a formal abuse potential assessment is not required and that a summary of literature and clinical data relevant to the low-risk abuse liability potential of DFMO in the NDA is adequate to support acceptance and review?

FDA Response: This approach appears reasonable. A final determination of the adequacy of the data and literature provided to support approval will be made during review of the original NDA submission.

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor acknowledges the Agency's response.

Discussion During Meeting: Discussion did not occur during the meeting.

Biopharmaceutics and Associated Analytical Methods

3. Does the Agency agree with the Sponsor's evaluation of the (b) (4) bioanalytical method and concur that this method is adequate to support analysis of clinical PK samples from Studies 3b and 14?

FDA Response: Your proposed bioanalytical method appears acceptable to support the analysis of clinical PK samples from Studies 3b and 14. The adequacy of the bioanalytical method will be assessed at the time of NDA review.

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor acknowledges the Agency's response.

Discussion During Meeting: Discussion did not occur during the meeting.

4. **Does the Agency agree with the Sponsor's plans to support dosage and administration recommendations, including those regarding potential admixtures suitable for dosing of crushed tablets?**

FDA Response: Your proposed plan appears acceptable. The adequacy of the data to support labeling will be determined at the time of NDA review.

The proposal to submit chemical compatibility data for a range of foods and liquids to be used to prepare an extemporaneous formulation for administration to patients with trouble swallowing tablets is acceptable. The results of that data will be compared to the proposed labelling for preparations of extemporaneous formulations for veracity at the time of NDA review.

In addition, we recommend that you submit comparative dissolution data (individual, mean, SD, figures, f2 value, sampling timepoints: 5, 10, 15, 20, 30, and 45 minutes, etc.) between the crushed and whole tablets using a QC dissolution medium that is found acceptable by FDA and at least three different media (e.g., pH 1.2, 4.5, and 6.8).

(b) (4)

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor acknowledges the Agency's response. USWM acknowledges the Agency's agreement on the proposal for chemical compatibility evaluation and will execute the experiments as proposed. USWM will also execute the recommendation that comparative dissolution data be generated comparing crushed and whole tablets. USWM intends to employ three media for this evaluation: 0.1 N HCl, pH 4.5, and pH 6.8. The QC dissolution method USWM will submit in the NDA employs the 0.1 N HCl medium. (b) (4)

Discussion During Meeting: Discussion did not occur during the meeting.

Clinical Pharmacology

5. **Does the Agency concur that the Sponsor's biopharmaceutics and clinical pharmacology package and submission plans are adequate to support NDA acceptance and review?**

FDA Response: Your proposed biopharmaceutics and clinical pharmacology package appears acceptable to support NDA filing and review. Provide appropriate dose justification in the NDA submission to support the proposed dosage regimen.

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor acknowledges the Agency's response. The clinical pharmacology summary will include a discussion/justification of dose selection.

Discussion During Meeting: Discussion did not occur during the meeting.

Clinical

6. **Does the Agency agree with the Sponsor's submission plans for the clinical information for the NDA, including plans for reports, datasets, records and administrative information in Module 5 and its plans for clinical summaries in Modules 2.7.3 and 2.7.4?**

FDA Response: In general, the proposed clinical information appears acceptable. Please comment on the decision not to include data from Study 14 to support the evaluation of efficacy in the application.

We note that you do not intend to submit an ISE. An ISE is required in applications submitted to the FDA. As previously noted in the September 24, 2020 meeting and per FDA guidance, the commercial sponsor may split the ISE and ISS across Module 2 and Module 5, with the narrative portions located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3.

Please include in your submission (a) SAS programs that produced all efficacy results, (b) all raw as well as derived variables in .xpt format, (c) SAS programs used to derive various analysis populations, including the primary analysis population and key secondary populations for sensitivity and supportive analyses (d) SAS programs by which the derived variables were produced from the raw variables, for example, the SAS program(s) for deriving response status (such as CR, PR SD, PD) from original individual tumor measurements, and (e) results of any interim analysis if ever performed.

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor confirms and clarifies that its plans are to present a written summary of clinical efficacy in Module 2.7.3 and will include relevant appendices of tables, figures, and datasets in Module 5 as part of the Study 3b and 3bvs. ANBL0032 Comparator study reports. Because no pooled efficacy analyses are planned, the analysis datasets, programs and TLFs for the Study 3b analysis and the

ANBL0032 comparison will be located with the individual clinical study reports in Modules 5.3.5.1 and 5.3.5.4., respectively.

The Sponsor further acknowledges the Agency's comments regarding the SAS programs – the details specified in parts (a), (b), (c) and (d) are planned for inclusion. However, the Sponsor wishes to clarify that neither the ANBL0032 nor Study 3b datasets include tumor measurement information considered in deriving response status, which is only pertinent to making determinations of response during treatment of active disease. In the target patient population (HRNB patients in remission) observation of new lesions rather than changes in tumor measurements, along with additional clinical work up, are considered in the determination of relapse outcome. The Sponsor refers to the discussion presented for Question 7.

Discussion During Meeting: Discussion did not occur during the meeting.

7. **Does the Agency agree that the Sponsor's planned clinical efficacy package is adequate to support acceptance and review of the NDA?**

FDA Response: No. Although the topline efficacy analysis based on investigator-assessed imaging appear to support filing of the planned NDA, as discussed during our May 3, 2021 and June 29, 2021 meetings, efficacy analyses based on blinded independent review will be required to support filing of your planned application.

- a. Please submit the updated efficacy analysis based on the independent review and await FDA concurrence that the efficacy data based on blinded independent review supports filing of the NDA prior to its submission. A final determination of the fileability of the application will depend upon the results of the analyses based on blinded independent review.
- b. With respect to the proposed blinded independent review, we have the following comments:
 - i. You propose to include a single reader for each patient's images. The charter should specify a blinded independent review process which includes two separate readers, with a pre-specified adjudication process for any discrepant reads between reviewers.
 - ii. Submit the charter for FDA review prior to conducting the independent review.
 - iii. Comment on whether the independent review will include evaluation of bone marrows for the patients who had relapses in the bone marrow. Refer to Additional FDA Comment #14.
 - iv. Provide a description of how patients will be selected for the audit, as well as an analysis of potential bias inherent to the proposed methodology.

- c. Additionally, please clarify whether the dates of all follow-up assessments and the results of any efficacy assessments for ANBL0032 will be included as part of the NDA package and when you will have clarity with respect to whether US WorldMeds will be able to include data or reports from the protocol-specified central imaging review for patients in the NO DFMO group assessed in Study ANBL0032.
- d. In the NDA, provide the following:
 - i. A tabular overview of the frequency of efficacy assessments on Studies 3b, ANBL0032, and Study 14 which clearly indicates any differences in assessments and follow-up frequency.
 - ii. A description of post-recurrence treatment in patients in both ANBL0032 and Study 3b to aid in the interpretation of overall survival data.
- e. As stated in the June 29, 2019 meeting minutes, in order to understand the quality of the data that will be used to support the NO DFMO analysis set, we need to understand the process for how the data were collected and transferred from COG. Please provide the standard operating procedure (SOP) document used to describe how the data was collected and transferred, including if the data was transferred using electronic case report forms vs. scanned paper documents. We acknowledge your response in the prior meeting minutes that this document would be requested from COG for inclusion in the NDA submission.
- f. Finally, as noted in the Preamble of the May 3, 2021 meeting, given the complexity of this study design and the uncertainty introduced by the retrospective use of data to design an external control, our determination regarding whether substantial evidence of effectiveness has been demonstrated will be based on our overall assessment of the results of multiple independent analyses for primary and secondary endpoints to evaluate the consistency and robustness of observed results with respect to various assumptions required for these analyses.

US WorldMeds' Response Received via Email on October 23, 2021:

(b) (4)

(b) (4)

Discussion During Meeting: FDA acknowledged the rationale put forth in the appended document, “Sponsor Evaluation of ICR for the DFMO program”, and discussed by US WorldMeds during the meeting. FDA stated that given the nature of the data supporting the application, an assessment of bias was critical to the application and a determination that the data provided comprise an adequate and well-controlled trial. FDA stated that the use of an independent review would aid in the understanding of potential bias and is considered essential given the nature of the data.

US WorldMeds provided clarification regarding the assessment of EFS events, stating that scans used to detect relapse are captured in the database, but confirmed biopsy results (which may be used to confirm or refute suspected relapse detected on scans) are not included in the database.

US WorldMeds suggested that they could provide patient surveillance narratives for patients with relapse events to aid in the understanding of assessment of these events. FDA suggested that narratives also be provided for patients with independent assessments which are discrepant from investigator assessments. FDA also stated that narratives for these patients may be provided during the review based on additional discussion with FDA. US WorldMeds suggested that clinical data be incorporated in the independent review. FDA requested that the charter be provided prior to conduct of the independent review for concurrence, and that FDA would provide feedback informally over email.

FDA stated that although it would be ideal to include an independent review of EFS events in the ANBL0032 trial in the proposed application, it would be acceptable to limit the independent review to patients in Study 3b.

8. **Does the Agency agree that the Sponsor’s planned clinical safety package is adequate to support acceptance and review of the NDA?**

FDA Response: The pooled safety population consisting of approximately 300 patients with HRNB treated with the RP2D of DFMO appears acceptable. Please clarify the number of patients in the pooled safety database (Study 3b and Study 14) with HRNB in remission after front-line therapy (i.e., excluding patients with relapsed/refractory disease) who received the proposed RP2D of 750mg/m² BID, as well as the number of patients with relapsed refractory disease who received

the proposed RP2D. The pooled safety database should include a flag for each of these populations.

We refer to Additional FDA Comment #19 in the September 24, 2020 meeting minutes, which requested that the Pre-NDA meeting package define Adverse Events of Special Interest (AESI) for DFMO and approach to analysis. This does not appear to be included in the current meeting package. In the original NDA submission, include a list of the AESIs for DFMO, including hearing loss, and an analysis and discussion of these events in the Summary of Clinical Safety (SCS). Flag these events in the AE datasets included in the original submission and in the 120-day safety update.

With respect to the planned 120-day safety update, please indicate how many patients remain on Study 14 and are anticipated to contribute additional safety data. The safety update should include narratives for any SAEs, deaths, or discontinuations due to toxicity.

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor acknowledges the Agency's response. The Sponsor provides the following requested clarification regarding the number of patients in the planned pooled safety population receiving the RP2D after initial up front treatment vs. following relapse/refractory treatment in Table 1 below. The Sponsor notes that the numbers by strata for Study 14 are preliminary as strata placement for analysis purposes is still subject to cleaning against programmatic rules consistent with those applied to Study 3b. The Sponsor further acknowledges and agrees to providing a study-level strata variable with an appropriate flag variable identifying patient as in remission after up-front treatment or in remission after treatment for relapsed/refractory in the pooled safety database.

Table 1: Pooled and Study Level Safety Breakdown by Patient Groups (First Remission after Up-front Treatment or Remission after Relapsed/Refractory Treatment)

	Study 3b N	Study 14 N	Pooled Total N	Additional Study 3b Safety Data Discussed in CSR and SCS ¹ N
In remission after initial up-front treatment	Stratum 1 41	Strata 1 and 2 181	222	44
In remission after treatment for relapsed/refractory disease	Stratum 2 11	Strata 3 and 4 78	89	5
Study Total	52	259	311	49

¹ Study 3b Transfer patients transferred from Study 3 to Study 3b.

The Sponsor further acknowledges and agrees to include the Agency's requests regarding AESI and narratives.

Discussion During Meeting: Discussion did not occur during the meeting.

Regulatory

9. **Does the Agency agree that the plans for sources of content for the draft prescribing information to be submitted with the NDA appear appropriate based on the Sponsor's plans to reference a combination of data to which it has right of reference and the Agency's previous conclusions of safety and efficacy for Ornidyl as a reference listed drug (RLD)?**

FDA Response: The planned sources of content for the draft prescribing information appear reasonable. Final labeling will be negotiated during review of the planned NDA. Note that our prior findings of efficacy for Ornidyl are not relevant to your planned NDA given the differences in the approved indication for Ornidyl and the indication you plan on seeking for DFMO. Please also refer to the section below on the 505(b)(2) regulatory pathway for details regarding the content and format of your planned NDA submission.

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor acknowledges the Agency's response.

Discussion During Meeting: Discussion did not occur during the meeting.

10. **Does the Agency agree that promotional materials (e.g., advertisements, sales aids, websites), intended for dissemination or publication within 120 days following marketing approval are not required to be included in the NDA?**

FDA Response: Yes, we agree that promotional materials are not required to be included in the original NDA submission. We advise that you reach out to the Office of Prescription Drug Products (OPDP) directly with any questions related to the plans for your promotional materials.

For information about submitting promotional materials, see the final guidance for industry Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor acknowledges the Agency's response.

Discussion During Meeting: Discussion did not occur during the meeting.

11. The Sponsor requests participation in the Real-Time Oncology Review (RTOR) pilot program. Will the Agency grant participation of the DFMO program into the RTOR pilot program?

FDA Response: FDA would like to discuss the proposal to participate in RTOR and have the following comments.

- a. We refer you to the minutes for the Type B, CMC-only, Pre-NDA meeting on October 15, 2020, which were issued November 10, 2020. As noted, inclusion of an alternative DS supplier (b) (4) are dependent on the bridging data. In the pre-submission package #1 of your RTOR proposal, include a full Module 3 submission, highlighting the bridging data, specifically the manufacturing process differences between the two DS suppliers and comparative complete dissolution profile data between DP manufactured with DS from the two vendors.
- b. It appears that you intend to submit clinical information including CSRs, clinical summaries and datasets prior to the submission of the results of the independent review. Clarify whether you intend for the clinical summaries and datasets to include only the efficacy results based on the investigator review. Submitting summaries and datasets which do not include the IRC-assessed results may result in confusion and would not facilitate meaningful early review, which is the purpose of the RTOR program.
- c. We refer to Additional Comment #18 below regarding the Assessment Aid. Use of the Assessment Aid is strongly encouraged, particularly in applications included in the RTOR program.

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor acknowledges the Agency's response and would like to specifically respond to the comments regarding the two drug substance sources planned for inclusion in the NDA and its related plans for the RTOR. The Sponsor confirms that its proposed plans for the first RTOR pre-submission package would comprise a complete Module 3, inclusive of bridging data between the (b) (4) and Scinopharm drug substances sources.

USWM proposes to include two suppliers of Drug Substance within the NDA. As part of its RTOR submission plans, USWM intends to include a full Module 3 submission within the first pre-submission package. The Module 3 submission will include the bridging data supporting the use of two suppliers of Drug Substance. The manufacturing differences between the two Drug Substance suppliers will be discussed within the submission. Comparative complete

dissolution profile data between Drug Product manufactured with Drug Substance from the two suppliers will be provided as well.

The results from the formal in vitro biowaiver dissolution testing on DFMO tablets have been generated, and a comprehensive report will be provided within Module 3 of the first pre-submission package. An excerpt from the dissolution profile data is provided in Table 1. (b) (4)

the acceptance criterion for BCS 3 drugs (such as eflornithine drug substance) is Not Less Than (b) (4) % Dissolved in 15 minutes for each of the following media: 0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer. Table 1 demonstrates that the percent dissolved in 15 minutes for DFMO primary registration tablets with (b) (4) and ScinoPharm (SPT) Drug Substance meets this criterion for each medium, thus demonstrating comparative dissolution for drug product manufactured with either drug substance.

Table 1: Comparative Dissolution Results for DFMO Primary Registration Tablets with either (b) (4) or ScinoPharm (SPT) Drug Substance

Primary Registration Tablet Batch No. (drug substance supplier)	%Dissolved in 15 min		
	0.1 N HCl	pH 4.5	pH 6.8
20112 (b) (4)	91	90	85
20332 (SPT)	86	91	85
20333 (SPT)	88	89	87

The Sponsor wishes to revisit the request for RTOR participation based on the discussion for Question 7. (b) (4)

Discussion During Meeting:

(b) (4) FDA stated that a revised proposal for RTOR could be provided over email.

Post-Meeting Addendum: We acknowledge that you have confirmed that you will submit the data we outlined in the CMC pre-NDA meeting and in this meeting package for review of the bridging between the two drug substance

manufacturers. We acknowledge the comparative dissolution results in Table 1 of your response to our response. We remind you to provide full dissolution profile data within the NDA submission.

12. **Does the Agency agree that the DFMO NDA is a candidate for synchronized review with select foreign regulatory authorities through participation in Project Orbis?**

FDA Response: We appreciate your willingness to participate in Project Orbis. A determination of whether the NDA will be included in Project Orbis will be made upon receipt of the complete application. Please indicate the status of interactions with other regulatory agencies with respect to the proposed application.

US WorldMeds' Response Received via Email on October 23, 2021:

(b) (4)

Discussion During Meeting: FDA acknowledged US WorldMeds' timeline of current and planned interactions with other regulatory agencies. Given the

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preliminary nature of interactions thus far and uncertainty with respect to the timing of application review at each agency, FDA deferred a final decision regarding participation in RTOR until closer to the time of the NDA submission. FDA suggested that US WorldMeds provide an update regarding interactions with international regulatory agencies over email.

13. Does the Agency agree that the Sponsor's plans for the content of the submission are acceptable to support filing and a request for priority review of the planned NDA?

FDA Response: Although the proposed content of the application appears acceptable, a determination regarding fileability of the application will be made upon review of the application. Similarly, a determination of whether the application is granted priority review will be made upon review of the NDA.

US WorldMeds' Response Received via Email on October 23, 2021: The Sponsor acknowledges the Agency's response.

Discussion During Meeting: Discussion did not occur during the meeting.

ADDITIONAL FDA COMMENTS

Clinical

14. With respect to the primary analysis population in Study 3b, indicate how many patients experienced a relapse in the bone marrow as the EFS event.
15. Confirm that full protocols, including all protocol amendments, for each study providing data to support the planned NDA will be submitted in the original NDA.
16. FDA acknowledges the updated statistical analysis plan (SAP) version 1.0 for the comparison of efficacy results from Study 3b and ANBL0032. In the SAP, please include a section summarizing the SAP amendments for the comparative study. Additionally, include a summary of major protocol amendments of ANBL0032 outlining any changes in amendments that are related to the selection rules for control patients or any variables used in the propensity score model in the comparative study.
17. We refer to Additional FDA Comment #17 in the meeting minutes for the September 24, 2020 meeting and reiterate the following advice regarding safety narratives.

In the original NDA submission, ensure that the following components are

included in each safety narrative summary. In the event one or more elements are not available for a given narrative, provide justification for the inability to obtain the data.

- a. Patient age and gender
 - b. Signs and symptoms related to the AE being discussed
 - c. An assessment of the relationship of exposure duration to the AE occurrence
 - d. Pertinent medical history
 - e. Concomitant medications with start-dates relative to the AE
 - f. Pertinent physical exam findings
 - g. Pertinent test results (e.g., lab data, ECG data, biopsy data)
 - h. Discussion of the diagnosis as supported by available clinical data
 - i. For events without a definitive diagnosis, a list of the differential diagnoses
 - j. Treatment provided
 - k. Action taken for investigational agent (e.g. discontinued, dose-reduced, treatment delayed)
 - l. Re-challenge results (if performed)
 - m. up information
18. The Oncology Center for Excellence (OCE) has developed an Assessment Aid to facilitate FDA's assessment of NDA/BLA applications (including supplements). The Assessment Aid is based on the FDA Multidisciplinary Review template with most sections divided into two parts, clearly delineated to emphasize ownership of each position as either the Applicant's position or the FDA's position. The applicant fills in their positions in the relevant sections.

FDA would like to offer you the use of the Assessment Aid for the NDA for DFMO. If you choose to participate, FDA would expect receipt of the completed Assessment Aid as part of the complete NDA package or within 30 days of submission. The Assessment Aid (AA) instructions and template are included as an addendum to these meeting minutes. In general, the AA should be concise and only include critical information. Please see the following link to the FDA website describing this program:

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

Clinical Pharmacology

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" (available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-pharmacology-labeling-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:

19. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, provide time to the first dose modification, and reasons for the dose modifications in support of the proposed dose and administration.
20. What are the exposure-response relationships for efficacy, safety, and biomarkers?
21. What is the effect of DFMO on the QT/QTc interval?
22. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
23. 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.
24. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Apply the following advice in preparing the clinical pharmacology sections of the original 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 PK parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with minimum and maximum values as appropriate.
27. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the PK datasets should be consistent with the numbers used in the clinical datasets.
 - a. Provide all concentration-time and derived PK 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.

- b. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
28. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to the following FDA documents of “Guidance for Industry”:
- a. [Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications](#)
 - b. [Model | Data Format](#)
29. 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.
30. 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.
31. In Module 5 of your submission, incorporate race and ethnicity, in addition to other covariates, in the exposure-response (for safety and effectiveness) analyses. Include an assessment to determine if the data are of sufficient quantity and quality to permit an analysis to detect a clinically meaningful difference. Provide complete datasets, model codes or control streams, output listings, and final study reports used to support these analyses.

US WorldMeds’ Response Received via Email Regarding all Additional FDA Comments on October 23, 2021: The Sponsor acknowledges and appreciates the additional comments from the Agency.

The Sponsor notes that the Agency makes reference to an Assessment Aid template as an appendix to the minutes in Comment 18. Can the Agency provide the template now or will it be included as an appendix to the final meeting minutes?

The Sponsor proposes to further review the comments and request any additional clarifications needed via general correspondence in follow up to the meeting.

POST-MEETING ADDENDUM

The contents of a complete application could not be agreed upon in the absence of top-line data reflecting blinded, independent review of EFS events in the proposed efficacy population in Study 3b. See FDA's response to Question 7 and the discussion of this response during the meeting for additional details.

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. Because DFMO does not contain a new active ingredient and has orphan designation for the proposed indication, an application for DFMO seeking the proposed indication would be exempt from PREA requirements.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that 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 Information² and Pregnancy and Lactation Labeling Final Rule³ 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.

² <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

³ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

- 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 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:

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- 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.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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 at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).⁴ In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had

⁴ 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>.
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challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.⁵

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 DP that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed DP and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies 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 literature or on the other studies 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 the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for 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 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 in an NDA 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.

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.

⁵ <http://www.regulations.gov>

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 DP 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*.⁶

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:

- RTOR⁷: In general, the data submission should be fully CDISC-compliant to

⁶ <https://www.fda.gov/media/85061/download>

⁷ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

facilitate efficient review.

- Assessment Aid⁸

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

- US WorldMeds to submit the charter prior to conducting the independent review.
- US WorldMeds to submit the updated efficacy analysis based on the blinded independent review. Following review of the summary-level efficacy results based on blinded independent review, FDA will advise US WorldMeds regarding the fileability of the proposed application.

ATTACHMENTS

- NDA/BLA Multi-Disciplinary Review and Evaluation
- Instructions for Completing the NDA/BLA Multi-Disciplinary Review and Evaluation

143 Page(s) of Multidisciplinary Review Template have been Withheld in Full immediately following this page

⁸ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>
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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/

ASHLEY R LANE
11/22/2021 03:58:00 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 144875
Request Receipt Date	February 5, 2020
Product	Eflornithine (DFMO)
Indication	High-risk neuroblastoma
Drug Class/Mechanism of Action	irreversible inhibitor of ornithine decarboxylase (ODC)
Sponsor	Dr. Giselle Sholler
ODE/Division	OOD/DO2
Breakthrough Therapy Request (BTDR) Goal Date (within <u>60 days</u> of receipt)	April 5, 2020

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

Eflornithine (DFMO) is intended for the treatment of newly diagnosed high-risk neuroblastoma.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

3. Was the BTDR submitted to a PIND?

☐ YES ☒ NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹?

☒ YES ☐ NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

- i. Only animal/nonclinical data submitted as evidence ☐
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

Disease Background and Current Treatment Options

Neuroblastoma (NBL) is an embryonal tumor of the autonomic nervous system with tumors arising in tissues of the sympathetic nervous system, typically in the adrenal medulla or paraspinal ganglia. Approximately 650 cases are

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

diagnosed in the US each year^{1,2}. Patients with NBL are classified into low, intermediate or high-risk groups at diagnosis based on age, tumor location, tumor histology and differentiation, N-myc proto-oncogene protein (MYCN) amplification, ploidy and chromosomal aberrations. Approximately 50% of patients with newly diagnosed NBL will have high-risk disease (HR-NBL) at diagnosis. The 2-year event-free survival (EFS) rate and overall survival (OS) rate for patients with HR-NBL is 60-70% and 80-90%, respectively.³ The 5-year EFS rate and OS for HR-NBL rate is 40-60% and 55-75%, respectively.^{2,4} This BTDR is limited to patients with newly diagnosed high risk NBL.

Eflornithine (DFMO): Mechanism of Action and Clinical Development Program

Eflornithine (DFMO) is an irreversible inhibitor of the enzyme ornithine decarboxylase, the first and rate-limiting step in the biosynthesis of polyamines. The sponsor states that inhibition of polyamine synthesis results in growth arrest of malignant cells and inhibits neoplastic transformation. (b) (4), (b) (5)

intravenous (limited use) and topical formulations are FDA-approved for non-oncological indications. (b) (4), (b) (5)

In December 2018, a preliminary BTDR meeting was held with the Sponsor to discuss 2-year EFS data from their single-arm trial (Study 3/3b). At that time, the multicenter, single arm 2-year EFS data presented was improved over literature based, historical control 2-year EFS estimates. While the Division found this initial data encouraging, the Sponsor was encouraged to provide a contemporaneously matched comparative analysis to further support the single arm data.

With this submission, the Sponsor has provided the following:

- Single arm, open-label, multi-center study, Study 3/3b
- Contemporaneously matched control using data from Children's Oncology Group (COG) study ANBL0032
- Historical controls based on literature

There is an ongoing randomized trial comparing DMFO with maintenance therapy (dinutuximab and retinoic acid) to maintenance therapy alone for patients with newly diagnosed HR-NBL which could serve to confirm the observed benefit in this single arm trial.

The sponsor is an academic investigator working to transfer the entire commercial IND (IND 144875) to a commercial sponsor (KC Pharma, LLC and USWorldMeds).

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.**

The sponsor considers 2-year event-free-survival (EFS) in a single-arm trial compared to a contemporaneous control group to be a clinically meaningful endpoint to support this BTDR. To support the findings, the sponsor also included overall survival (OS) data for the same population.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:**

- A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).
- A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

DO2 agrees that a statistically significant and clinically meaningful improvement in EFS or OS is a direct measure of the clinical benefit of a treatment for this disease. DO2 may accept comparisons to a contemporaneous well-matched control for rare tumors types, or tumors for which it may be difficult to accrue patients, depending on both the quality of the data and the magnitude and duration of effect.

- c. **Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.**

None.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Current standard therapy for newly diagnosed, metastatic, high-risk neuroblastoma includes induction with high-dose, multi-agent chemotherapy and best feasible primary tumor resection, consolidation with myeloablative chemotherapy followed by autologous stem cell transplantation and radiation to the primary tumor site and bony metastases, and post-consolidation therapy with dinutuximab (FDA approved, 2015) in combination with granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and cis-retinoic acid.

There are no FDA-approved treatments and no known curative treatments for patients with neuroblastoma who are refractory to the frontline therapy described above. Patients are encouraged to enroll on clinical trials or are treated with various off-label chemotherapy regimens, 131I-MIBG, allogeneic transplant, or palliative care.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

No other drugs have received breakthrough therapy designation for this indication.

11. Information related to the preliminary clinical evidence:

- a. **Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s),**

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

This BTDR is supported by the results from one clinical trial, NMTRC003/3b (Study 3/3b), compared to a propensity matched, contemporaneous external control.

NMTRC003/3b (Study 3/3b) was a multi-center, open label, single agent study for children with newly diagnosed HR-NBL with no evidence of disease (NED) or no active disease (NAD) at the end of up-front therapy. The primary endpoint was event-free survival (EFS) at 2 years, where EFS was defined as the first day of administration of study drug until first occurrence of relapse, progressive disease, secondary cancer, death or last contact with the patient. Patients (n=100) were enrolled between June 2012 and February 2016 and received 27 cycles of oral DFMO at a dose of 750 mg/m² ±250 mg/m² on each day of a 28-day cycle. Key eligibility criteria included age 0-21 years, histologic verification of NBL at the time of original diagnosis, remission at the end of upfront therapy (where upfront therapy is defined as 5-7 cycles of chemotherapy, surgery, consolidation, radiation and up to 6 cycles of anti-GD2 antibody with retinoic acid), and greater than 30 days and less than 120 days from previous therapy.

2-year EFS and OS results are shown in Table 1.

Table 1 2-year EFS and OS (Study 3/3b)

	Study 3/3b (n=100)
2-year EFS rate (95% CI)	84% * (0.77, 0.92)
2-year OS rate (95% CI)	99% (0.97, 1.00)

*compared to a historical control rate of 70%

In support of these findings, the Sponsor provided contemporaneous external control based on Children's Oncology Group (COG) study ANBL0032. Patients who were treated on the COG study, and then who went on to the 3/3b study (n=81) were compared to patients who were treated on the COG Study, and then were observed, receiving no additional treatment (see Figure 1). All patients received identical protocol-defined therapy up until the initiation of DFMO treatment.

Patients from the COG Study were analytically matched (using propensity scoring) 3:1 to the patients from Study 3/3b using covariate data collected from the COG database. The propensity score, or the probability of receiving DFMO based on the patient's observed covariates, was estimated via logistic regression controlling for the following variables:

- MYCN
- response to induction therapy
- disease status at the end of up-front therapy
- disease status of pre-immunotherapy
- stage
- age
- sex
- dichotomized time from enrollment of the COG Study to end of immunotherapy (<186 days versus >186 days).

Figure 1: COG Study Analysis Population

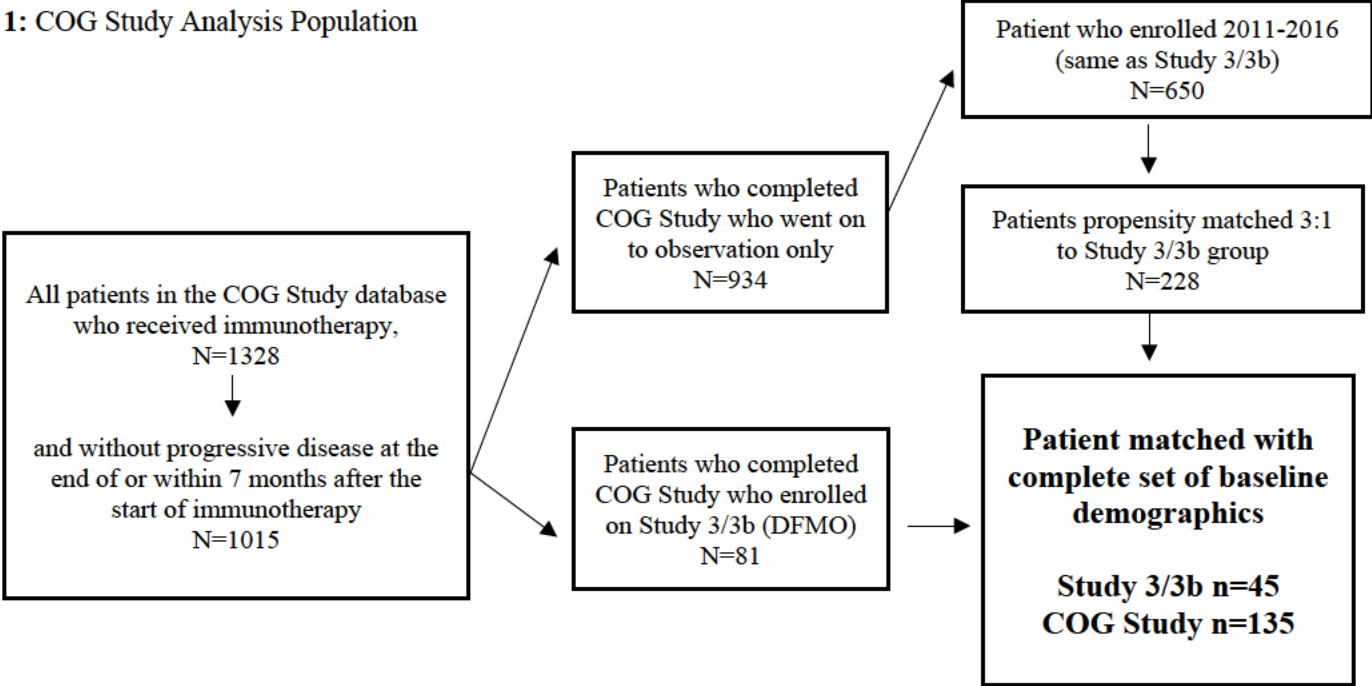


Table 2 Demographic and Disease Characteristics for Study 3/3b DFMO Combo and COG Study No DFMO (adapted from BTDR background)

Characteristics		Study 3/3b DFMO COMBO (Stratum 1) Complete Case Population for match analysis (n=45)	COG Study NO DFMO Complete Case population after propensity score matching (n=135)
Age Categorization at Diagnosis	< 18 months	9 (20.0%)	21 (15.6%)
	18 mo – 6 years	31 (68.9%)	99 (73.3%)
	> 6 years	5 (11.1%)	15 (11.1%)
Sex	Male	23 (51.1%)	75 (55.6%)
	Female	22 (48.9%)	60 (44.4%)
Stage at Diagnosis	2B	4 (8.9%)	8 (5.9%)
	3	3 (6.7%)	14 (10.4%)
	4	37 (82.2%)	110 (81.5%)
	4S	1 (2.2%)	3 (2.2%)
MYCN	AMP	26 (57.8%)	82 (60.7%)
	Non-AMP	19 (42.2%)	53 (39.3%)
Histology	Unfavorable	40 (88.9%)	123 (91.1%)
	Favorable	5 (11.1%)	12 (8.9%)
Response at End of Induction Therapy (pre-stem cell transplant)	CR	22 (48.9%)	69 (51.1%)
	VGPR	14 (31.1%)	45 (33.3%)
	PR	9 (20.0%)	21 (15.6%)
Response at End of Consolidation (pre-immunotherapy)	CR	22 (48.9%)	68 (50.4%)
	VGPR	11 (24.4%)	39 (28.9%)
	PR	12 (26.7%)	28 (20.7%)
Response at End of COG Study (conclusion of immunotherapy)	CR	39 (86.7%)	120 (88.9%)
	VGPR	4 (8.9%)	14 (10.4%)
	PR	2 (4.4%)	1 (0.7%)
Dichotomized time from enrollment of the COG Study to end of immunotherapy	<186 days	21 (46.7%)	56 (41.5%)
	>186 days	24 (53.3%)	79 (58.5%)

AMP=amplified; Non-AMP=non-amplified; CR=complete response; VGPR=very good partial response; PR=partial response; MR=mixed response; UNK=unknown; NED=no evidence of disease; MIBG=iodine-131-meta-iodobenzylguanidine

The Division agrees that the COG arm was well matched and that it is an appropriate, well-defined contemporaneous source of comparator data. The Division acknowledges that there are caveats to interpretation of external control data and will require additional information (e.g. reasons for censoring) in order to more reliably interpret the outcome data presented below for the purposes of a potential a marketing application. The data presented in this package is appropriate for this stage of development and is sufficient to provide preliminary evidence of clinical benefit.

Results

The Kaplan-Meier plots (Figures 2 and 3) display the resulting EFS and OS curves per treatment arm (where treatment arms are defined as patients who were observed after completing COG Study with no additional treatment [No DFMO] or patients who went on to receive DFMO on Study 3/3b[DFMO COMBO]). Estimates of the 2-year rates and 5-year rates of EFS and OS (Table 3) were numerically greater on the DFMO COMBO arm as compared to the No DFMO arm.

Hazard ratios for EFS and OS, comparing the overall probability of events or deaths between arms for the observed follow-up period, were also provided (Table 3). There is some uncertainty in the estimates of 5-

year landmark rates in the COG Study matched subset, as well as for the hazard ratios due to different rates of censoring by arm; however, this is appropriate for this stage of development.

Figure 2: Kaplan-Meier Estimates of EFS 3/3b DFMO vs COG Study (no DFMO) (Sponsor provided)

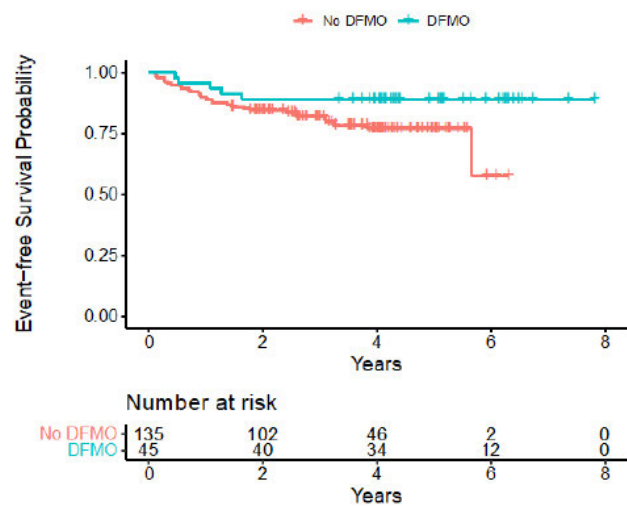


Figure 3: Kaplan-Meier Estimates of OS 3/3b DFMO vs COG Study (no DFMO) (Sponsor provided)

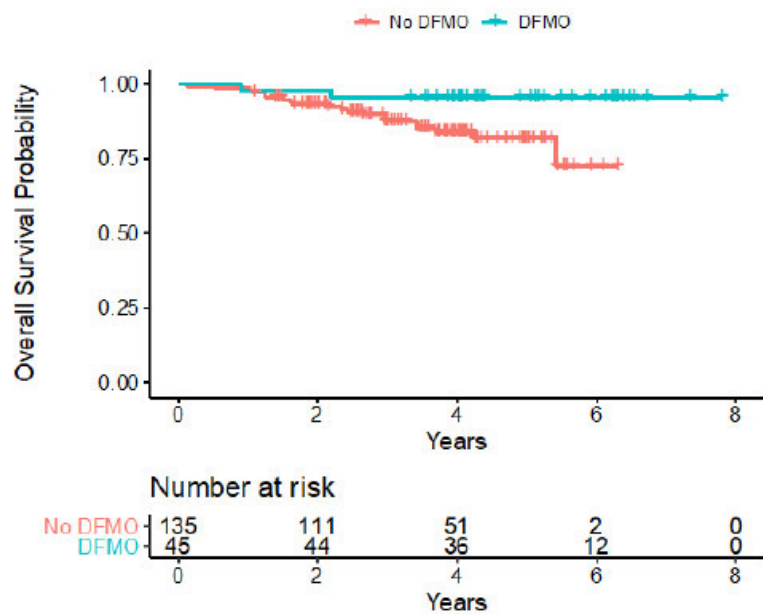


Table 3 Estimates of 2- and 5-year Event Free Survival and Overall Survival Probabilities for DFMO COMBO (Study 3/3b) and Control (COG Study) Populations (Sponsor Provided)

	Estimate	Study 3/3b DFMO COMBO (n=45)	COG Study MATCHED (n=135)
EFS	2-year Rate (95% CI)	89% (80, 99)	84% (79, 91)
	5-year Rate (95% CI)	89% (80, 99)	77% (69, 85)
	Hazard Ratio (95% CI)	0.404 (0.153, 1.068)	
OS	2-year Rate (95% CI)	98% (94, 100)	93% (89, 98)
	5-year Rate (95% CI)	96% (90, 100)	82% (74, 91)
	Hazard Ratio (95% CI)	0.210 (0.048, 0.914)	

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

DO2 finds the EFS and OS data compelling as preliminary evidence of clinical benefit based on the following:

1. A consistent, clinically meaningful improvement in EFS and OS was observed in a robust sample size of patients treated with DFMO compared to a well matched contemporaneous external control, as well as historical controls.
2. All of the patients in Study 3/3b and COG Study received the same, protocol-defined upfront therapy making the COG Study an appropriate comparator arm. Baseline characteristics were analytically well matched by propensity scoring between arms.
3. The development program includes an ongoing randomized study to confirm the preliminary clinical evidence of benefit.

Safety

In Study 3/3b, 59% of the population did not report any related adverse events over the 2 years of DFMO treatment. Grade 2-3 transaminitis (<10 X ULN) was the most common toxicity which usually resolved without holding DFMO. Seventy-six percent of patients enrolled on study had pre- existing hearing loss due to previous treatment; of those, an increase in hearing loss was observed in 9 patients but all recovered and returned to baseline. All patients were able to continue on DFMO and complete study regardless of adverse events. The safety profile observed in Study 3/3b is consistent with that observed in other DFMO studies conducted in similar populations by the Sponsor.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

DO2 recommends that this BTDR be granted for HR-NBL based on a clinically meaningful improvement in event-free survival and overall survival compared to an analytically well-matched contemporaneous control arm. These findings are also supported by historical controls.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The sponsor is conducting an ongoing randomized trial for pediatric patients with newly diagnosed HR-NBL. Patients will receive upfront treatment for HR-NBL (as described above) then be randomized 1:1 to receive DMFO with maintenance therapy (dinutuximab and retinoic acid) or maintenance therapy alone. This study is intended to confirm the preliminary clinical benefit observed in Study 3/3b.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation: n/a

14. List references, if any:

1. Howlader N, Noone AM, Krapcho M, et al., eds.: SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Bethesda, Md: National Cancer Institute, 2012.
2. PDQ® Pediatric Treatment Editorial Board. PDQ Neuroblastoma Treatment. Bethesda, MD: National Cancer Institute. Updated 02/06/2020.
3. Yu, Alice L., et al. "Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma." *New England Journal of Medicine* 363.14 (2010): 1324-1334.
4. Pinto, Navin R., et al. "Advances in risk classification and treatment strategies for neuroblastoma." *Journal of clinical oncology* 33.27 (2015): 3008.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Revised 3/18/19/M. Raggio

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/

AMY K BARONE
03/31/2020 11:09:56 AM

SUZANNE G DEMKO
03/31/2020 11:17:17 AM

B HARPREET SINGH
03/31/2020 04:11:51 PM