

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**215500Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

**NDA/BLA Multi-disciplinary Review and Evaluation**

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

|                               |                                                                                                                                                                                                            |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>       | 505(b)(2) New Drug Application (NDA)                                                                                                                                                                       |
| <b>Application Number(s)</b>  | 215500                                                                                                                                                                                                     |
| <b>Priority or Standard</b>   | Priority                                                                                                                                                                                                   |
| <b>Submit Date(s)</b>         | November 21, 2022                                                                                                                                                                                          |
| <b>Received Date(s)</b>       | November 21, 2022                                                                                                                                                                                          |
| <b>PDUFA Goal Date</b>        | May 21, 2023                                                                                                                                                                                               |
| <b>Division/Office</b>        | Division of Oncology 2 / Office of Oncologic Drugs                                                                                                                                                         |
| <b>Review Completion Date</b> | <i>Electronic stamp date</i>                                                                                                                                                                               |
| <b>Established Name</b>       | eflornithine                                                                                                                                                                                               |
| <b>(Proposed) Trade Name</b>  | IWILFIN                                                                                                                                                                                                    |
| <b>Pharmacologic Class</b>    | Ornithine decarboxylase inhibitor                                                                                                                                                                          |
| <b>Code name</b>              | DFMO                                                                                                                                                                                                       |
| <b>Applicant</b>              | US World Meds, LLC (USWM)                                                                                                                                                                                  |
| <b>Formulation(s)</b>         | Tablet: 192 mg                                                                                                                                                                                             |
| <b>Dosing Regimen</b>         | Administered orally twice daily, with or without food, for two years or until recurrence of disease or unacceptable toxicity<br><br>The recommended dosage is based on body surface area (BSA) as follows: |

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{Eflornithine [DFMO]}

|                                                                   |                                                                                                                                                                                                                          |                                          |                           |  |
|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|---------------------------|--|
|                                                                   |                                                                                                                                                                                                                          | <b>Body Surface Area (m<sup>2</sup>)</b> | <b>Dosage</b>             |  |
|                                                                   |                                                                                                                                                                                                                          | >1.5                                     | 768 mg orally twice a day |  |
|                                                                   |                                                                                                                                                                                                                          | 0.75 to 1.5                              | 576 mg orally twice a day |  |
|                                                                   |                                                                                                                                                                                                                          | 0.5 to < 0.75                            | 384 mg orally twice a day |  |
|                                                                   |                                                                                                                                                                                                                          | 0.25 to < 0.5                            | 192 mg orally twice a day |  |
| <b>Applicant Proposed Indication(s)/Population(s)</b>             | To reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy                                                                                    |                                          |                           |  |
| <b>Recommendation on Regulatory Action</b>                        | Traditional Approval                                                                                                                                                                                                     |                                          |                           |  |
| <b>Recommended Indication(s)/Population(s)</b><br>(if applicable) | To reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy |                                          |                           |  |

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**REVIEWERS OF MULTI-DISCIPLINARY REVIEW AND EVALUATION**

|                                                            |                        |
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| <b>Division Director (DHOT)</b>                            | John Leighton          |
| <b>Division Director (OCP)</b>                             | Stacy Shord            |
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| <b>Deputy Division Director (OOD)</b>                      | Nicole Drezner         |
| <b>Office Director (or designated signatory authority)</b> | N/A                    |

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

## ADDITIONAL REVIEWERS OF APPLICATION

|                                                                 |                                                                                                                                    |
|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| <b>OPQ</b>                                                      | Xiao Hong Chen, Xing Wang, Rajan Pragani, Haripada Sarker, Jiao Yang, Nathan Davis, Mei Ou, Tom Oliver, Paresma Patel, Steve Rhieu |
| <b>Microbiology</b>                                             | Jiao Yang, Nathan Davis                                                                                                            |
| <b>OPDP</b>                                                     | Mispa Ajua-Alemanji, Rachael Conklin                                                                                               |
| <b>DMPP</b>                                                     | Ruth Mayrosh, Barbara Fuller                                                                                                       |
| <b>OSI</b>                                                      | Lee Pai-Scherf, Michele Fedowitz                                                                                                   |
| <b>OSE/DEPI</b>                                                 | Fang Tian, Orestis Panagiotou                                                                                                      |
| <b>OSE/DMEPA</b>                                                | Tingting Gao, Janine Stewart, Ashleigh Lowery, Colleen Little                                                                      |
| <b>OSE/DRISK</b>                                                | Naomi Boston                                                                                                                       |
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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

DMPP=Division of Medical Policy Programs

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

## GLOSSARY

ADME            absorption, distribution, metabolism, excretion

AE                adverse event

AUC             Area under the curve

|                  |                                                        |
|------------------|--------------------------------------------------------|
| BCC              | Beat Childhood Cancer                                  |
| BLA              | biologics license application                          |
| BDL              | below detection limit                                  |
| BICR             | blinded independent central review                     |
| BRF              | Benefit Risk Framework                                 |
| BSA              | body surface area                                      |
| CBC              | complete blood count                                   |
| CDER             | Center for Drug Evaluation and Research                |
| CDTL             | Cross-Discipline Team Leader                           |
| CFR              | Code of Federal Regulations                            |
| C <sub>max</sub> | Concentration maximum                                  |
| CMC              | chemistry, manufacturing, and controls                 |
| COG              | Children’s Oncology Group                              |
| COSTART          | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF              | case report form                                       |
| CRP              | C-reactive protein                                     |
| CSR              | clinical study report                                  |
| CT               | computed tomography                                    |
| CYP              | cytochrome                                             |
| DFMO             | eflornithine HCl                                       |
| ECG              | electrocardiogram                                      |
| ECOG             | Eastern Cooperative Oncology Group                     |
| EFS              | Event Free Survival                                    |
| ESR              | erythrocyte sedimentation rate                         |
| FDA              | Food and Drug Administration                           |

|           |                                                                         |
|-----------|-------------------------------------------------------------------------|
| GCP       | good clinical practice                                                  |
| GI        | gastrointestinal                                                        |
| GLP       | good laboratory practice                                                |
| GRMP      | good review management practice                                         |
| hr        | hour                                                                    |
| HRNB      | High Risk Neuroblastoma                                                 |
| HVA       | homovanillic acid                                                       |
| ICH       | International Conference on Harmonization                               |
| IND       | Investigational New Drug                                                |
| IP        | intraperitoneal                                                         |
| ISE       | integrated summary of effectiveness                                     |
| ISS       | integrated summary of safety                                            |
| ITT       | intent to treat                                                         |
| IV        | intravenous                                                             |
| MCV       | mean corpuscular volume                                                 |
| MedDRA    | Medical Dictionary for Regulatory Activities                            |
| MIBG      | imaging test that uses metaiodobenzylguanidine as a tracer              |
| Min       | minute                                                                  |
| MRI       | magnetic resonance imaging                                              |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA       | new drug application                                                    |
| NME       | new molecular entity                                                    |
| NOEL      | No Observed Effect Levels                                               |
| nRBC      | nucleated red blood cell                                                |
| OCS       | Office of Computational Science                                         |

|                  |                                               |
|------------------|-----------------------------------------------|
| OPQ              | Office of Pharmaceutical Quality              |
| OS               | Overall Survival                              |
| OSE              | Office of Surveillance and Epidemiology       |
| OSI              | Office of Scientific Investigation            |
| PD               | pharmacodynamics                              |
| PI               | prescribing information                       |
| PK               | pharmacokinetics                              |
| PMC              | postmarketing commitment                      |
| PMR              | postmarketing requirement                     |
| PP               | per protocol                                  |
| PREA             | Pediatric Research Equity Act                 |
| PRO              | patient reported outcome                      |
| RBC              | red blood cell                                |
| REMS             | risk evaluation and mitigation strategy       |
| SAE              | serious adverse event                         |
| SAP              | statistical analysis plan                     |
| SOC              | standard of care                              |
| t <sub>1/2</sub> | half life                                     |
| TEAE             | treatment emergent adverse event              |
| VMA              | vanillylmandelic acid                         |
| WBC              | white blood cell                              |
| WHODRL           | World Health Organization Drug Reference List |

## 1. EXECUTIVE SUMMARY

### 1.1. Product Introduction

Eflornithine is an oral irreversible inhibitor of the enzyme ornithine decarboxylase (ODC), the first and rate-limiting enzyme in the biosynthesis of polyamines and a transcriptional target of *MYCN*.

Oral eflornithine is not currently approved in the United States.

The New Drug Application (NDA) was submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following proposed indication:

- To reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy

Eflornithine is administered orally twice daily for two years or until recurrence of disease or unacceptable toxicity. The proposed recommended dosage is based on body surface area (BSA), as follows:

| Body Surface Area (m <sup>2</sup> ) | Dosage                                    |
|-------------------------------------|-------------------------------------------|
| >1.5                                | 768 mg (four tablets) orally twice a day  |
| 0.75 to 1.5                         | 576 mg (three tablets) orally twice a day |
| 0.5 to < 0.75                       | 384 mg (two tablets) orally twice a day   |
| 0.25 to < 0.5                       | 192 mg (one tablet) orally twice a day    |

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The FDA review team recommends traditional approval of eflornithine to reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy. The statutory requirement for demonstration of substantial evidence of effectiveness is met based on the efficacy results from one adequate and well-controlled clinical



{Eflornithine [DFMO]}

investigation, as defined in 21 CFR 314.126, and confirmatory evidence, to establish the effectiveness of DFMO for the proposed indication. According to FDA Guidance (FDA Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, 2019), approval based on a single adequate and well-controlled trial with confirmatory evidence may be acceptable depending upon the persuasiveness of the trial, robustness of the confirmatory evidence, seriousness of the disease and unmet medical need, and whether it is ethical and practicable to conduct more than one adequate and well-controlled investigation.

The Applicant submitted results of a single externally controlled trial (ECT) and supportive data to provide evidence of efficacy for DFMO to reduce the risk of relapse in pediatric patients with HRNB who have completed multiagent, multimodality therapy. The ECT was designed to compare data from Study 3(b), a multi-center, open-label, single arm trial of DFMO monotherapy for up to 2 years in pediatric patients with HRNB in remission after immunotherapy, to an external control arm constructed from patients with HRNB enrolled on Study ANBL0032, a multi-center, open-label, randomized trial of immunotherapy plus standard up-front therapy vs. up-front therapy alone.

The population for the Applicant's primary analysis of efficacy included 90 DFMO-treated patients and 270 control patients from Study ANBL0032 who met the criteria for the comparison, had complete data for specified clinical covariates, and were matched (1:3) using propensity scores. A full description of the comparative efficacy populations and the criteria for inclusion in the primary analysis is provided in Section 8.1.3. The primary endpoint was event-free survival (EFS), defined as the time from the end of immunotherapy until the first occurrence of disease progression, relapse, secondary cancer, or death due to any cause. Overall survival (OS), defined as the time from the end of immunotherapy until as death due to any cause, was a secondary endpoint.

The Applicant's primary analysis resulted in a hazard ratio (HR) for EFS of 0.48 (95% Confidence Interval [CI]: 0.27, 0.85) and 0.32 (95% CI: 0.15, 0.70) for OS, favoring the DFMO arm. FDA conducted multiple sensitivity and supportive analyses to evaluate potential threats to study validity; analyses to assess the impact of potential factors including differences between the investigational and control arms, and analyses evaluating index date, immortal time, follow-up, confounding, and contemporaneity of populations are described in detail in Sections 8.1.4 and 8.3. The estimated treatment effect based on these analyses generally appeared to be robust to potential sources of bias.

For regulatory purposes, randomized controlled trials (RCTs) are generally required to assess the

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

{Eflornithine [DFMO]}

effect of a drug on a time-to-event endpoint (e.g., event-free survival, overall survival) because randomization balances both known and unknown prognostic factors across study arms. In specific rare circumstances, if the conduct of an RCT is considered infeasible or would lack adequate equipoise, a scientifically rigorous ECT may be considered as the primary source of data to demonstrate substantial evidence of effectiveness. However, FDA regulations stipulate that for such a trial to be considered adequate and well-controlled, a valid analysis of the treatment effect must be based on “comparable patients or populations” (21 CFR 314.126).

In 2015, FDA initially recommended that a randomized trial would be required to scientifically assess the effect of DFMO as a maintenance therapy to prevent relapse in patients with high-risk neuroblastoma. However, a randomized trial was not conducted at that time and preliminary results of a propensity-score matched analysis of Study 3(b) submitted as part of a Breakthrough Therapy Designation Request for eflornithine for the proposed indication suggested a large apparent treatment effect. The feasibility of an RCT was further adversely impacted by public dissemination of the results of Study 3(b), which were first published in 2018.

As discussed in the 2023 FDA Draft Guidance for Industry: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products, ECTs differ in several important ways from RCTs. Most notably, randomization is the most powerful design feature to facilitate balance in known and unknown confounding influences and is not a feature of externally controlled designs. As a result, there may be differences in baseline patient characteristics or concomitant treatments in the trial population compared to the external control population that may lead to differences in outcomes that are independent of the investigational treatment. The 2019 FDA Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products notes that the level of support for effectiveness provided by an ECT is strengthened if the following conditions are present:

- the natural history of a disease is well defined,
- the external control population is very similar to that of the treatment group,
- concomitant treatments that affect the primary endpoint are not substantially different between the external control population and the trial population, and
- the results provide compelling evidence of a change in the established progression of disease (such as partial or complete response in a disease where spontaneous regression is not observed).

Specifically, in this application, the review team notes that the natural history and poor prognosis of HRNB are well defined in the published literature, the external control population is generally comparable to the treatment group, differences in concomitant therapy would be primarily

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limited to supportive care treatments as there are no available treatments in this setting, and the results provided compelling evidence that disease progression or death was delayed, as described in further detail in Section 8.1.7.

Following careful review, FDA determined that the submitted external control data in this application were of high quality due to their provenance and the large set of individual patient-level trial data, and the results of sensitivity analyses were generally consistent with the Applicant's primary analysis. Based on review of the study design, study conduct, and submitted data, the FDA concluded that the ECT was adequate and well-controlled with a clear statement of objectives, an appropriately constructed external control design with appropriate patient selection, reliable clinical assessments to evaluate the effect of the drug, and adequate analysis of the results of the study to assess the effect of the drug.

The data supporting this application were considered in the context of the specific clinical setting. HRNB is a rare and life-threatening disease with a high unmet need. Prognosis after relapse is poor and there are no available therapies for the proposed disease setting. Although an RCT of DFMO in this disease setting could potentially have been conducted prior to the publication of Study 3(b) results, at the time of this review a new RCT was considered to have significant feasibility challenges, providing an appropriate context for consideration of an external control.

Regarding the types of evidence that may be considered confirmatory, the 2019 Substantial Evidence draft guidance states that "compelling mechanistic evidence in the setting of well-understood disease pathophysiology, may be sufficient to provide substantial evidence of effectiveness of a new drug or a new indication." While mechanistic evidence would generally be obtained from clinical testing using a relevant and well understood pharmacodynamic endpoint, evidence can also be collected from other sources such as animal studies. Given this application is based on a proposed cytostatic mechanism of action of DFMO as a single agent for patients with HRNB in remission, clinical response rate data are not expected. As such, the review team relied heavily on non-clinical studies as confirmatory evidence.

The underlying pathophysiology of the *ODC* and *MYCN* pathways in neuroblastoma is well understood, creating a setting in which it is appropriate to consider the possibility of leveraging mechanistic data as confirmatory evidence. The review team carefully reviewed data submitted by the Applicant and identified in an independent FDA literature search and found it to provide strong mechanistic support, as the drug directly targets these underlying critical oncogenic pathways in this disease. In particular, the review team finds the mechanistic evidence provided by two well-established, relevant animal models of neuroblastoma which showed that

eflornithine prevents or delays tumor formation in mice who have no initial evidence of disease to be compelling and appropriate as confirmatory evidence of eflornithine's effectiveness. A full discussion of the nonclinical confirmatory evidence is provided in Section 5 of this review. The review team noted that LIN28 overexpression is observed in multiple tumor types, and there have been multiple negative trials of eflornithine in adults with cancer, however the *ODC1* and *MYCN* genes are largely not considered major drivers of tumors in which studies of eflornithine were negative, summarized further in Section 8.1.5 and Table 54. In contrast, these genes are particularly relevant in neuroblastoma and aberrations of *ODC* and *MYCN* are correlated with poor prognosis in this disease. In addition, pediatric solid tumors have largely different ontogeny and biology from adult tumors, with the latter being more likely to have substantially higher mutational burdens and multiple driver mutations. Thus, the lack of activity reported in other adult tumor types was not felt to necessarily portend a lack of activity in pediatric neuroblastoma, and the non-clinical data and results from relevant animal models were felt to provide confirmatory evidence necessary to support substantial evidence of an improvement in EFS.

The finding of substantial evidence of effectiveness is necessary, but not sufficient on its own, for FDA approval. The approval decision also requires a determination that the drug is safe for the intended use, i.e., that the benefits of the drug outweigh its risks under the conditions of use defined in labeling. The safety profile of eflornithine is notable for hearing loss, myelosuppression, and elevated liver enzymes. Although eflornithine can cause serious adverse reactions, these safety concerns are adequately addressed by product labeling, and eflornithine will be prescribed by oncologists with knowledge of how to monitor, identify, and manage the toxicities described in product labeling.

Given the complex nature of this application, an Oncology Drugs Advisory Committee meeting was held on October 4, 2023. Regarding the voting question, "Has the Applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?", 14 members voted "yes" and 6 members voted "no." The discussion among panel members generally supported that the clinical and nonclinical evidentiary package was sufficiently strong in the setting of a high unmet medical need and that there would be serious feasibility challenges in conducting a new prospective RCT of eflornithine in the proposed disease setting.

In summary, the review team determined that the statutory requirement for substantial evidence of effectiveness has been met to conclude that eflornithine reduces the risk of relapse in patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy. The factors leading to

this determination, as described throughout this review and in FDA’s presentations at the ODAC meeting, are highly specific to this application, which involves a treatment for a rare pediatric population with a life-threatening condition for which there are no available therapies to prevent the risk of relapse and for which an ECT design was deemed appropriate based on the individual development plan and disease setting. The ECT was derived from clinical trial patient-level data providing a uniquely comparable, high quality external control data source where results of primary and sensitivity analyses were robust in the evaluation of potential sources of bias, along with strong nonclinical confirmatory evidence based on a relevant animal model of the disease. While sufficient in the context of this unique application, such a development program is highly unlikely to be easily replicated in future marketing applications. Furthermore, the benefit-risk assessment for the proposed indication is favorable.

The FDA review teams recommend traditional approval of eflornithine for the following indication:

“to reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.”

### 1.3. Benefit-Risk Assessment (BRA)

#### Benefit-Risk Summary and Assessment

Neuroblastoma is a rare malignant solid tumor of neural crest cells occurring primarily in young pediatric patients. It accounts for 7-10% of childhood cancers, with a disproportionately higher share of childhood cancer mortality (Yan et al, 2020). Patients are stratified into low, intermediate, and high-risk groups in accordance with international guidelines developed by the International Neuroblastoma Risk Group (Monclair et al, 2009). Approximately 50% of patients are diagnosed with high-risk neuroblastoma (HRNB) based on age and tumor characteristics (DuBois et al, 2022).

Typical front-line multi-modality therapy for HRNB includes induction chemotherapy, surgical resection if indicated for any residual tumor, consolidative high dose chemotherapy with subsequent hematopoietic autologous stem cell transplantation (ASCT) and radiation, followed by immunotherapy and differentiating therapy with 13-cisretinoic acid (cis-RA) (Yu et al, 2021). The goal of front-line treatment is to eliminate tumors to achieve remission. Patients in remission receive no further pharmacologic therapy; however, there is a high risk of relapse, with most relapses occurring within the first 2 years after up-front treatment. The EFS rate in patients who have received current standard of care therapy is reported to be 66% at 2 years and 50% at 5 years (Irwin et al, 2021). After relapse, survival is poor, with a 5-year overall survival (OS) of less than 10% (Moreno et al, 2020). There are no FDA-approved therapies to reduce the risk of relapse in patients with HRNB in remission after completion of front-line therapy.

Eflornithine is an oral irreversible inhibitor of the enzyme ornithine decarboxylase (ODC), the first and rate-limiting enzyme in the biosynthesis of polyamines and a transcriptional target of *MYCN*. Polyamines play critical roles in differentiation and proliferation of mammalian cells and are essential for neoplastic transformation. In preclinical studies, inhibition of polyamine synthesis by eflornithine restored the balance of the LIN28/Let-7 metabolic pathway, which is involved in regulation of cancer stem cells and glycolytic metabolism, by decreasing protein expression of the oncogenic drivers MYCN and LIN28B in *MYCN*-amplified neuroblastoma.

Eflornithine (Ornidyl) was FDA-approved in 1990 in an intravenously administered injectable formulation for West African Sleeping Sickness,

but never marketed due to commercial viability reasons unrelated to safety or efficacy. Ornidyl is the reference listed drug intended to support the current 505(b)(2) application, relying upon FDA’s prior conclusions of nonclinical and clinical safety data. Eflornithine (Vaniqa) topical cream was approved for the reduction of unwanted facial hair in women in 2000. There are no existing oncologic indications for eflornithine.

The Applicant submitted a 505(b)(2) NDA based on the results of an externally controlled trial (ECT) comprised of a single-arm trial, Study 3(b), compared to an external control arm constructed from patients enrolled on the National Cancer Institute (NCI)/Children’s Oncology Group (COG)-sponsored clinical trial, Study ANBL0032.

Study 3(b) (NMTRC003(b); NCT02395666), entitled “A Phase II preventative study of DFMO as a single agent in patients with HRNB in remission,” is a multi-center, open-label, single arm trial of eflornithine monotherapy for up to 2 years in pediatric patients with HRNB who completed standard of care up-front therapy including immunotherapy. The trial enrolled patients from June 2012 to February 2016 across 22 sites in the U.S. Stratum 1, which provided the primary efficacy data for the experimental arm of the ECT, enrolled 105 patients who were in remission at the end of up-front therapy defined as chemotherapy (5-7 cycles), surgery as indicated, consolidation therapy as indicated, radiation therapy as indicated, or anti-ganglioside 2 (GD2) antibody therapy with retinoic acid up to 6 cycles. The primary endpoint was EFS at 2 years compared to a benchmark control rate of 70% based on clinical trial results from Study ANBL0032. Patients were treated until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, death, or discontinuation from the study treatment due to any other reason. Patients were followed for 5 years after completing DFMO for a total study duration of 7 years.

Study ANBL0032 is a large, Children’s Oncology Group (COG)-sponsored, multi-center, open-label, randomized trial of immunotherapy plus standard up-front therapy vs. up-front therapy alone in patients with newly diagnosed HRNB who had previously received induction and consolidation therapy, and who demonstrated at least a partial response prior to autologous stem cell transplant treatment. Patients were enrolled between November 2004 and July 2015 at 197 sites including 172 in the United States, as well as sites in Australia, New Zealand, and Canada. The major efficacy outcome measure for ANBL0032 was investigator-assessed EFS, defined as the time from randomization to the first occurrence of relapse, progressive disease, secondary malignancy, or death.

The efficacy population for the comparative analysis of Study 3(b) and ANBL0032 included patients from both studies who were less than 21

years of age with histologic verification of HRNB and who demonstrated at least a partial response based on imaging, with no evidence of disease in the bone marrow, at the end of immunotherapy, and who did not experience an EFS event prior to starting eflornithine therapy (for Study 3(b)), or for at least 30 days from the end of immunotherapy (for ANBL0032). Eligible patients on Study 3(b) received immunotherapy on ANBL0032 or were treated according to the ANBL0032 protocol off study; notably, 94% of patients in the primary matched population from Study 3(b) had been treated on ANBL0032.

A total of 90 eflornithine-treated patients who met the criteria for the comparison and had complete data for specified clinical covariates were matched (1:3) using propensity scores to 270 ANBL0032 control patients for a comparison of outcomes across treatment groups. The primary endpoint was event-free survival (EFS), defined as the time from the end of immunotherapy until the first occurrence of disease progression, relapse, secondary cancer, or death due to any cause. A secondary endpoint was overall survival (OS), defined as time from the end of immunotherapy until death due to any cause.

The Applicant's proposed primary analysis resulted in a hazard ratio for EFS of 0.48 (95% CI: 0.27, 0.85) and 0.32 (95% CI: 0.15, 0.70) for OS, favoring the eflornithine arm. Multiple sensitivity analyses were conducted to assess the impact of potential differences between the investigational and control arms, including analyses evaluating index date, immortal time, follow-up, confounding, and contemporaneity of populations. These sensitivity analyses, along with other supportive analyses conducted in subgroups of the data or to evaluate alternative estimands, provided generally consistent efficacy results for EFS and OS. In addition to the results of the single externally controlled trial, supportive data submitted in the application included non-clinical data and data from activity-estimating studies of eflornithine in related populations. The clinical supportive evidence included data from a small number of patients from a second stratum of Study 3(b) which enrolled patients with relapsed/refractory neuroblastoma, as well as data from an expanded access program.

The pooled safety population included 360 patients with newly diagnosed or relapsed/refractory high-risk neuroblastoma in Study 3(b) (N=101; NCT02679144) and Study 14 (N=259; NCT02679144) who received eflornithine orally twice daily for a maximum of 2 years. Safety data collection was limited per protocol, as these studies were investigator-initiated and not initially intended to support a marketing application. In this pooled safety population, the most common ( $\geq 5\%$ ) adverse reactions were hearing loss (11%), otitis media (10%), pyrexia (7%), pneumonia (5%) and diarrhea (5%). The most common ( $\geq 2\%$ ) Grade 3 or 4 laboratory abnormalities were increased ALT (11%), increased AST (6%),



decreased neutrophils (4.2%), and decreased hemoglobin (3.3%). Proposed warnings for product labeling included myelosuppression, hepatotoxicity, and hearing loss.

The external control data in this application was of high quality due to its provenance and the large set of individual patient-level trial data, and the magnitude of the observed estimated treatment effect was large. Based on review of the study design, study conduct, and submitted data, the FDA concluded that the ECT was adequate and well-controlled with a clear statement of objectives, an appropriately constructed external control design with appropriate patient selection, reliable clinical assessments to evaluate the effect of the drug, and adequate analysis of the results of the study to assess the effect of the drug. These factors were considered in the context of the disease; HRNB is a rare and life-threatening disease with a high unmet need. Prognosis after relapse is poor and there are no available therapies in the proposed disease setting.

In most oncology applications, the evidentiary package is supported by dose-dependent tumor response data in early-stage studies with or without additional clinical data showing early activity or efficacy in other cancer indications. Given the suggested cytostatic mechanism of action of DFMO, response rate data are not expected in this clinical setting, and unique to this application, nonclinical data supporting the mechanism of action and animal models relevant to the proposed indication were considered as potential confirmatory evidence. The review team determined that confirmatory evidence providing strong mechanistic support was derived from the well-understood pathophysiology of the *ODC* and *MYCN* pathways in this disease, the mechanism of action of eflornithine in vitro, and evidence of in vivo tumor preventative activity in two well-established, relevant animal models of neuroblastoma.

Given the complex nature of this application, an Oncology Drugs Advisory Committee meeting was held on October 4, 2023. Regarding the voting question, “Has the Applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?”, 14 members voted yes, and 6 members voted no. The discussion among panel members generally supported that the clinical and nonclinical evidentiary package was sufficiently strong in the setting of a high unmet medical need and that there would be serious feasibility challenges in conducting a new prospective RCT of eflornithine in the proposed disease setting.

While there are limitations of non-randomized trials as previously described, FDA may exert regulatory flexibility in determining the type and amount of data required for a particular drug to meet the statutory standard; in some cases, this can involve evidence from non-randomized study

designs that produce less certainty in some circumstances when a better design is not feasible or ethical. The 2019 draft guidance entitled “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products” states that “in certain settings, a somewhat greater risk (compared to placebo-controlled or other randomized superiority trials) of false positive conclusions – and therefore less certainty about effectiveness – may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy...for an unmet medical need. The data supporting effectiveness could, despite the greater risk of error, support a conclusion that there is substantial evidence of effectiveness.”

While an RCT in this disease setting could potentially have been conducted prior to the publication of Study 3(b) results, the review team considers it unlikely that an RCT could feasibly be completed at this time. In the context of the strength of the scientific evidence, the feasibility of an RCT, and the unmet medical need in this pediatric patient population with a life-threatening disease, the review team determined that the statutory requirement for demonstration of substantial evidence of effectiveness for DFMO to reduce the risk of relapse in patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior induction, consolidation, and anti-GD2 immunotherapy, has been met. Based on a favorable benefit-risk assessment, FDA recommends traditional approval of DFMO for the following indication:

“to reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.”

| Dimension                                        | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Conclusions and Reasons                                                                                                 |
|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| <a href="#"><u>Analysis of Condition</u></a>     | <ul style="list-style-type: none"> <li>• Neuroblastoma is a rare malignant solid tumor of neural crest cells occurring primarily in young pediatric patients. It affects approximately 800 patients per year in the United States, accounting for 7-10% of childhood cancers, with a disproportionately higher share of childhood cancer mortality (Yan et al, 2020).</li> <li>• Patients are stratified into low, intermediate, and high-risk groups in accordance with international guidelines developed by the International Neuroblastoma Risk Group (Monclair et al, 2008).</li> <li>• Approximately 50% of patients are diagnosed with high-risk neuroblastoma (HRNB) based on age, stage, <i>MYCN</i> status, and tumor histology (DuBois et al, 2022).</li> </ul>  | High-risk neuroblastoma is a rare, life-threatening disease.                                                            |
| <a href="#"><u>Current Treatment Options</u></a> | <ul style="list-style-type: none"> <li>• Typical front-line multi-modality therapy for HRNB includes induction chemotherapy, surgery, hematopoietic autologous stem cell transplantation, radiation, and immunotherapy (Yu et al, 2021). The goal of front-line treatment is to eliminate tumors to achieve remission.</li> <li>• Patients in remission receive no further pharmacologic therapy after up-front therapy; however, half of patients relapse within 5 years (Irwin et al, 2021). After relapse, survival is poor, with 5-year overall survival (OS) of less than 10% (Moreno et al, 2020).</li> <li>• There are no FDA-approved therapies to reduce the risk of relapse in patients with HRNB in remission after completion of front-line therapy.</li> </ul> | There is an unmet medical need for effective therapy to prevent relapse in patients with HRNB after front-line therapy. |

| Dimension      | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>Benefit</u> | <ul style="list-style-type: none"> <li>• The Applicant submitted a single externally controlled trial comprised of data from Study 3(b), a multi-center, open-label, single arm trial of eflornithine monotherapy for up to 2 years in pediatric patients with HRNB in remission after immunotherapy, compared to an external control arm constructed from patients enrolled on Study ANBL0032, a multi-center, open-label, randomized trial of immunotherapy plus standard up-front therapy vs. up-front therapy alone.</li> <li>• The efficacy population for the comparative analysis of Study 3(b) and ANBL0032 included patients from both studies who were less than 21 years of age with histologic verification of HRNB and who demonstrated at least a partial response based on imaging, with no evidence of disease in the bone marrow, at the end of immunotherapy, and did not experience an EFS event prior to starting eflornithine therapy (for Study 3(b)), or for at least 30 days from the end of immunotherapy (for ANBL0032). Eligible patients on Study 3(b) received immunotherapy on ANBL0032 or were treated according to the ANBL0032 protocol off study; notably, 94% of patients in the primary matched population from Study 3(b) had been treated on ANBL0032</li> <li>• A total of 90 eflornithine-treated patients who met the criteria for the comparison and had complete data for specified clinical covariates were matched (1:3) using propensity scores to 270 ANBL0032 control</li> </ul> | <p>The review team considered the use of an ECT to be acceptable in this specific development program, in the setting of a rare disease with a well-defined natural history and poor prognosis, and considering the large estimated treatment effect and feasibility of an RCT at the time of the review. The review team determined that the study was adequate and well-controlled with a clear statement of objectives, an appropriately constructed external control design with appropriate patient selection, and reliable assessments to evaluate the effect of the drug.</p> <p>The Applicant and the FDA conducted multiple sensitivity analyses, along with other supportive analyses conducted in subgroups of the data or to evaluate alternative estimands, which provided generally consistent efficacy results for EFS and OS. These analyses indicate that the observed results are robust to many of the assumptions for the non-randomized trial design as well as those</p> |

| Dimension | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|           | <p>patients for a comparison of outcomes. The primary endpoint was event-free survival (EFS) and a secondary endpoint was overall survival (OS).</p> <ul style="list-style-type: none"> <li>• The primary analysis resulted in a hazard ratio for EFS of 0.48 (95% CI: 0.27, 0.85) and 0.32 (95% CI: 0.15, 0.70) for OS, favoring the eflornithine arm. Multiple sensitivity analyses were conducted to assess the impact of potential differences between the investigational and control arms, including analyses regarding index date, immortal time, follow-up, and contemporaneity of populations.</li> <li>• In addition to the single externally controlled trial, supportive evidence included nonclinical data and data from activity-estimating studies of eflornithine in related populations. The limited supportive clinical data included a small number of patients from a second stratum of Study 3(b) which enrolled patients with relapsed/refractory neuroblastoma, as well as data from an expanded access program.</li> </ul> | <p>required for the corresponding analytic methodology.</p> <p>Confirmatory evidence providing strong mechanistic support was derived from the well-understood pathophysiology of disease, the mechanism of action of eflornithine in vitro, and evidence of in vivo tumor preventative activity in two well-established, relevant animal models of neuroblastoma.</p> <p>While there are limitations to non-randomized trials, FDA may exert regulatory flexibility where appropriate and rely on study designs that produce less certainty in specific circumstances when a randomized design is not feasible. While a randomized controlled trial in this disease setting could potentially have been conducted prior to the publication of Study 3(b) results, the review team considers it unlikely that a randomized controlled trial could feasibly be completed at this time. In the context of the strength of the</p> |

| Dimension                                | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | scientific evidence, the feasibility of a randomized trial, and the unmet medical need in this pediatric patient population with a life-threatening disease, the review team determined that the statutory requirement for substantial evidence of effectiveness of DFMO to reduce the risk of relapse in patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy has been met. |
| <a href="#">Risk and Risk Management</a> | <ul style="list-style-type: none"> <li>• The pooled safety population included 360 patients with newly diagnosed or relapsed/refractory high-risk neuroblastoma in Study 3(b) (N=101; NCT02679144) and Study 14 (N=259; NCT02679144) who received eflornithine orally twice daily for a maximum of 2 years.</li> <li>• Safety data collection was limited as these studies were investigator-initiated. Study 3(b) collected Grade 2 or higher AEs and laboratory data were not systematically collected. Study 14 collected only Grade 3 or higher AEs.</li> <li>• In the pooled safety population, the most common (<math>\geq 5\%</math>) adverse reactions were hearing loss (11%), otitis media (10%), pyrexia (7%),</li> </ul> | <p>The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease.</p> <p>Although DFMO can cause serious adverse reactions, these safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. DFMO will be prescribed by oncologists who routinely</p>                                                                                      |



| Dimension | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Conclusions and Reasons                                                                                                                                                                                                                |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|           | <p>pneumonia (5%) and diarrhea (5%). The most common (<math>\geq 2\%</math>) Grade 3 or 4 laboratory abnormalities were increased ALT (11%), increased AST (6%), decreased neutrophils (4.2%), and decreased hemoglobin (3.3%).</p> <ul style="list-style-type: none"> <li>• Proposed warnings for product labeling included myelosuppression, hepatotoxicity, and hearing loss.</li> <li>• Notably, the population of patients with HRNB who have completed initial multimodality therapy are at risk for hearing loss due to receipt of platinum chemotherapy; this hearing loss may continue to emerge or worsen in the years following treatment. However, based on the review of available data, hearing loss appears to be a risk associated with DFMO.</li> <li>• There were no Grade 5 treatment-emergent adverse events.</li> </ul> | <p>monitor, identify, and manage the toxicities described in the USPI; therefore, the risk mitigation strategies included in the label are considered sufficient and a REMS was not considered necessary for the safe use of DFMO.</p> |

#### 1.4. Patient Experience Data

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

|                          |                                                                                     |                                                                                 |
|--------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| <input type="checkbox"/> | The patient experience data that was submitted as part of the application, include: | No clinical outcome assessment data were submitted as part of this application. |
|--------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|

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

|                          |                                                                                                                                    |  |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------|--|
| <input type="checkbox"/> | Clinical outcome assessment (COA) data, such as                                                                                    |  |
| <input type="checkbox"/> | Patient reported outcome (PRO)                                                                                                     |  |
| <input type="checkbox"/> | Observer reported outcome (ObsRO)                                                                                                  |  |
| <input type="checkbox"/> | Clinician reported outcome (ClinRO)                                                                                                |  |
| <input type="checkbox"/> | Performance outcome (PerfO)                                                                                                        |  |
| <input type="checkbox"/> | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) |  |
| <input type="checkbox"/> | Patient-focused drug development or other stakeholder meeting summary reports                                                      |  |
| <input type="checkbox"/> | Observational survey studies designed to capture patient experience data                                                           |  |
| <input type="checkbox"/> | Natural history studies                                                                                                            |  |
| <input type="checkbox"/> | Patient preference studies (e.g., submitted studies or scientific publications)                                                    |  |
| <input type="checkbox"/> | Other: (Please specify)                                                                                                            |  |
| <input type="checkbox"/> | Patient experience data that was not submitted in the application, but was considered in this review.                              |  |



X

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Cross-Disciplinary Team Leader

Diana Bradford, MD

## 2. THERAPEUTIC CONTEXT

### 2.1. Analysis of Condition

#### The Applicant's Position:

##### **Description of Disease**

Neuroblastoma is a rare pediatric cancer affecting approximately 800 patients per year in the US. Although rare, neuroblastoma is the most common extracranial solid tumor in children, accounting for approximately 8% of all childhood cancers and 15% of childhood cancer mortality ([Brodeur 2016](#)).

Neuroblastoma is a solid cancerous tumor that begins in the nerve cells outside the brain of infants and young children. It can start in the nerve tissue near the spine in the neck, chest, abdomen, or pelvis, but it most often begins in the adrenal glands. Neuroblastoma develops most often in infants and young children, with 90% of diagnoses occurring by age 5.

Patients are stratified by several risk factors into low, intermediate, and high-risk groups in accordance with international guidelines developed by the International Neuroblastoma Risk Group (Monclair 2009) which have recently been revised ([Irwin 2021](#)).

Children with low- or intermediate-risk neuroblastoma have an excellent prognosis with 5 year overall survival (OS) probabilities of greater than 90%; however, those characterized as having high risk neuroblastoma (HRNB), which accounts for approximately 50% of all neuroblastoma patients, have a much poorer prognosis ([Park 2008](#), [Maris 2007](#)). Various sources suggest 5-year OS probabilities of only 50% for HRNB children from initial diagnosis ([Yu 2010](#), [Park 2008](#)).

##### **Standard of Care**

The current standard of care for HRNB includes three main phases of treatment: induction, consolidation, and maintenance. Treatment includes chemotherapy and surgical resection (induction), high-dose chemotherapy with autologous stem cell transplantation (ASCT) and radiation (consolidation), followed by anti-ganglioside 2 (anti-GD2) immunotherapy and 13-cis-retinoic acid (also known as isotretinoin, cis-RA).

The most recent evolution of the standard of care occurred when a clinical investigation of anti-GD2 antibody, ch14.18 (dinutuximab, Unituxin®) supported improved EFS when added to then-current maintenance therapy ([Yu 2010](#)). ANBL0032 was a large phase III randomized open-label trial in HRNB patients. Patients were randomized to an induction regimen of cis-RA (Regimen A), or cis-RA plus sargramostim, dinutuximab and aldesleukin (Regimen B). The results of the

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study supported registration of Unituxin in the United States in 2015; however, the 2010 publication resulted in broad trial participation and adoption of the therapy into the standard of care years prior to approval. Since its approval, dinutuximab is recommended as part of the standard COG HRNB treatment protocol (until just recently, the standard COG HRNB protocol administered dinutuximab concomitantly with sargramostim [GM-CSF] and aldesleukin [IL-2]; however, concomitant use of IL-2 is no longer recommended [[Ladenstein 2018](#)]). The goal of standard upfront therapy is to clear tumors from the body thereby achieving remission.

Following completion of up-front therapy, patients are followed closely for signs of recurrence by routine clinic visits and radiographical imaging studies. In the current standard of care, no further pharmacotherapy is recommended. Patients that experience relapse are referred to second-line therapy to try to treat their disease back into remission; however, such patients often experience multiple relapses and have a very poor long-term prognosis. Based on a recent COG meta-analysis of relapsed HRNB studies, patients enrolled in such studies had a 4-year progression free survival rate of 6% and OS rate of 20% ([London 2017](#)). The overall survival rate in this more recent paper represents only minor improvement over the approximately 15% 4-year OS rate reported a decade earlier by Santana ([Santana 2008](#)). The clearest way to accomplish further improvement in HRNB overall survival rates is to improve the ability to maintain patients in remission, minimizing the occurrence of relapse that is associated with such high mortality.

The ANBL0032 study supported the latest improvement in long term outcomes for HRNB patients; however, reported event free survival (EFS) rates with maintenance therapy that incorporates ch14.18 therapy remain at only ~60% at 4 to 5 years from the beginning of immunotherapy ([Yu 2014](#), [Yu 2021](#), [Desai 2022](#)). Hence, there is a large, unmet medical need for more effective treatments for patients with refractory or relapsed neuroblastoma with disease in bone and/or bone marrow. The Applicant's clinical program was specifically designed to investigate if extended maintenance with single agent DFMO for two years following the completion of immunotherapy could further improve EFS beyond the rates reported from ANBL0032.

### **DFMO Offers Specific and Targeted Chemopreventative Therapy**

DFMO (Difluoromethylornithine, Eflornithine) is a specific, enzyme-activated, irreversible inhibitor of ornithine decarboxylase (ODC), a key enzyme in mammalian polyamine biosynthesis. Polyamines are also essential for neoplastic transformation, making inhibition of ODC activity an attractive target for cancer chemoprevention. Inhibition of polyamine synthesis by DFMO results in growth arrest of a number of malignant and non-malignant mammalian cells and has been shown to inhibit the promotion and progression phases of carcinogenesis. DFMO inhibits cell growth of various types of cancer cells, including neuroblastoma (NB).

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DFMO as a chemopreventative agent has shown efficacy as an inhibitor of bladder, colon, esophagus, small and large intestine, liver, mammary gland, glandular stomach, skin, pancreas, and tongue carcinogenesis in *in vivo* animal models (Meyskens 2008).

Additionally, DFMO has shown selective targeting of cancer stem cells (CSCs). In NB, the CD114+ subpopulation has been defined as CSCs, which drives tumor relapse and chemoresistance (Agarwal 2015, Hsu 2013). Beat Childhood Cancer's (BCC) recent work utilizing *in vivo* and *in vitro* models of NB suggest that CSCs may be selectively targeted by DFMO via its inhibition of ODC. Treatment of MYCN-amplified BE(2)C and non-MYCN amplified CHLA90 NB cell lines demonstrated that DFMO preferentially targets CD114+ cells at physiologic doses, resulting in both loss of CD114 viability and induction of senescence.

DFMO reduced neurosphere formation and tumor initiating capability in *in vivo* xenograft mice models and also caused a decrease in the prevalence of tumor initiating cells as measured by extreme limiting dilutions analysis (ELDA). These results suggest that DFMO prevents tumor initiation and relapse of NB through targeted inhibition of CSCs and induction of senescence (Avequin 2018).

Preclinical models provided foundational support for clinical evaluations of DFMO in the neuroblastoma patient population. The earliest work with DFMO in HRNB focused on patients with active relapsed/refractory disease (Saulnier Sholler 2015), and provided initial evidence of effectiveness. The initial efficacy and good tolerability supported by this early published work, led to the clinical program which evaluated DFMO as a therapy for HRNB patients achieving remission to reduce the risk of relapse.

#### The FDA's Assessment:

FDA agrees that neuroblastoma is a rare malignant solid tumor of neural crest cells occurring primarily in young pediatric patients. It accounts for 7-10% of childhood cancers, with a disproportionately higher share of childhood cancer mortality (Yan et al, 2020). Patients are stratified into low, intermediate, and high-risk groups in accordance with international guidelines developed by the International Neuroblastoma Risk Group. Approximately 50% of patients are diagnosed with high-risk neuroblastoma (HRNB) based on age and tumor characteristics (Monclair, 2009).

The mechanism of action of DFMO and nonclinical data are described in Section 5.

## Analysis of Current Treatment Options

### The Applicant's Position:

The US standard of care for HRNB involves induction, consolidation and immunotherapy maintenance involving multiple agents and modalities of treatment. Relapse in HRNB is common in patients that complete multimodality therapy. The most recent data published from the Children's Oncology Group (COG) showed that for those who responded to up-front therapy, the event free survival (EFS) from the start of immunotherapy was  $67\% \pm 4\%$  at two years, but dropped to  $59\% \pm 5\%$  at 4 years (Yu 2014) and similar rates are reported in the most recent literature from the same COG study (Yu 2021, Desai 2022). Those who relapse following front-line therapy, or who are refractory to initial therapy, often respond transiently to additional interventions but have a high rate of subsequent relapse, generally 80–90% within 2 years (London 2017, Santana 2008, Wagner 2009). Once relapsed, patients have significantly poorer prognosis, with 5-year survival rate dropping to  $<10\%$  (Basta 2016). Patients who do not respond to up-front therapy are considered refractory and follow individualized, highly variable treatment plans for which there are limited options and even poorer long-term outcomes. However, initially refractory and relapsed patients can achieve remission at which point it is critically important to maintain remission.

There are no current therapies approved or used routinely off-label following completion of standard induction, consolidation and maintenance treatment for HRNB. In the current standard of care, patients achieving remission at the end of immunotherapy discontinue pharmacotherapy and are monitored at regular intervals via imaging studies to assess for potential recurrence of disease.

Relapse most commonly occurs in the first 24 months following the end of treatment (up-front or relapse therapy). Maintenance therapy over a similar timeframe in other pediatric cancers, such as leukemia, has been effective in preventing relapse and improving survival in those patients.

### The FDA's Assessment:

FDA agrees with the Applicant's description of current treatment options for high-risk neuroblastoma. Typical front-line multi-modality therapy for HRNB includes induction chemotherapy, surgical resection if indicated for residual tumor, consolidative high dose chemotherapy with subsequent hematopoietic autologous stem cell transplantation (ASCT) and radiation, followed by immunotherapy and differentiating therapy with 13-cisretinoic acid (cis-

RA) (DuBois et al, 2022). The goal of front-line treatment is to eliminate tumors to achieve remission. Patients in remission receive no further pharmacologic therapy, however there is a risk of relapse, with most relapses occurring within the first 2 years after up-front treatment. The historical EFS rate is 66% at 2 years and 50% at 5 years. After relapse, survival is poor, with 5-year overall survival (OS) of less than 10%.

There are currently no FDA-approved therapies to reduce the risk of relapse in patients with HRNB after front-line therapy.

### **3. REGULATORY BACKGROUND**

#### **3.1. U.S. Regulatory Actions and Marketing History**

##### The Applicant's Position:

##### **US Regulatory History**

DFMO has previously been approved by the FDA in an intravenously administered (IV) injectable formulation for the treatment of *Trypanosoma brucei gambiense* infection (also known as West African trypanosomiasis or West African Sleeping Sickness) and in a topical cream formulation (Vaniqa®, NDA 021,145, in 2000) for the treatment of unwanted facial hair in women. Although approved, Ornidyl was never marketed in the US due to commercial viability reasons unrelated to safety or efficacy. Ornidyl is currently approved by the WHO for use in pediatric patients to treat West African Sleeping Sickness as part of a Nifurtimox–eflornithine combination therapy (NECT) treatment regimen. Ornidyl is administered in this regimen via IV infusion at 400 mg/kg/day (200 mg/kg every 12 hours). Interestingly, the WHO specifically states that the NECT protocol is better tolerated in children than in adults with the most common adverse effects being abdominal pain, nausea, vomiting and headache. Vaniqa remains available in the US and is actively marketed. DFMO is not approved for the treatment of HRNB in any market. The regulatory history of DFMO in participating Project Orbis country applications is described in each respective Module 1 section.

##### **US Regulatory Framework**

The Applicant (USWM, LLC) and its collaborators herein submit a 505(b)2 application for registration of DFMO HCl monohydrate immediate release oral tablets. Ornidyl is the reference listed drug (RLD) for which the Applicant intends to rely upon the FDA's prior conclusions of safety and the approved product labeling to support its current application. The Applicant has

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performed an extensive review of DFMO safety and, while not necessarily required to support its reliance on Ornidyl as an RLD, the Applicant is including summaries of regulatory filings, scientific literature, and data from additional nonclinical studies (gathered by new right of reference (RoR) agreements) in an effort to provide the Agency with a highly comprehensive and relevant safety package for review as well as facilitating efforts in participating in Project Orbis for applications in countries where there is not an available reference product.

The Applicant has received right of reference (RoR) from Sanofi, current holder of US INDs [REDACTED] (b) (4)

[REDACTED] and NDA 19,879 (ORNIDYL Injection; IV eflornithine HCl), to all data and information on file under these applications. Sanofi has been able to provide the Applicant only with partial access to reports submitted under these applications and the Applicant is therefore unable to locate some source reports containing nonclinical data considered pertinent to the review of the planned NDA. However, such information was included in the original Ornidyl application, summarized in a prior DFMO Investigator's Brochure (dated August 24, 1987) and in FDA's Reviewer Approval Package for NDA 19,879 ([ORNIDYL 1990](#)); hence, the Applicant is providing summaries of these nonclinical data. The data source for these summaries will collectively be referenced as "Ornidyl". For ease of FDA's review, the 1987 DFMO Investigator Brochure, Ornidyl NDA Pharm/Tox Drug Approval Package, and the RoR letter from Sanofi are included in the application.

In addition to its reliance on Ornidyl as an RLD and access to source reports and summary documents via Sanofi's authorization, the Applicant also has obtained RoR from the National Cancer Institute to its DFMO IND [REDACTED] (b) (4) and certain available source reports relating to nonclinical investigations of DFMO. The Applicant anticipates that such NCI reports were included in the original Ornidyl application; but because the full contents of the prior application cannot be verified by Sanofi, the rights to reference NCI's IND has been separately obtained and the key reports made available to the Applicant through this route have also been directly included in the NDA for completeness and ease of review.

#### The FDA's Assessment:

FDA agrees with the Applicant's description of the US regulatory history of eflornithine. Eflornithine (Ornidyl) was FDA-approved in 1990 in an intravenously administered injectable formulation for West African Sleeping Sickness, but never marketed due to commercial viability reasons unrelated to safety or efficacy. Ornidyl is the reference listed drug intended to support the current 505(b)2 application, relying upon FDA's prior conclusions of nonclinical and clinical



safety data. Eflornithine (Vaniqa) topical cream was approved for the reduction of unwanted facial hair in women in 2000. There are no existing oncologic indications for eflornithine.

## **Summary of Presubmission/Submission Regulatory Activity**

### **The Applicant's Position:**

USWM, LLC (Applicant) is the Sponsor of the NDA and the Commercial IND, 144,875. The development of DFMO for HRNB was initiated under research IND (b) (4), held by Sponsor-Investigator, Dr. Giselle Sholler. For clarity, the term “Applicant” will be used to refer to USWM unless otherwise specified.

USWM has licensed the rights to the clinical data package supporting the NDA and continues to manage the development program in close collaboration with Dr. Sholler. Early guidance meetings relating to the design of studies and potential registration pathways were held between FDA and Dr. Sholler including a Type B meeting on November 18, 2015, and a Type C meeting on February 23, 2016.

The product received orphan drug designation (ODD) on November 22, 2017, issued to KC Pharma, the clinical trial material supply partner to Dr. Sholler prior to USWM's involvement. The ODD was transferred to the Applicant on September 19, 2020.

Dr. Sholler opened the Commercial IND 144,875 on July 21, 2019, which was transferred to the Applicant following execution of the license agreement between the parties.

The Applicant's DFMO program received Breakthrough Therapy Designation on April 3, 2020. An initial comprehensive multidisciplinary breakthrough therapy meeting (the “Initial Type B Meeting”) was held September 24, 2020, and a CMC-focused Type B meeting (the “CMC Type B Meeting”) was held October 15, 2020. As an outcome of these meetings, the Applicant and Agency agreed that a pre-NDA meeting should be requested in order to continue discussions on the plans for the application prior to its submission.

Prior to the preNDA meeting, the Agency advised that a statistical analysis plan (SAP) for efficacy outcome comparisons in the Applicant's Study 3b compared to external control database ANBL0032 should be submitted for FDA review and input. The Applicant submitted 3 draft versions of the SAP to the Agency (the first draft was discussed at an informal teleconference on February 19, 2021, the second draft was reviewed in a Type B meeting on May 3, 2021, and the third and final draft was reviewed in a Type B meeting on June 29, 2021). The SAP was finalized, and topline results along with the Applicant's proposals for nonclinical, clinical pharmacology, biopharmaceutics, clinical efficacy and clinical safety packages for the NDA



were proposed in a Type B preNDA meeting held on October 25, 2021. As a result of the preNDA meeting, the Applicant agreed to conduct a blinded independent central review of imaging for the primary treated analysis population in support of the Study 3b vs. ANBL0032 comparison in the planned efficacy package. A draft charter and statistical analysis plan for the BICR was reviewed by the Agency with recommendations provided in an Advice Letter dated January 13, 2022. Upon completion of the BICR, the Applicant submitted topline results to the Agency on August 26, 2022 to confirm the acceptability of the proposed clinical efficacy package. In an Advice Letter dated October 7, 2022, FDA agreed with the Applicant's plans to proceed with an NDA submission based on the planned efficacy package and further agreed with the Applicant's proposals for participation in the Real Time Oncology Review pilot program and Project Orbis.

**Table 1: Key FDA Interactions**

| Type of Meeting                         | Date               | Purpose                                                                                                                                             |
|-----------------------------------------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pre-USWM</b>                         |                    |                                                                                                                                                     |
| Type B Meeting                          | November 18, 2015  | Discuss a proposed Phase II study design and a potential registration pathway for DFMO in pediatric high-risk neuroblastoma                         |
| Type C Meeting                          | February 23, 2016  | Discuss the design of proposed pivotal studies and a potential registration pathway for DFMO in pediatric high-risk neuroblastoma.                  |
| <b>USWM</b>                             |                    |                                                                                                                                                     |
| BTD Initial Type B Meeting              | September 24, 2020 | Discuss clinical, nonclinical, biopharmaceutic and clinical pharmacology components of the DFMO program.                                            |
| BTD Initial Type B CMC Meeting          | October 15, 2020   | Discuss plans for an accelerated CMC development program and specific CMC-related questions regarding the nonclinical package proposed for the NDA. |
| Draft SAPv0.1 – Informal Teleconference | February 19, 2021  | Discuss Statistical Analysis Plan for the Comparison of Study 3b to ANBL0032 External Control Database to DFMO IND 144,875                          |
| Draft SAPv0.2 – Type B Meeting          | May 3, 2021        | Discuss the final proposal for the statistical analysis plan prior to finalization.                                                                 |

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| Type of Meeting                                   | Date                           | Purpose                                                                                                                                                                                                                                                            |
|---------------------------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Draft SAPv0.3 – Type B Meeting                    | June 29, 2021                  | Discuss the final proposal for the statistical analysis plan.                                                                                                                                                                                                      |
| preNDA Type B Meeting                             | October 25, 2021               | Discuss plans for application, request RTOR and Project Orbis participation                                                                                                                                                                                        |
| <b>Advice Letters and Informal Communications</b> |                                |                                                                                                                                                                                                                                                                    |
| Advice Letter                                     | January 13, 2022.              | Feedback on BICR Charter and SAP Addendum                                                                                                                                                                                                                          |
| Advice Request via Email Communications           | July 19, 2022 – August 8, 2022 | Details on comparison of ScinoPharm drug substance (planned commercial source) to (b) (4) drug substance (prior investigational source), and drug product stability plan, in response to (b) (4) decision not to maintain its DMF for eflornithine drug substance. |
| Information Request                               | September 2, 2022              | Additional information regarding BICR topline results provided August 26, 2022                                                                                                                                                                                     |
| Advice Letter                                     | October 7, 2022                | Agreement to participate in RTOR and Project Orbis, requests related to efficacy package to be addressed in NDA                                                                                                                                                    |

**The FDA’s Assessment:**

FDA generally agrees with the Applicant’s description of pre-NDA submission interactions, except as described below.

FDA originally recommended that a randomized controlled trial be conducted to evaluate the efficacy of eflornithine in the proposed patient population. In Meeting Minutes dated May 23, 2013, FDA considered Study 3(b) to be “exploratory”. In Meeting Minutes dated November 18, 2015, FDA stated that a “randomized controlled trial is required to scientifically assess the effect of DFMO as a maintenance therapy.” However, despite this early recommendation, a randomized controlled trial was not conducted.

The primary study supporting efficacy in this application, Study 3(b), was originally conducted under a research IND and subsequently transferred to the Applicant for further development. On November 22, 2017, Orphan Drug Designation was granted for the treatment of neuroblastoma.

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In 2018, a preliminary Breakthrough Therapy Designation (BTD) discussion was held with FDA to discuss the results of the pivotal trial, Study 3(b), compared to a historical control rate from COG Study ANBL0032; FDA recommended that the sponsor provide patient-level data from the studies intended to support the request, including Study ANBL0032. On April 3, 2020, FDA granted BTD for the treatment of pediatric patients with high-risk neuroblastoma with no evidence of disease or no active disease after first-line multiagent, multimodality therapy based on propensity score matched external control data from Study ANBL0032.

At the pre-NDA meeting in October 2021, FDA stated that the proposed comparison to Study ANBL0032 appeared acceptable, but determination of substantial evidence of effectiveness would be based on an overall assessment of the results of multiple independent analyses.

On March 29, 2023, the CDER Medical Policy and Program Review Committee (MPPRC) met to discuss NDA 215500. Refer to Section 9 for a summary of conclusions from the MPPRC meeting.

On April 24, 2023, FDA met with the Applicant to discuss concerns regarding the ability of the data included in the NDA to establish substantial evidence of effectiveness.

On October 4, 2023, an Oncologic Drug Advisory Committee (ODAC) meeting was held to discuss the evidence of effectiveness of eflornithine for the proposed indication. Refer to Section 9 of this review for details.

#### **4. SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY**

##### **4.1. Office of Scientific Investigations (OSI)**

Two clinical investigators (CI), Drs. Deanna Mitchell (site # 08), Keith August (site # 11), the sponsor-investigator, Dr. Giselle Sholler, the NDA sponsor, US WorldMeds, LLC, and the imaging CRO, (b) (4) were inspected. In addition, an Op-13 investigation was conducted for COG to ensure the reliability and acceptance of the transferred data to be used as an external control for Study NMTRC003b.

The above inspections did not reveal significant findings. Studies NMTRC003b and BCC001 appear to have been conducted adequately and the data generated by the inspected clinical investigators, the imaging CRO and submitted by the sponsor appear acceptable in support of the proposed indication.

The investigation of COG revealed no discrepancies between the data submitted to the NDA and the study data from ANBL0032 housed at COG that served as the external control for Study NMTRC003b. OSI found that data transfer procedures between COG and BCC were followed as planned. No discrepancies were noted between the Study ANBL0032 data database at COG and the data submitted to the NDA for 40 subjects and variables of interest identified by the review team. Specifically, the following were verified:

- COG's data collection, handling, and management processes and procedures
- Study ANBL0032 data storage, curation, aggregation, and transfer procedures
- The electronic platforms used to store and transfer the data are in compliance with applicable regulations and password protected
- Study ANBL0032 Data Transfer Agreements between COG and BCC/USWM procedures were followed
- Accuracy of the data submitted to the NDA for 40 subjects and variables of interest identified by the review team.

Refer to separate Clinical Inspection Summary, uploaded to DARRTs on April 19, 2023, for additional details.

{Eflornithine [DFMO]}

## 4.2. Product Quality

The Applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends approval of NDA 215500 for IWILFIN™ (eflornithine) tablets, for oral use.

The levels of excipients in eflornithine tablets are below the levels in previously approved oral products with the exception of Silicified Microcrystalline Cellulose ( (b) (4); 220 mg/eflornithine tablet). The amount of (b) (4) administered to humans at the maximum recommended daily dose of 8 eflornithine tablets (1536 mg/day free base) is 1760 mg/day (220 mg x 8 tablets), which is slightly higher than the maximum daily exposure of (b) (4) (1600 mg/day) given with generic (b) (4). The maximum daily exposure of microcrystalline cellulose in FDA approved oral products is 29,520 mg/day. Overall, based on the totality of data and the proposed clinical indication, there are no nonclinical safety concerns with the proposed levels of (b) (4) in the drug product.

The CMC review team consulted the nonclinical review team regarding the Applicant's proposed specification limit (b) (4) for three drug product impurities (b) (4). Based on a maximum clinical dose of 1536 mg/day free base, the daily intake for each impurity at the proposed specification of (b) (4) % would be (b) (4) mg/day, which rounds up to (b) (4) mg per ICH Q3B(R2) and thus exceeds the ICH Q3B(R2) qualification threshold of 0.2% or 3 mg total daily intake (TDI; whichever is lower). There is no nonclinical safety data to justify the proposed specification level of (b) (4) %. Thus, the CMC review team advised the Sponsor to lower the specification limits for these three impurities to be consistent with ICH Q3B(R2) or provide adequate justification (e.g., a toxicity risk assessment) for the proposed impurity level. The Applicant subsequently lowered the specification limit for (b) (4) to no more than (b) (4) %.

Refer to Integrated Quality Review uploaded to DARRTs on April 21, 2023 for additional details.

## 4.3. Clinical Microbiology

Refer to the CMC review uploaded to DARRTs on April 21, 2023.

#### **4.4. Devices and Companion Diagnostic Issues**

No device or companion diagnostic data were submitted in the application.

## 5. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

### 5.1. Executive Summary

#### The FDA's Assessment:

The Applicant's proposed indication for NDA 215500 is to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma (HRNB) who have completed multiagent, multimodality therapy. Neuroblastoma, an embryonal tumor arising from the sympathetic nervous system, is the most common extracranial solid tumor in children. HRNB is an aggressive form that occurs in approximately 50% of neuroblastoma patients and is often characterized by amplification of the *MYC* family member, *MYCN*. Following completion of therapy and remission, > 50% of children with HRNB relapse, and survival after relapse is poor (Herd et al. 2019). Ornithine decarboxylase (ODC), a direct transcriptional target of *MYCN* (Bello-Fernandez et al. 1993), is the rate limiting enzyme of polyamine biosynthesis. When polyamines (putrescine, spermidine, spermine) are elevated, they act as oncometabolites that contribute to cell hyperproliferation in neuroblastoma and other *MYC*-driven cancers (Casero et al. 2018). Overexpression of *ODC1*, the gene encoding ODC, is found in *MYCN*-amplified neuroblastoma and predicts poor therapeutic outcome (Hogarty et al. 2008). In addition, patients with tumors overexpressing *ODC1* exhibit inferior survival compared to those with low *ODC1* even when stratified by *MYCN* status (Hogarty et al. 2008, Bassiri et al. 2015, Geerts et al. 2010), suggesting a role for ODC in neuroblastoma independent of *MYCN*.

Eflornithine (DFMO) is an irreversible inhibitor of the enzyme ODC. To support submission of NDA 215500 for eflornithine tablets (IWILFIN) under the 505(b)(2) pathway, the Applicant is relying on published literature references and FDA's previous findings of nonclinical safety for the reference listed drug (RLD) Ornidyl [intravenous (IV) eflornithine HCl, NDA 19879]. The Applicant also submitted pharmacology data and embryo-fetal development and carcinogenicity studies to the NDA. To support the use of eflornithine for the proposed indication, the Applicant submitted published scientific literature references and unpublished pharmacology data evaluating the role of eflornithine in the prevention and growth of neuroblastoma. In addition, the Applicant is relying on FDA's previous findings of mechanism of action from Ornidyl. Based on the mechanism of action, the established pharmacological class of eflornithine is an ornithine decarboxylase inhibitor. To facilitate FDA's review and in recognition of eflornithine's limited utility as an anti-cancer agent over several decades of clinical investigation, the FDA nonclinical team also conducted an independent scientific literature-based assessment evaluating the effect of eflornithine/DFMO in neuroblastoma. In general, most of the published literature identified in the FDA's literature-based assessment were consistent with the studies and published literature provided by the Applicant, with both supporting the cytostatic mechanism of

action of eflornithine in neuroblastoma.

Published literature has explored the in vitro and in vivo role of eflornithine in neuroblastoma. Wallick et al. (2005) reported that incubation of *MYCN*-amplified neuroblastoma cell lines with 5 mM (5000  $\mu$ M) eflornithine inhibited ODC activity and depleted polyamine pools, leading to G1 cell cycle arrest and inhibition of in vitro neuroblastoma cell growth. Incubation with  $\geq 2.5$  mM (2500  $\mu$ M) eflornithine reduced the in vitro proliferation of *MYCN*-amplified and *MYCN* non-amplified neuroblastoma cells, although *MYCN* non-amplified cells were less sensitive to eflornithine and higher drug concentrations were generally needed to inhibit proliferation of these cell lines (Hogarty et al. 2008). Eflornithine concentrations shown to induce in vitro anti-proliferative activity in neuroblastoma cell lines are generally much higher than those achievable at the intended clinical dose [clinical  $C_{\max}$  of 20.9  $\mu$ g/mL ( $\sim 88$   $\mu$ M) at the recommended human dose of  $1500 \pm 500$  mg/m<sup>2</sup>/day eflornithine HCl monohydrate ( $1152 \pm 384$  mg/m<sup>2</sup>/day free base)]. Eflornithine does not bind substantially to human plasma proteins, so total  $C_{\max}$  values are relevant.

The miRNA binding protein LIN28 is an oncogenic driver in cancer stem cells (Zhou et al. 2013). In cancer, LIN28A/B activation results in post-transcriptional downregulation of the tumor suppressor Let-7, which leads to overexpression of oncogenic targets such as *MYC* (Balzeau et al. 2017). Specifically, the LIN28/Let-7 pathway regulates cellular signaling involved in driving the epithelial/mesenchymal transition (EMT) and affects cellular processes including the regulation of cancer stem cells and glycolytic metabolism. LIN28B also blocks neuronal differentiation in neuroblastoma cells (Balzeau et al. 2017), and high *LIN28B* expression has been reported to be associated with worse survival outcomes in patients with neuroblastoma (Diskin et al. 2012). Investigators have shown that downregulation of polyamines results in decreased hypusination and activation of the translation initiation factor eIF-5A, thereby leading to reduced LIN28 expression (Paz et al. 2014). Consistent with this, Lozier et al. (2014) demonstrated that incubation with eflornithine reduced LIN28B and *MYCN* protein levels; increased Let-7 miRNA levels; and inhibited in vitro neurosphere formation in high *LIN28B/MYCN*-expressing neuroblastoma cells. Since in vitro neurosphere formation requires the presence of cancer stem cells within wells, these data suggest that eflornithine reduces neural stem cell numbers. Lozier et al. (2014) also showed that treatment with 2% eflornithine in the drinking water reduced in vivo glycolytic metabolism in *LIN28B/MYCN*-expressing neuroblastoma xenografts implanted in mice. Alternatively, eflornithine did not substantially affect mean tumor volume in this xenograft model compared to vehicle control. Overall, treatment with eflornithine restored balance to the LIN28/Let-7 axis, thus reducing glycolytic metabolism and neurosphere formation in neuroblastoma (Lozier et al. 2014).

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In publications identified by the FDA-initiated independent scientific literature-based assessment, two separate research groups evaluated the effect of eflornithine on tumor initiation and progression using transgenic mice that overexpress the human *MYCN* transgene (*TH-MYCN*) in neural crest cells. Homozygous (*TH-MYCN* +/+) mice and to a lesser extent hemizygous (*TH-MYCN* +/-) mice develop spontaneous neuroblastoma that recapitulates the disease (Weiss et al. 1997) and thus, this well-established transgenic mouse model of neuroblastoma is clinically relevant for the indication. Treatment with 1% eflornithine from birth onward increased tumor-free survival in homozygous (*TH-MYCN* +/+) mice and prevented tumor formation in ~84% of treated hemizygous (*TH-MYCN* +/-) mice (Hogarty et al. 2008). In addition, treatment with 1% eflornithine beginning on Day 25 after tumor onset slightly delayed tumor progression and extended tumor-free survival in *TH-MYCN* +/+ mice compared to controls. Rounbehler et al. (2009) also demonstrated that treatment with 1% eflornithine delayed the onset and incidence of neuroblastoma formation in *TH-MYCN* mice and improved survival compared to controls.

The Applicant also submitted unpublished pharmacology data from the laboratory of Dr. Giselle Sholler to support the proposed role of eflornithine in neuroblastoma initiation and progression. Incubation with single agent eflornithine at concentrations up to 2500  $\mu\text{M}$  did not substantially affect in vitro cell viability or apoptosis in five human neuroblastoma cell lines; however, incubation with eflornithine induced concentration-dependent in vitro cellular senescence (i.e., stable cell cycle arrest) in *MYCN*-amplified and *MYCN* non-amplified neuroblastoma cells. Statistically significant findings were generally seen at eflornithine concentrations  $\geq 500 \mu\text{M}$ , but effects were observed in some cell lines beginning at concentrations as low as 50  $\mu\text{M}$ . These data suggest that eflornithine has the potential to induce cellular senescence in neuroblastoma cells at clinically relevant concentrations (i.e., clinical  $C_{\text{max}}$  of  $\sim 88 \mu\text{M}$  at the recommended human dose of  $1152 \pm 384 \text{ mg/m}^2/\text{day}$ ). According to Kumari and Jat (2021), cellular senescence is associated with stable proliferation arrest and can prevent proliferation of potentially cancerous cells. Further, senescent cells are unresponsive to mitogenic stimuli but are still metabolically active. Thus, the ability of eflornithine to induce senescence in neuroblastoma cells suggest a potential role for eflornithine in preventing neuroblastoma relapse and tumorigenesis. In keeping with this, eflornithine reduced in vitro neurosphere formation at concentrations  $\geq 500 \mu\text{M}$  and  $\geq 100 \mu\text{M}$  in *MYCN*-amplified and *MYCN* non-amplified neuroblastoma cells, respectively. Although there are discrepancies in the literature regarding the extent of eflornithine activity in *MYCN*-amplified versus *MYCN* non-amplified neuroblastoma cells (Hogarty et al. 2008, Rounbehler et al. 2009, Lozier et al. 2014), the data from Dr. Sholler's laboratory and Koomoa et al. (2013) suggest a role for eflornithine in both subsets of neuroblastoma, which is consistent with clinical data from Study 3(b) suggesting that the observed treatment effect is not limited to patients with *MYCN* amplification.

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To further evaluate the cytostatic action of eflornithine in mouse models, the Applicant used extreme limiting dilution analysis (ELDA), an established method to measure the frequency of tumor-initiating cells within a tumor cell population (den Hollander et al. 2022). In an ELDA experiment that relevantly models the proposed clinical indication, limited numbers of *MYCN*-amplified neuroblastoma cells were injected in nude mice and treatment with 2% eflornithine was initiated in the drinking water beginning on the day of cell injection (i.e., prior to tumor formation). Treatment with 2% eflornithine (equivalent to at least 6900 mg/m<sup>2</sup>/day free base) reduced the rate of tumor formation and improved event-free survival in mice. Western blot analysis confirmed that eflornithine reduced LIN28B and *MYCN* protein expression in tumors compared to untreated controls, indicating pharmacodynamic evidence of on-target eflornithine activity. Notably, eflornithine also reduced the *in vivo* expression of SOX2, a marker of EMT, suggesting eflornithine is driving cells towards a more differentiated state. The effect of eflornithine was not evaluated in *MYCN* non-amplified tumor models using similar tumor prevention study designs. Overall, available pharmacology data suggest that eflornithine is cytostatic rather than cytotoxic and targets tumor initiating cells. Although published literature indicates that eflornithine may inhibit neuroblastoma cell proliferation at high concentrations unlikely to be clinically achievable, the totality of nonclinical data suggests that eflornithine's primary mechanism of action as a single agent in neuroblastoma is suppression of tumor-initiating cells, thereby preventing or delaying tumor formation, rather than inhibition of established tumor growth. Eflornithine was developed over 40 years ago (LoGiudice et al. 2018), and the nonclinical findings described above are consistent with results from previous clinical studies focusing on tumor growth inhibition rather than prevention. Although there is no available data evaluating the *in vivo* activity of eflornithine in tumor prevention mouse models of *MYCN* non-amplified neuroblastoma, *in vitro* data showed activity in both *MYCN*-amplified and *MYCN* non-amplified cells. The mechanism of action of eflornithine in *MYCN* non-amplified neuroblastoma has not been fully elucidated; however, *MYCN* gene signatures or elevated ODC1 levels have been identified in high-risk tumors without *MYCN* amplification (Valentijn et al. 2012, Hogarty et al. 2008). Further, Bassiri et al. (2015) hypothesize that polyamine depletion may affect the tumor microenvironment and subsequently modulate the immune response to prevent tumor proliferation.

Overall, the totality of nonclinical pharmacology data supports a mechanism by which eflornithine could prevent or delay HRNB relapse in patients who are in remission. As described in Section 1 of this review, under certain circumstances, FDA can conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness. Ultimately, the FDA review team concluded that strong nonclinical mechanistic support and data from relevant animal models of disease provide sufficient confirmatory evidence to substantiate the results of the single externally controlled trial in the setting of a rare

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disease with established pathophysiology. Eflornithine targets drivers of neuroblastoma pathophysiology and tumor-initiating cells. In addition, there is confirmatory evidence from two well-established, relevant animal models of neuroblastoma exhibiting that eflornithine prevents or delays tumor formation in mice who have no initial evidence of disease. Importantly, the ELDA and *TH-MYCIN* transgenic mouse models evaluate clinically relevant endpoints and provide pharmacodynamic evidence of on-target eflornithine activity. Although doses used in these mouse studies are approximately 2- to 9-fold higher than the recommended human dose, mice were given 1-2% eflornithine in the drinking water, so the estimated mouse doses are based on typical average water consumption and thus may vary amongst individual animals. Overall, the nonclinical pharmacology data submitted by the Applicant supports a cytostatic mechanism of action in neuroblastoma and is further supported by published data from other independent investigators.

Considering the strength of the nonclinical data, the potential for nonclinical mechanistic data to contribute to the confirmatory evidence needed to establish substantial evidence of effectiveness for this Application was discussed with an Advisory Committee at a meeting held on October 4, 2023. For further description of the ODAC meeting, see Section 9 of this review.

The Applicant is relying on FDA's previous findings of nonclinical pharmacokinetics (PK/ADME) from the RLD Ornidyl, including oral studies. The Applicant established a scientific bridge between oral eflornithine tablets (IWILFIN) and the IV administered RLD Ornidyl (NDA 19879) using 52-week oral toxicology studies in rats and Beagle dogs as described in Crowell et al. (1994). The data described in this literature publication is scientifically relevant to the proposed product because the studies used the same active pharmaceutical ingredient (eflornithine) as contained in the applicant's drug product, and the doses used in the reported animal studies are scientifically relevant to the proposed human dose. To further support continuous daily oral dosing of eflornithine, the Applicant submitted study reports for oral embryofetal development studies in rats and rabbits and 104-week oral carcinogenicity studies in mice and rats. The Applicant is relying on FDA's previous findings of safety for the RLD Ornidyl for the genotoxicity data needed to support approval of eflornithine tablets (IWILFIN) in the current indication.

The GLP status of the 52-week oral repeat-dose toxicology studies is unknown because they are considered legacy studies; however, the FDA review team considered the study designs adequate for review based on the methods and results described in Crowell et al. (1994). Once daily oral administration of up to 1600 mg/kg (9600 mg/m<sup>2</sup>) eflornithine in rats or up to 200 mg/kg (4000 mg/m<sup>2</sup>) eflornithine in dogs did not result in drug-related mortality, which exceeds the

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recommended human dose of  $1152 \pm 384$  mg/m<sup>2</sup>/day free base based on body surface area (BSA). Toxicokinetics were not conducted in the 52-week toxicology studies, so exposure comparisons based on AUC could not be made with the recommended human dose of IWILFIN. In the rat study, treatment with  $\geq 800$  mg/kg (4800 mg/m<sup>2</sup>) eflornithine via oral gavage resulted in skin toxicity (alopecia, abrasions, abscesses, and histologic necrotic or chronic dermatitis) and liver necrosis. Additional findings in rats included histologic glandular inflammation in the stomach; reduced mean body weight and food consumption; increased mean platelets and leukocytes; and decreased mean hemoglobin, glucose, and urinary pH compared to controls. In the dog study, treatment with  $\geq 50$  mg/kg (1000 mg/m<sup>2</sup>) eflornithine via oral capsules resulted in skin toxicity (alopecia, skin hyperkeratosis), thickened conjunctiva, mucoid conjunctivitis, and cystic crypts in the duodenum. Additional findings in dogs included reduced body weight; increased prothrombin time; and decreased mean cholesterol, total protein, and red blood cell (RBC) parameters compared to controls. Consistent with nonclinical findings, anemia has been seen clinically with oral eflornithine and rash and alopecia were seen in some patients given eflornithine. Hearing loss, which is included as a warning in the IWILFIN label, was not specifically evaluated in nonclinical studies.

Stand-alone fertility studies were not submitted to the NDA. Although the proposed indication is for pediatric patients with HRNB who have completed therapy and have no evidence of disease/no active disease, at least half of patients relapse after up-front therapy, and approximately 80% of high-risk relapses occur within 2 years of diagnosis (Basta et al. 2016). After relapse, survival is poor (i.e., 5-year overall survival < 10%). Thus, taking into account the totality of nonclinical data and the high and rapid rate of HRNB recurrence, the proposed patient population is covered by ICH S9 and a stand-alone fertility study is not needed to support marketing for the proposed indication.

To further support continuous oral dosing, the Applicant submitted GLP-compliant 104-week oral carcinogenicity studies in B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> mice and Fischer-344 rats for which they have the right to reference. The results of these studies were previously reviewed by Dr. Alexander H. Putman and discussed with the FDA Executive Carcinogenicity Assessment Committee (ECAC) under another NDA. These carcinogenicity studies were conducted over 20 years ago to support the development of eflornithine as a chemopreventative agent, and the ECAC was not involved in the design of either study. Plasma concentrations were measured in the carcinogenicity studies, but AUC values were not determined. In the 104-week mouse study, animals received eflornithine in the diet at doses of 100, 300, or 1000 mg/kg/day (approximately 2.2 times the clinical C<sub>max</sub> of 20.9 µg/mL at the recommended human dose of  $1152 \pm 384$  mg/m<sup>2</sup>/day). In the 104-week rat study, animals received eflornithine via oral gavage at doses of 150, 300, or 600 mg/kg/day (approximately 10.5 times the clinical C<sub>max</sub> of 20.9 µg/mL at the recommended human dose of  $1152 \pm 384$  mg/m<sup>2</sup>/day). There were no eflornithine-related neoplasms in mice or

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rats under the conditions tested; however, FDA did not conduct confirmatory statistical analyses. The ECAC did not concur that the 104-week carcinogenicity study in mice or the data from male rats in the 104-week rat study were adequate; thus, Section 13.1 of the proposed IWILFIN label was updated to only include the lack of drug-related neoplasms in female rats.

The Applicant submitted GLP-compliant embryo-fetal development studies in rats and New Zealand White rabbits for which they have the right to reference. Toxicokinetics were not assessed in either study, so animal to human comparisons are provided based on BSA dose. Once daily administration of eflornithine via oral gavage to pregnant rats during the period of organogenesis (gestation Days 6 to 17) was not teratogenic and did not affect embryo-fetal survival at doses up to 200 mg/kg/day [1200 mg/m<sup>2</sup>/day; approximately 0.8-2 times the recommended human dose of 1152 ± 384 (768-1536) mg/m<sup>2</sup>/day based on BSA]. Treatment with 200 mg/kg/day eflornithine resulted in a statistically significant 10% decrease in mean fetal body weight compared to controls and an increase in the incidence of skeletal variations (presence of a 14th rudimentary rib, 14th full rib, and 27th presacral vertebrae). In the rabbit study, once daily administration of eflornithine via oral gavage to pregnant rabbits during the period of organogenesis (gestation Days 7 to 20) was not teratogenic at doses up to 135 mg/kg/day (1620 mg/m<sup>2</sup>/day; approximately 1-2 times the recommended human dose of 1152 ± 384 mg/m<sup>2</sup>/day based on BSA). Treatment with eflornithine resulted in abortions in one rabbit dosed with 15 mg/kg/day (180 mg/m<sup>2</sup>/day; approximately 0.1-0.2 times the recommended human dose of 1152 ± 384 mg/m<sup>2</sup>/day based on BSA) and one rabbit dosed with 135 mg/kg; however, there were not similar findings at the mid dose level of 45 mg/kg/day. Although this finding did not appear to be dose-dependent, it did occur at the high dose level, so a relationship to eflornithine cannot be definitively ruled out. Treatment with 135 mg/kg eflornithine resulted in reduced gravid uterine weight accompanied by a slight decrease in implantation sites; increased pre-implantation and post-implantation loss; increased early resorptions; and an up to 17% decrease in mean fetal body weights compared to controls. Although the increases in pre- and post-implantation losses were not statistically significant compared to controls, additional analyses of individual data demonstrated a higher magnitude of pre- and post-implantation loss in rats dosed with 135 mg/kg eflornithine compared to controls. As a result, these effects were considered drug-related and were added to the proposed IWILFIN label. There was also a slight increase in unossified talus (skeletal variation) at 135 mg/kg compared to controls; however, historical control data from the conducting laboratory were not provided for comparison.

In addition, there was clear evidence of embryoletality in non-GLP oral dose range-finding embryofetal development studies at higher dose levels of eflornithine. Rats exhibited increased early resorptions and post-implantation loss compared to controls concomitant with decreased numbers of viable fetuses beginning at 300 mg/kg/day (1800 mg/m<sup>2</sup>/day; approximately 1-2 times the recommended human dose of 1152 ± 384 mg/m<sup>2</sup>/day based on BSA) eflornithine, with 100%

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post-implantation loss and no viable fetuses occurring at  $\geq 800$  mg/kg/day (4800 mg/m<sup>2</sup>/day; approximately 3-6 times the recommended human dose of  $1152 \pm 384$  mg/m<sup>2</sup>/day based on BSA). Rabbits exhibited increased early resorptions, post-implantation loss, and dead fetuses and decreased live fetuses beginning at 240 mg/kg/day (2880 mg/m<sup>2</sup>/day; approximately 2-4 times the recommended human dose of  $1152 \pm 384$  mg/m<sup>2</sup>/day based on BSA), with 100% post-implantation loss and no viable fetuses occurring at 500 mg/kg/day (6000 mg/m<sup>2</sup>/day; approximately 4-8 times the recommended human dose of  $1152 \pm 384$  mg/m<sup>2</sup>/day based on BSA). Thus, the pharmacology/toxicology team included embryofetal development animal data from the oral studies in Section 8.1 and a warning for embryo-fetal toxicity in the label for IWILFIN. Consistent with the recommendations for teratogenic or embryo-lethal but non-genotoxic drugs described in the FDA Guidance for Industry Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations, and considering the eflornithine terminal half-life of 3.5 hours, FDA recommends advising males and females of reproductive potential to use effective contraception during treatment with IWILFIN and for 1 week after the last dose. The Applicant did not evaluate the presence of eflornithine in milk; however, because of potential adverse effects of IWILFIN on a breastfeeding child, the review team recommends advising patients not to breastfeed during treatment with IWILFIN and for 1 week after the last dose.

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of IWILFIN for reducing the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy. The FDA nonclinical team recommends approval with the use of nonclinical mechanistic data as confirmatory evidence for establishing substantial evidence of effectiveness for this Application. The underlying pathophysiology of the *ODC* and *MYCN* pathways in neuroblastoma is well understood, creating a setting in which it is appropriate to consider the possibility of leveraging mechanistic data as confirmatory evidence. The review team carefully reviewed data submitted by the Applicant and identified in an independent FDA literature search and found it to provide strong mechanistic support, as the drug directly targets these underlying critical oncogenic pathways in this disease. In particular, the review team finds the mechanistic evidence provided by two well-established, relevant animal models of neuroblastoma which showed that eflornithine prevents or delays tumor formation in mice who have no initial evidence of disease to be compelling and appropriate as confirmatory evidence of eflornithine's effectiveness.

## 5.2. Referenced NDAs, BLAs, DMFs

### The Applicant's Position:

The Applicant has received right of reference (RoR) from Sanofi, current holder of US  
INDs

(b) (4)

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(b) (4) and NDA 19,879 (ORNIDYL Injection; IV eflornithine HCl), to all data and information on file under these applications. Sanofi has been able to provide the Applicant only with partial access to reports submitted under these applications and the Applicant is therefore unable to locate some source reports containing nonclinical data considered pertinent to the review of the planned NDA. However, such information was included in the original Ornidyl application, summarized in a prior DFMO Investigator's Brochure (dated August 24, 1987) and in FDA's Reviewer Approval Package for NDA 19,879 ([ORNIDYL 1990](#)); hence, the Applicant is providing summaries of these nonclinical data. The data source for these summaries will collectively be referenced as "Ornidyl".

In addition to its reliance on Ornidyl as an RLD and access to source reports and summary documents via Sanofi's authorization, the Applicant also has obtained RoR from the National Cancer Institute to its DFMO IND (b) (4) and certain available source reports relating to nonclinical investigations of DFMO. The Applicant anticipates that such NCI reports were included in the original Ornidyl application; but because the full contents of the prior application cannot be verified by Sanofi, the rights to reference NCI's IND has been separately obtained and the key reports made available to the Applicant through this route have also been directly included in the NDA for completeness and ease of review.

#### The FDA's Assessment:

The FDA acknowledges the Applicant's position. The Applicant submitted full study reports for embryofetal development studies and carcinogenicity studies.

### **5.3. Pharmacology**

#### Primary pharmacology

DFMO (Difluoromethylornithine, Eflornithine) is a specific, enzyme-activated, irreversible inhibitor of ornithine decarboxylase (ODC), a key enzyme in mammalian polyamine biosynthesis. Polyamines are also essential for neoplastic transformation, making inhibition of ODC activity an attractive target for cancer chemoprevention. Inhibition of polyamine synthesis by DFMO results in growth arrest of a number of malignant and non-malignant mammalian cells and has been shown to inhibit the promotion and progression phases of carcinogenesis. DFMO inhibits cell growth of various types of cancer cells, including neuroblastoma (NB).



{Eflornithine [DFMO]}

**Table 2: Kinetic Parameters of DFMO Binding Enzymatic Binding and ODC Inhibition**

|          | <b>K<sub>inact</sub>(min<sup>-1</sup>)</b> | <b>S.E.M.</b> | <b>K<sub>D</sub> (μM)</b> | <b>S.E.M.</b> |
|----------|--------------------------------------------|---------------|---------------------------|---------------|
| D/L-DFMO | 0.15                                       | ±0.03         | 2.2                       | ±0.4          |

Described in Qu N, Ignatenko NA, Yamauchi P, Stringer DE, Levenson C, Shannon P, Perrin S, Gerner EW. Inhibition of human ornithine decarboxylase activity by enantiomers of difluoromethylornithine. *Biochem J.* 2003 Oct 15;375(Pt 2):465-70.

Additionally, DFMO has shown selective targeting of cancer stem cells (CSCs). In NB, the CD114+ subpopulation has been defined as CSCs, which drives tumor relapse and chemoresistance ([Agarwal 2015](#), [Hsu 2013](#)). Beat Childhood Cancer's (BCC) recent work utilizing *in vivo* and *in vitro* models of NB suggest that CSCs may be selectively targeted by DFMO via its inhibition of ODC. Treatment of MYCN-amplified BE(2)C and non-MYCN amplified CHLA90 NB cell lines demonstrated that DFMO preferentially targets CD114+ cells at physiologic doses, resulting in both loss of CD114 viability and induction of senescence.

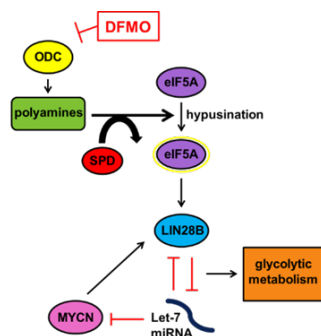
***FDA Additional Comment:*** The FDA sent an Information Request to clarify what the data source/reference is for the BCC data described above. The Applicant subsequently cited Avequin et al. (2018) for these data.

Preclinical models provided foundational support for clinical evaluations of DFMO in the neuroblastoma patient population. The earliest work with DFMO in HRNB focused on patients with active relapsed/refractory disease ([Saulnier Sholler, 2015](#)), and provided initial evidence of effectiveness. The initial efficacy and good tolerability supported by this early published work, led to the clinical program which evaluated DFMO as a therapy for HRNB patients achieving remission to reduce the risk of relapse.

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{Eflornithine [DFMO]}

**Figure 1: Proposed Pathway for DFMO Effects on LIN28/Let-7 Axis and Glycolytic Metabolism in NB**Adapted from illustration in [Lozier, 2014](#)

In vitro studies have shown that DFMO irreversibly inhibited ODC activity in rat liver homogenates at concentrations  $> 0.01$  mM and resulted in antiproliferative effects in cell cultures of normal or neoplastic origins, e.g., in HTC cells (0.1 mM). Additionally, it produced a dose dependent inhibition of growth and dissolution of spheroids in cultured human oat carcinoma cells (0.05-0.5 mM) with similar effects in other neoplastic cell types ([ORNIDYL 1990](#), [Pegg 1987](#), [Poulin 1992](#)). Treatment of MYCN-amplified human neuroblastoma (NB) cells with DFMO induced G1 cell cycle arrest without causing apoptosis ([Wallick 2005](#)). In in vivo studies in rats, DFMO after single (12.5-400 mg/kg, i.p.) or repeat/continuous dose administration (dose levels ranging from 100 mg/kg, i.p., q12h to 200 mg/kg, i.p., q6h) resulted in dose related decreases in ODC activity in thymus, testes and prostate, with a greater effect in prostate ([ORNIDYL 1990](#)). Other actions of DFMO include blockade of putrescine biosynthesis in trypanosomes in mice infected with *T.b. brucei* or *T.b. rhodesiense*. Additionally, DFMO has been shown to be protective against coccidial infections in chickens ([ORNIDYL 1990](#)).

**FDA Additional Comment:** HTC cells are rat hepatoma tissue culture cells.

Central to the Applicant's initial registration program as a chemopreventative agent in HRNB patients in remission (sometimes described as no evidence of disease/no active disease [NED/NAD]), DFMO has shown selective targeting and suppression of cancer stem cells (CSCs). In NB, the CD114+ subpopulation has been defined as CSCs, which have been shown to drive tumor relapse and chemoresistance ([Agarwal 2015](#), [Hsu 2013](#)). Beat Childhood Cancer's (BCC) recent work utilizing *in vivo* and *in vitro* models of NB suggest that CSCs may be selectively targeted by DFMO through its inhibition of ODC. Treatment of MYCN-amplified BE(2)C and non-MYCN amplified CHLA90 NB cell lines demonstrate that DFMO preferentially targets

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{Eflornithine [DFMO]}

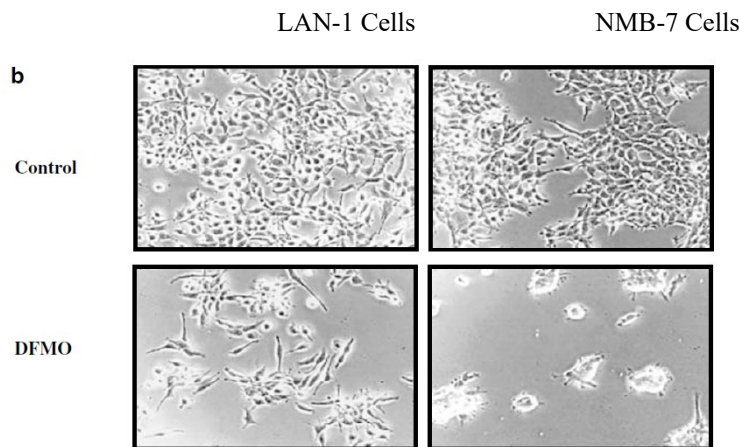
CD114+ cells at physiologic doses, resulting in both loss of CD114+ cell viability and induction of senescence. DFMO also reduced neurosphere formation and tumor initiating capability in xenograft mice models and decreased the prevalence of tumor initiating cells as measured by extreme limiting dilutions analysis (ELDA). These results suggest that DFMO has high utility in the prevention of tumor initiation and relapse of NB through targeted inhibition of CSCs and induction of senescence (Avequin 2018).

#### The FDA's Assessment:

The FDA acknowledges the Applicant's summary of nonclinical data from published literature references; see the FDA additional comments interspersed above. Literature references describing clinical studies (e.g., Saulnier Sholler et al. 2015) were not reviewed by the pharmacology/toxicology team and thus the results from these publications were not confirmed. A more in-depth review of findings from literature references cited by the Applicant and additional relevant literature references found by the FDA Reviewer are summarized below.

Wallick et al. (2005) demonstrated that incubation of *MYCN*-amplified LAN-1 and NMB-7 neuroblastoma cell lines with 5 mM (5000  $\mu$ M) eflornithine (DFMO) for 2-3 days inhibited ODC activity and depleted polyamine pools, leading to G1 cell cycle arrest and inhibition of neuroblastoma cell growth (Figure 2). Further, eflornithine-induced G1 cell cycle arrest was mediated by increased endogenous levels of cdk inhibitor protein p27Kip1 and corresponding Rb hypophosphorylation. Incubation with eflornithine also reduced *MYCN* protein levels in neuroblastoma cell lines (data not shown).

**Figure 2: Effect of 5 mM Eflornithine on *MYCN*-amplified Neuroblastoma Cell Growth**



Representative light micrographs (Figure excerpted from Wallick et al. 2005)

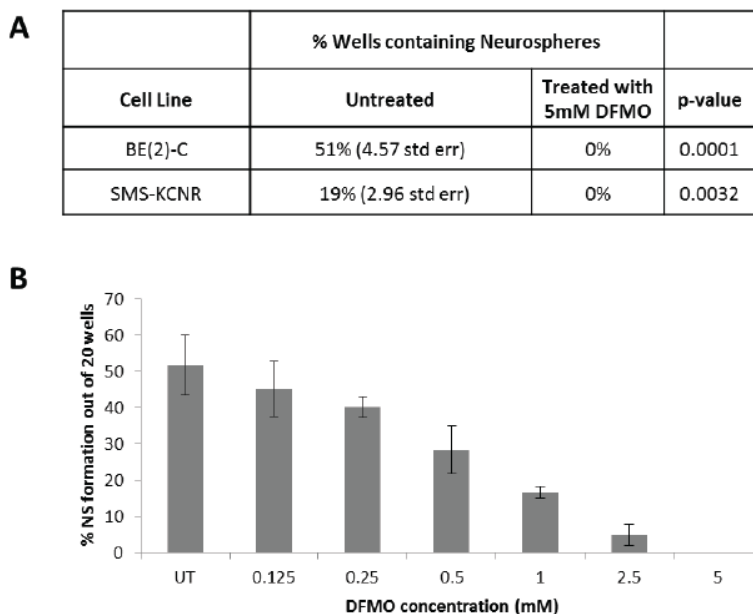
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{Eflornithine [DFMO]}

The Applicant's Figure 1 shown in the Applicant's Position was adapted from Lozier et al. (2014) and depicts the proposed pathway for eflornithine effects on the LIN28/Let-7 axis and glycolytic metabolism in neuroblastoma; however, the Applicant did not describe the data or provide text in their Position to support this pathway. ODC converts the polyamine precursor ornithine into the polyamine putrescine, which is then converted to the polyamines spermidine and spermine. Spermidine is a substrate needed for hypusination, a post-transcriptional modification of the translation initiation factor eIF-5A (Landau et al. 2010). eIF-5A is a direct regulator of the LIN28/Let-7 pathway (Paz et al. 2014), which regulates cellular signaling involved in driving the epithelial-mesenchymal transition (EMT; Balzeau et al. 2017). The miRNA binding protein LIN28 is an oncogenic driver in neuroblastoma and Let-7 is a miRNA that acts as a tumor suppressor. LIN28 and Let-7 interact via a double negative feedback loop (Viswanathan et al. 2009), and the LIN28/Let-7 pathway affects cellular processes including the regulation of cancer stem cells and glycolytic metabolism. High *LIN28B* expression has been reported to be associated with worse survival outcomes in patients with neuroblastoma (Diskin et al. 2012).

In Lozier et al. (2014), incubation with 5 or 10 mM eflornithine reduced LIN28B and MYCN protein levels and increased Let-7 miRNA levels in high *LIN28B/MYCN*-expressing BE(2)-C neuroblastoma cells and high *MYCN*/moderate *LIN28B*-expressing SMS-KCNR neuroblastoma cells (data not shown). Investigators conducted neurosphere assays using BE(2)-C cells to isolate, expand, and calculate the frequency of neural stem cells. Incubation with eflornithine resulted in a concentration-dependent decrease in neurosphere formation using BE(2)-C cells (Figure 3), suggesting eflornithine can reduce neural stem cell numbers. The IC<sub>50</sub> value was not calculated, but this Reviewer estimated it to be ~0.75 mM (750 µM). Incubation with 5 mM eflornithine also reduced neurosphere formation using SMS-KCNR cells.

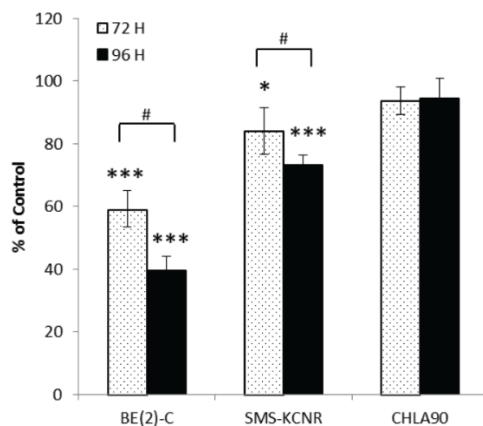
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**Figure 3: Effect of Eflornithine on Neurosphere Formation in Neuroblastoma Cells**

B: BE(2)-C cells; UT = Untreated; NS = Neurosphere (Figure excerpted from Lozier et al. 2014)

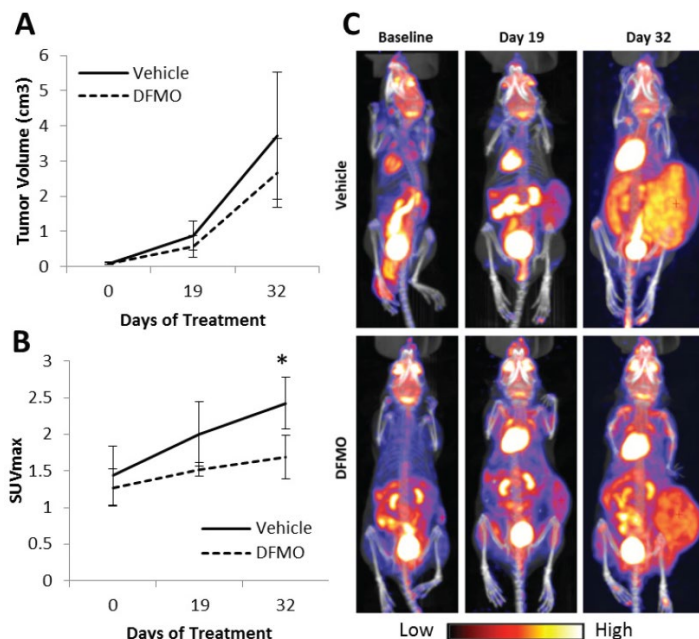
Next, investigators used combination ATP/cell assays to measure ATP levels and cell number (Lozier et al. 2014). Incubation with 10 mM eflornithine reduced the ratio of total ATP over total cell number (ATP/cell) in BE(2)-C and SMS-KCNR cells in a time-dependent manner. Eflornithine decreased ATP/cell up to 60.5% and 26.9% compared to untreated control in BE(2)-C and SMS-KCNR cells, respectively. Eflornithine did not substantially affect the ATP/cell level in CHLA90 neuroblastoma cells, which express low levels of LIN28B and MYCN. These data suggest that neuroblastoma cell lines with high *LIN28B* and *MYCN* gene expression are more sensitive to eflornithine.

**Figure 4: Effect of 10 mM Eflornithine on ATP/Cell Ratios in Neuroblastoma Cells Compared to Untreated Control**



\*,  $P < 0.05$ ; \*\*\*,  $P < 0.001$  compared to untreated control. #,  $P < 0.05$  comparing 72 vs. 96 hours  
(Figure excerpted from Lozier et al. 2014)

Since elevated glycolytic metabolism is common in many cancers, including neuroblastoma, investigators evaluated the effect of eflornithine on in vivo glycolytic metabolism by measuring PET activity (SUVmax) in female nude mice bearing *MYCN*-amplified SMS-KCNR xenografts (Lozier et al. 2014). Mice (4/group) were injected subcutaneously (SC) with SMS-KCNR cells in the right flank. When mean tumor volume was  $\sim 0.2 \text{ cm}^3$ , mice began receiving vehicle or 2% eflornithine (4 g in 200 mL; 20 mg/mL) in drinking water. PET/CT scans were conducted at baseline and 19 and 32 days after treatment initiation. Mice were fasted for at least 6 hours prior to 2'-deoxy-2'- $^{18}\text{F}$ -fluoro-D-glucose ( $^{18}\text{F}$ -FDG) injection for PET scans. Average tumor volume was quantified using CT scans. Treatment with eflornithine did not significantly affect mean tumor volume compared to vehicle control; however, there was a statistically significant decrease in SUVmax in mice treated with eflornithine compared to vehicle control (Figure 5), suggesting that eflornithine reduces glycolytic metabolism in neuroblastoma xenografts expressing high levels of *MYCN* and moderate levels of *LIN28B*.

**Figure 5: Effect of Eflornithine on Tumor Volume and  $^{18}\text{F}$ -FDG Uptake in Mice Bearing SMS-KCNR Neuroblastoma Xenografts**

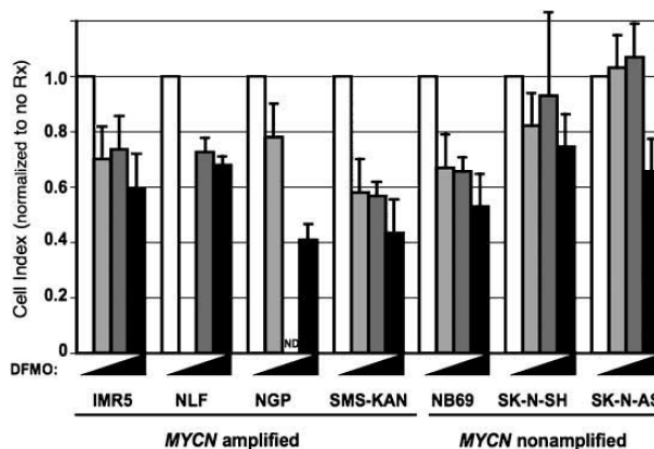
\*,  $P < 0.05$  compared to vehicle; Figure excerpted from Lozier 2014)

Overall, Lozier et al. (2014) demonstrated that treatment with eflornithine restored balance to the LIN28/Let-7 axis by decreasing LIN28 and increasing Let-7, and reduced glycolytic metabolism and neurosphere formation in *LIN28B/MYCN*-expressing neuroblastoma cells.

In another publication, Hogarty et al. (2008) demonstrated that high *ODCI* expression correlates with *MYCN* expression and is associated with poor survival in neuroblastoma. *MYCN* non-amplified high-risk tumors also overexpress *ODCI* compared to lower-risk tumors (data not shown). As assessed by cell index values obtained with the RT-CES platform, incubation with  $\geq 2.5$  mM eflornithine for 72 hours reduced the in vitro proliferation of *MYCN*-amplified and *MYCN* non-amplified neuroblastoma cells compared to untreated controls (Figure 6). *MYCN* non-amplified cells were less sensitive to eflornithine and higher concentrations were needed to see activity in these cell lines.

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{Eflornithine [DFMO]}

**Figure 6: Effect of Eflornithine on *MYCN*-amplified and Non-amplified Neuroblastoma Cell Proliferation**

Viable cell number is shown normalized to no treatment at 72 hours. White columns: control; light gray columns: 2.5 mM eflornithine; dark gray columns: 5 mM eflornithine; black columns: 10 mM eflornithine (Figure excerpted from Hogarty et al. 2008)

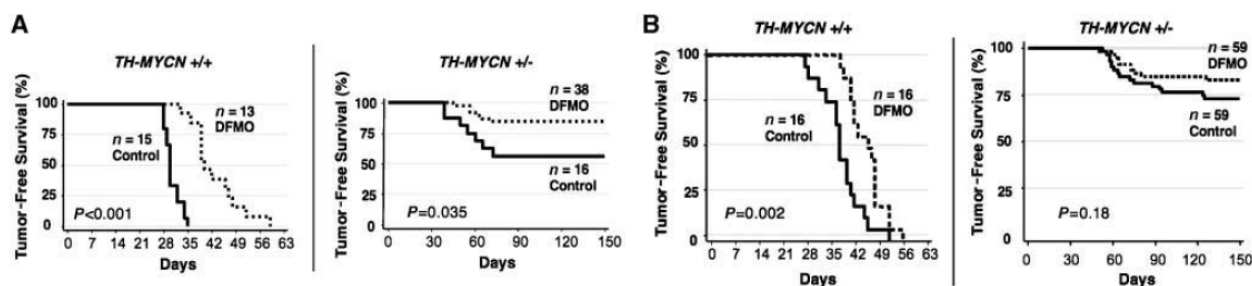
Investigators next evaluated the effect of eflornithine on tumor initiation and progression using transgenic mice homozygous for a neural crest–targeted *MYCN* transgene (*TH-MYCN*), which represent a well-established animal model of spontaneous neuroblastoma. These mice develop tumors that share biochemical features, orthologous genomic alterations, and histologic features with human *MYCN*-amplified neuroblastoma (Weiss et al., 1997; Chesler et al. 2007; Moore et al. 2008). In the initial experiment, mice received drinking water with or without 1% eflornithine from birth onward. Although all homozygous mice (*TH-MYCN* +/+) developed tumors as expected, treatment with eflornithine increased tumor-free survival (mean tumor latency of  $43 \pm 7$  days versus  $31 \pm 2$  days;  $P < 0.001$ ) compared to untreated control (Figure 7A). Seven out of 16 (44%) control hemizygous (*TH-MYCN* +/-) mice developed tumors, consistent with the historical penetrance of this phenotype, whereas only 6/38 (16%) eflornithine-treated mice developed tumors, suggesting that eflornithine prevented tumor initiation/formation in ~84% (32/38) of treated *TH-MYCN* +/- mice. DFMO-treated tumors exhibited decreased polyamine levels, thereby indicating on-target pharmacodynamic activity. Notably, additional tumors did not develop by Day ~150 following cessation of eflornithine treatment on Day 70, suggesting extended tumor protection. Investigators hypothesized that this is consistent with a finite window for embryonal tumorigenesis, and suggests that chronic ODC inhibition may not be needed for sustained therapeutic benefit. In a second experiment evaluating delayed treatment, mice received drinking water with or without 1% eflornithine beginning on Day 25 after tumor onset (post-weaning). Treatment with eflornithine delayed tumor progression in *TH-MYCN* +/+ mice,

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{Eflornithine [DFMO]}

with a mean time to palpable tumor burden of  $47.5 \pm 1.3$  days compared to  $38.6 \pm 1.5$  days in control mice (Figure 4B). Eflornithine also slightly but significantly extended tumor-free survival and time to death ( $49.2 \pm 1.3$  days) compared to untreated control ( $42.6 \pm 1.2$  days). Delayed eflornithine treatment slightly increased tumor-free survival in *TH-MYC**N* +/- mice compared to controls. Overall, these data suggest that earlier treatment with eflornithine is more effective than delayed treatment.

**Figure 7: Effect of Eflornithine on Tumor-Free Survival of *TH-MYC**N* +/- and *TH-MYC**N* +/- Mice**



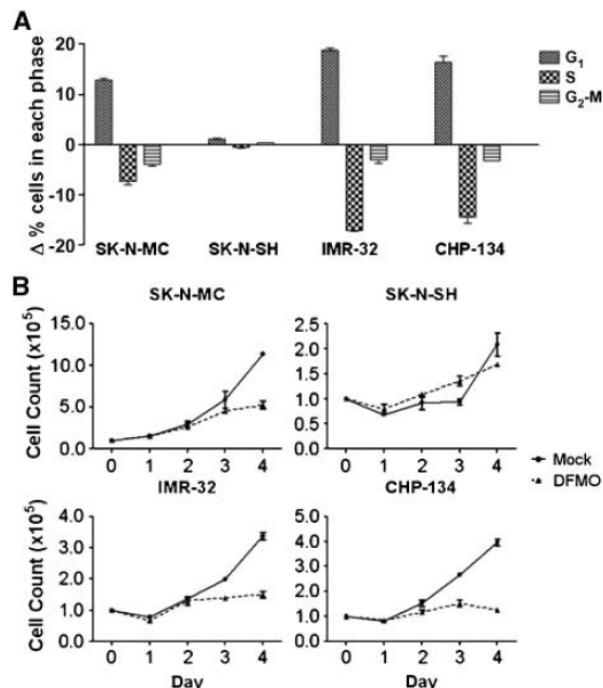
Treatment with DFMO started from birth (A) or 25 days post-weaning (B)  
(Figure excerpted from Hogarty et al. 2008)

Rounbehler et al. (2009) also evaluated the role of eflornithine in neuroblastoma prevention and growth. As assessed by cell cycle analysis and cell count, incubation with 5 mM eflornithine reduced the proliferation of the *MYCN*-amplified human neuroblastoma cell lines IMR-32 (1.8-fold *MYCN* amplification) and CHP-134 (2.2-fold *MYCN* amplification) but exhibited no activity in the *MYCN* non-amplified cell line SK-N-SH (1.2-fold *MYCN* amplification) and minimal activity in the *MYCN* non-amplified cell line SK-N-MC (1.0-fold *MYCN* amplification) (Figure 8). This finding of *MYCN*-dependence differs from Hogarty et al. (2008) and suggests that there are discrepancies in the literature regarding the activity of eflornithine in *MYCN*-amplified neuroblastoma versus *MYCN* non-amplified neuroblastoma.

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{Eflornithine [DFMO]}

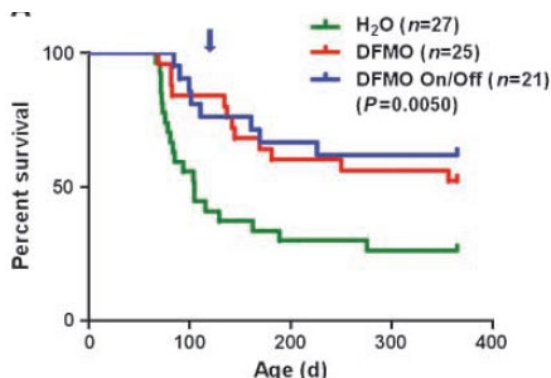
**Figure 8: Effect of 5 mM Eflornithine on In Vitro Human Neuroblastoma Cell Proliferation**

(Figure excerpted from Rounbehler et al. 2009)

Rounbehler et al. (2009) also investigated the effect of eflornithine on tumorigenesis and survival in *TH-MYC*N transgenic mice (Weiss et al. 1997). Beginning at 3 weeks of age, *TH-MYC*N mice were given drinking water with or without 1% eflornithine. By 1 year of age, 20/27 (74%) of untreated *TH-MYC*N mice developed neuroblastoma, compared to only 12/25 (48%) of eflornithine-treated *TH-MYC*N mice, suggesting suppression of tumor formation. Eflornithine also increased median survival to 139 days compared to 84 days in untreated mice. Thus, treatment with eflornithine delayed the onset/incidence of neuroblastoma in *TH-MYC*N mice and improved survival. In addition, one cohort of mice was given 1% eflornithine from 3 weeks of age until 120 days old. Tumors only developed in 8/21 (38%) of these mice, suggesting that transient rather than chronic exposure to eflornithine is sufficient for tumor prevention under the conditions of this study.

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{Eflornithine [DFMO]}

**Figure 9: Effect of 1% Eflornithine on Survival of *TH-MYC* Mice**

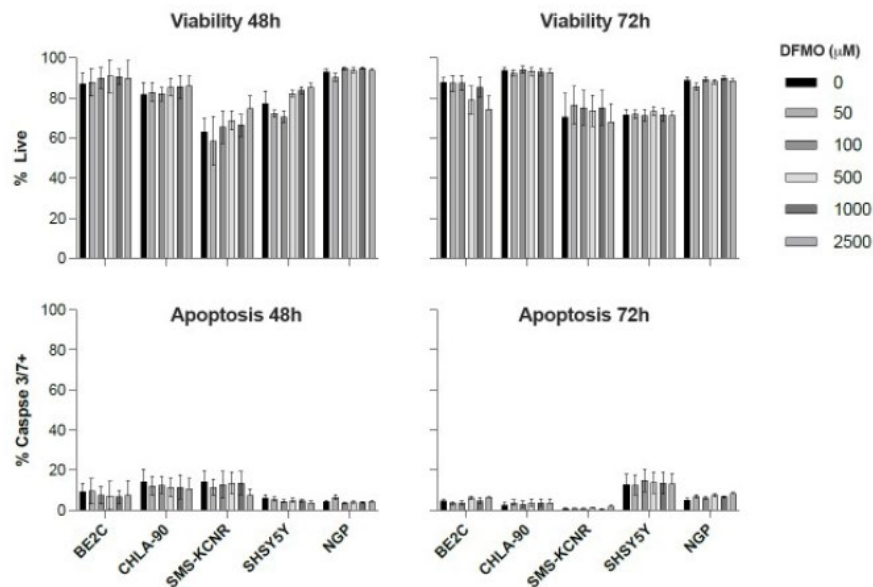
Blue arrow = the time (120 days) when one cohort of mice was taken off eflornithine  
(Figure excerpted from Roundbehler et al. 2009)

The Applicant's Position includes data from Avequin et al. (2018) evaluating the role of eflornithine in cancer stem cells and neuroblastoma prevention; however, this reference is an American Association for Cancer Research (AACR) Annual Meeting abstract that does not contain figures or tables to confirm the stated results. Given that meeting abstracts are generally not considered adequate to support mechanism of action and regulatory decisions for marketing applications, the FDA nonclinical team requested submission of these data and/or any unpublished pharmacology data to support the proposed mechanism of action. In response, the Applicant submitted pharmacology data to the NDA summarizing unpublished findings from the laboratory of their collaborator Dr. Giselle Sholler. These data generally support the findings described in the cited AACR Annual Meeting abstract (Avequin et al. 2018), except the submitted data did not address the Applicant's claim that eflornithine directly targets CD114+ cells.

Investigators initially evaluated the effect of eflornithine on in vitro cytotoxicity, apoptosis, and senescence. As assessed by flow cytometry, incubation with eflornithine at concentrations up to 2500  $\mu$ M for 48 or 72 hours did not substantially affect cell viability or apoptosis in five human neuroblastoma cell lines [BE(2)-C, CHLA-90, SMS-KCNR, SHSY5Y, and NGP] (Figure 10). BE(2)-C, SMS-KCNR and NGP cell lines are *MYCN*-amplified, whereas CHLA90 and SHSY5Y cells are *MYCN* non-amplified. These data suggest that eflornithine is not inducing a cytotoxic effect under the conditions tested.

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**Figure 10: Effect of Eflornithine on In Vitro Cell Viability and Apoptosis in Neuroblastoma Cells**

(Figure excerpted from Applicant's submission)

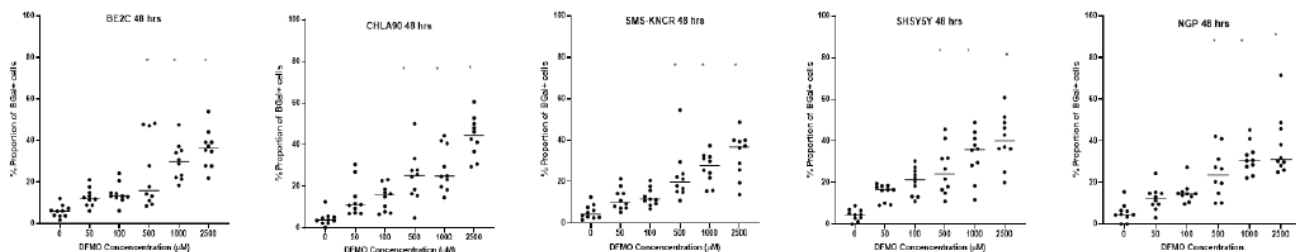
Investigators next stained eflornithine-treated neuroblastoma cells for  $\beta$ -galactosidase ( $\beta$ -gal) production as a marker of cellular senescence. Incubation with eflornithine for 48 or 72 hours resulted in a concentration-dependent increase in  $\beta$ -gal staining in all the neuroblastoma cell lines tested ( $n=5$ ) irrespective of *MYCN* amplification status (Figure 11), indicating induction of in vitro cellular senescence. Increases in  $\beta$ -gal-positive cells were seen beginning at concentrations  $\geq 50 \mu\text{M}$ , generally achieving statistically significant changes at concentrations  $\geq 500 \mu\text{M}$  compared to untreated controls (Figure 11). These data suggest that eflornithine is inducing a cytostatic effect under the conditions tested.

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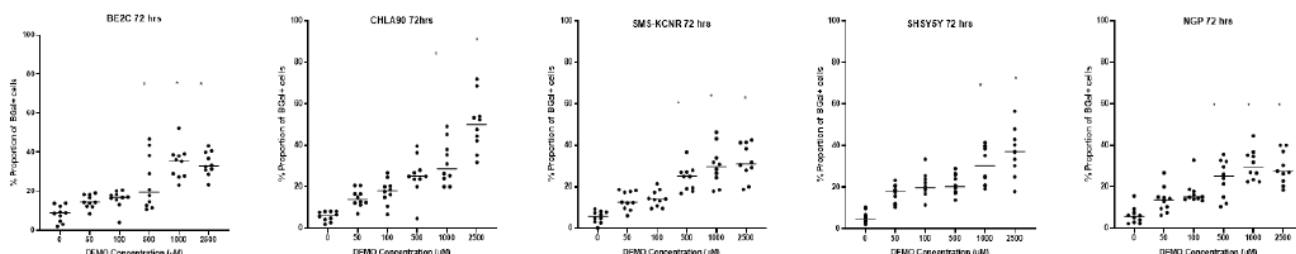
{Eflornithine [DFMO]}

**Figure 11: Effect of Eflornithine on In Vitro Cellular Senescence in Neuroblastoma Cells**

i) 48 hours



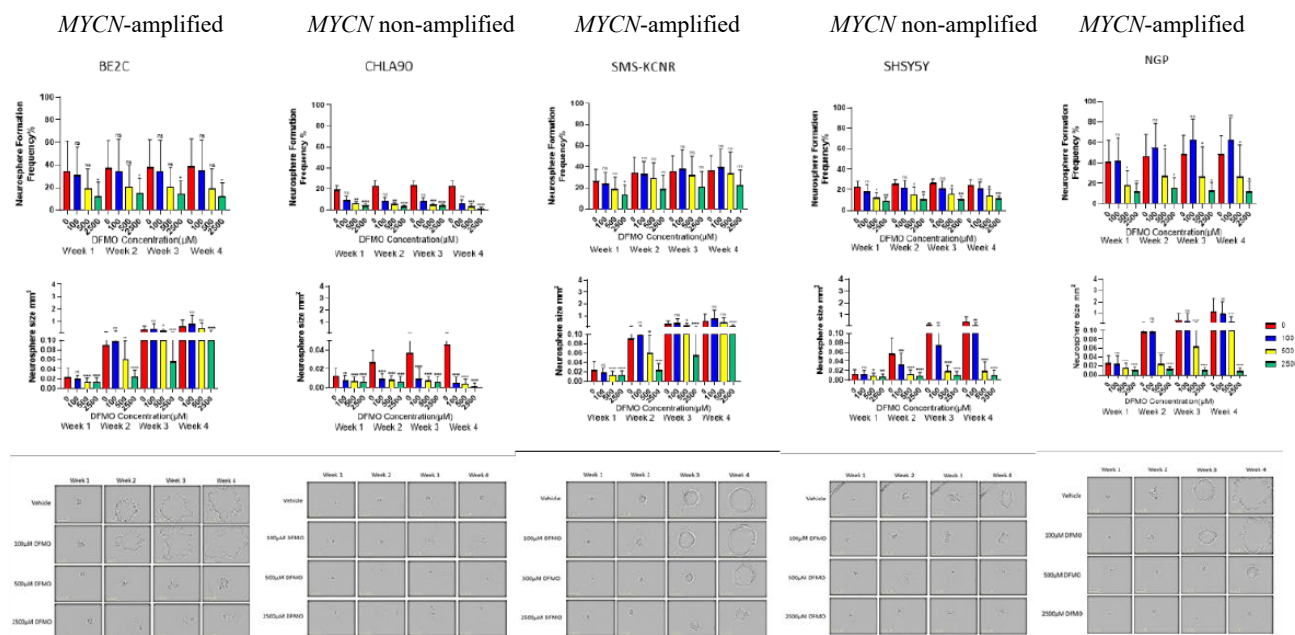
ii) 72 hours

\*,  $P < 0.05$  compared to untreated controls; (Figure excerpted from Applicant's submission)

Since neurosphere formation is a hallmark of tumor initiation in neuroblastoma, investigators evaluated the effect of eflornithine on neurosphere initiation/progression in neuroblastoma cell lines over 4 weeks. Incubation with eflornithine resulted in a concentration-dependent reduction in neurosphere formation and size compared to untreated controls (Figure 12). Eflornithine concentrations  $\geq 500 \mu\text{M}$  and  $\geq 100 \mu\text{M}$  were generally effective in *MYCN*-amplified cells [BE(2)-C, SMS-KCNR, and NGP] and *MYCN* non-amplified (CHLA90 and SHSY5Y) cells, respectively, suggesting that *MYCN* non-amplified cells are more sensitive to eflornithine under the conditions of this assay, although smaller neurospheres were generally formed with these cell lines compared to *MYCN*-amplified cell lines. These cell sensitivity data are inconsistent with literature findings discussed above (Lozier et al. 2014, Hogarty et al. 2008), in which *MYCN*-amplified cells were more sensitive to eflornithine.

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{Eflornithine [DFMO]}

**Figure 12: Effect of Eflornithine on Neurosphere Formation in Neuroblastoma Cells**

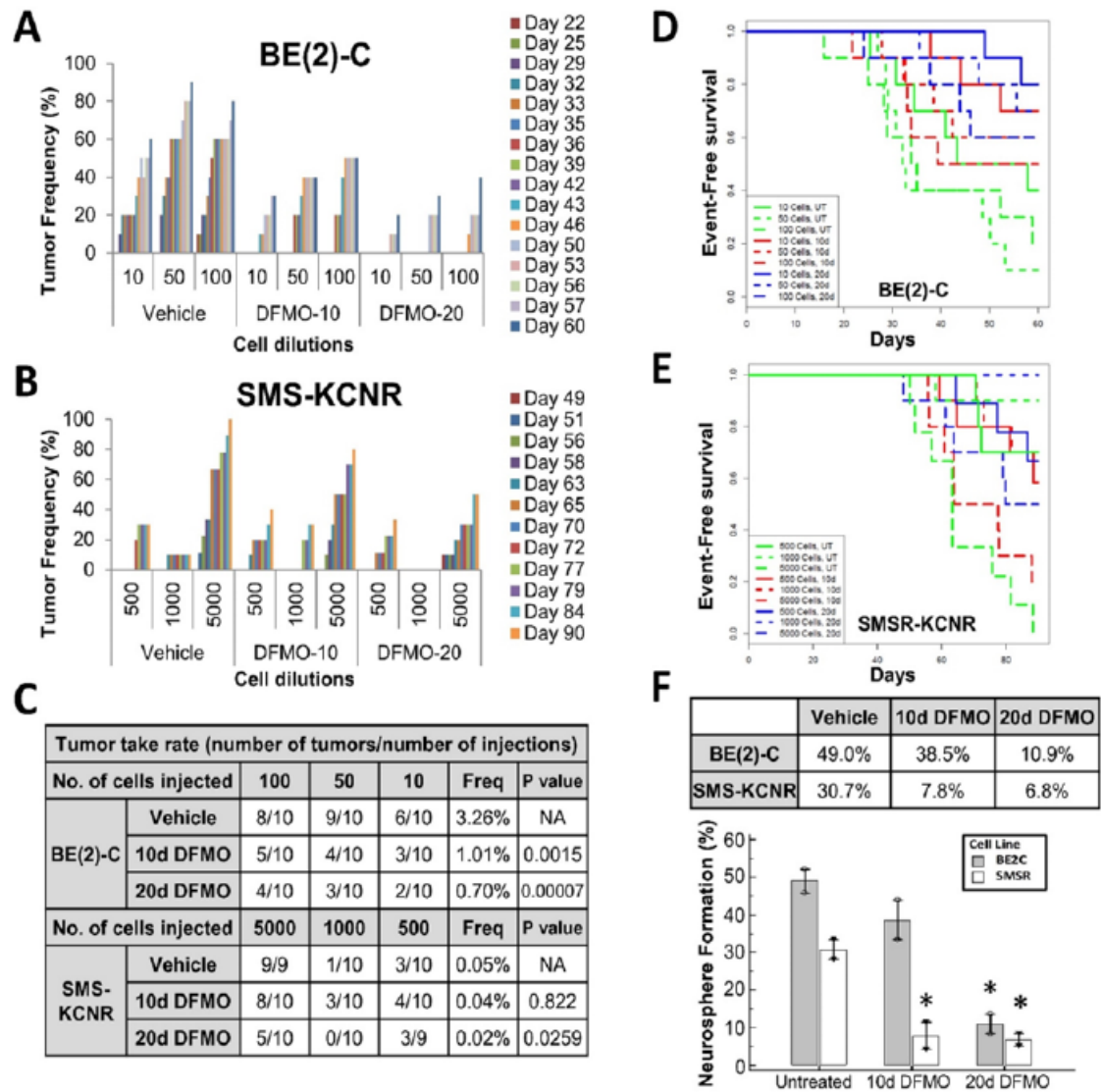
(Figure excerpted from Applicant's submission)

In another experiment, pre-treatment with 500 µM eflornithine for 10 and/or 20 days significantly inhibited neurosphere formation in *MYCN*-amplified BE(2)-C and SMS-KCNR cells (Figure 13F). To further evaluate these findings in tumor prevention mouse models, investigators used extreme limiting dilution analysis (ELDA), an established method to measure the frequency of tumor-initiating cells within a tumor cell population and tumorigenicity in subpopulations of cells (den Hollander et al. 2022). Investigators SC injected limiting dilutions (10-5000 cells) of viable BE(2)-C or SMS-KCNR cells pre-treated with either vehicle control or 500 µM eflornithine for 10 or 20 days into the right flank of nude mice (n = 10/group). Pre-treatment with eflornithine significantly suppressed *in vivo* formation of BE(2)-C ( $p < 0.001$ ) and SMS-KNR ( $p < 0.05$ ) tumors compared to vehicle controls, suggesting inhibition of tumor-initiating events. Longer eflornithine pre-treatment time (20 versus 10 days) correlated with greater suppression of tumor initiating capacity in both cell lines (Figure 13A-C). On Day 20, 80% of control mice formed BE(2)-C tumors following initial injection of 100 cells, compared to 40% of eflornithine-treated mice. Sixty percent of control mice formed BE(2)-C tumors following initial injection of 10 cells, compared to 20% of eflornithine-treated mice. Based on data in Figure 13C, eflornithine prevented BE(2)-C tumor formation in up to 80% (8/10) of mice dosed with eflornithine. Eflornithine-induced effects were less pronounced with SMS-KCNR

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tumors compared to controls, potentially because insufficient number of cells were injected to induce tumor formation in the 500 and 1000 cell control groups. Pre-treatment with eflornithine generally improved event-free survival in both mouse models compared to vehicle controls (Figure 13D-E).

**Figure 13: Effect of Eflornithine Pre-treatment on MYCN-Amplified Neuroblastoma Tumor Formation in Nude Mice**



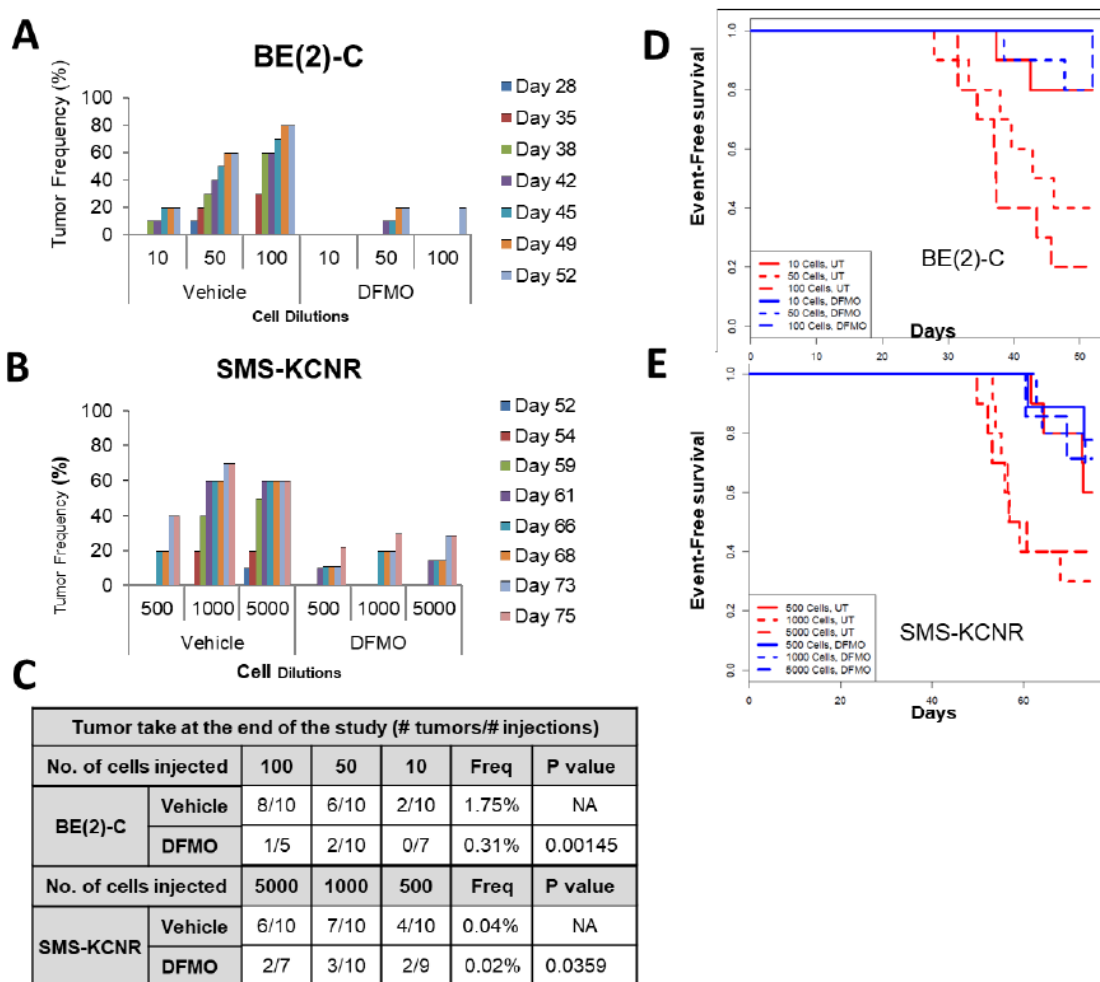
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{Eflornithine [DFMO]}

F panel: \*,  $p < 0.05$  compared to untreated control; (Figure excerpted from Applicant's submission)

In a second ELDA study designed to mimic the proposed clinical indication, investigators injected nude mice SC with BE(2)-C or SMS-KCNR cells at limiting cell dilutions (10-5000 cells). Mice were given untreated drinking water or 2% eflornithine (equivalent to at least 6900 mg/m<sup>2</sup>/day free base based on BSA; see calculations under Figure 14) in the drinking water beginning on the day of cell injection for 52 days (BE(2)-C) or 75 days (SMS-KCNR). Thus, visible/measurable tumors were not present at treatment initiation. Treatment with eflornithine resulted in lower rates of tumor formation in *MYCN*-amplified BE(2)-C ( $p < 0.001$ ) and SMS-KCNR ( $p < 0.05$ ) cells compared to untreated water. Eflornithine also delayed tumor formation, particularly BE(2)-C tumors. At the end of the study, 80% of control mice formed BE(2)-C tumors following initial injection of 100 cells, compared to 20% of eflornithine-treated mice. In addition, treatment with eflornithine increased event-free survival in mice bearing BE(2)-C ( $p < 0.001$ ) or SMS-KCNR ( $p < 0.005$ ) tumors compared to untreated controls.

{Eflornithine [DFMO]}

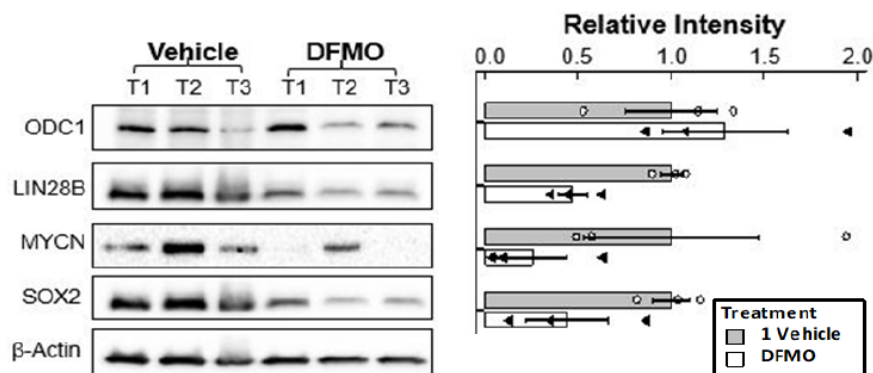
**Figure 14: Effect of Eflornithine on *MYCN*-Amplified Neuroblastoma Tumor Formation in Nude Mice**

2% eflornithine = 2 g eflornithine-HCl monohydrate powder in 100 mL water = 20 mg/mL = 84.51 mM. Assuming average water consumption of 3-5 mL/day, mice received at least 60 mg/day eflornithine HCl or 46 mg/day eflornithine free base, which is equivalent to ~9000 mg/m<sup>2</sup>/day HCl or 6900 mg/m<sup>2</sup>/day free base using an average mouse body weight of 0.02 kg (Figure excerpted from Applicant's submission)

Further, western blot analysis of excised tumors demonstrated that treatment with eflornithine reduced LIN28B and MYCN protein expression in vivo compared to untreated controls (Figure 15). Eflornithine also reduced the expression of SOX2, a marker of EMT, suggesting eflornithine is driving cells towards a more differentiated state.

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**Figure 15: Effect of Eflornithine on In Vivo LIN28, MYCN, and SOX2 Protein Expression in Neuroblastoma Tumors**

(Figure excerpted from Applicant's submission)

The FDA conducted an independent scientific literature-based assessment evaluating the effect of eflornithine/DFMO in neuroblastoma. Approximately 40 publications were reviewed, with publication dates ranging from 1980 to March 2023. Data from Hogarty et al. (2008) and Rounbehler et al. (2009), previously discussed above, were obtained from this literature search. Additional notable findings are described herein. Early preclinical studies demonstrated that eflornithine can induce the differentiation of neuroblastoma cells (Melino et al. 1988, Melino et al. 1991). Expanding on the findings of Wallick et al. (2005) in *MYCN*-amplified neuroblastoma cells, Koomoa et al. (2013) used *MYCN2* neuroblastoma cells containing a doxycycline-inducible *MYCN* transgene to grow *MYCN2* cells with (+) or without (-) *MYCN* overexpression. Investigators demonstrated that incubation with 5 mM eflornithine reduced in vitro intracellular polyamine levels, induced G1 cell cycle arrest, inhibited cell migration, induced p27Kip1 accumulation, and increased phosphorylation of AKT/PKB at Ser473 in *MYCN2* (+) and *MYCN2* (-) cells, providing additional evidence that eflornithine has in vitro activity in both *MYCN*-amplified and *MYCN* non-amplified neuroblastoma cells. Eflornithine-induced G1 cell cycle arrest was more pronounced in *MYCN2* (+) cells compared to *MYCN2* (-) cells. Eflornithine-induced cell migration was similar in *MYCN2* (+) and *MYCN2* (-) cells in a wound healing migration assay, but increased in *MYCN2* (+) cells compared to *MYCN2* (-) cells in a transwell migration assay, reflecting different assay methodologies (Koomoa et al. 2013). In another publication, Koomoa et al. (2008) provided data suggesting that eflornithine induces two opposing pathways in neuroblastoma, one leading to p27Kip1-mediated G1 cell cycle arrest and one leading to Akt/PKB-mediated cell survival. These paradoxical pathways provide a potential mechanism for the lack of cytotoxicity seen with eflornithine in neuroblastoma. Makena et al.

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(2018) concluded that eflornithine was not cytotoxic in vitro to a majority of neuroblastoma cell lines at concentrations up to 100  $\mu$ M; however, investigators did not conduct assays assessing a potential cytostatic effect. Consistent with previous publications, Schultz et al. (2021) demonstrated that eflornithine induces minimal in vivo anti-tumor activity against established *MYCN*-amplified patient-derived neuroblastoma xenografts. Although Evageliou et al. (2016) did not provide tumor growth/volume data, they demonstrated that treatment with 1% eflornithine in the drinking water improved survival compared to vehicle control in mice bearing established *MYCN*-amplified BE2C xenografts but not *MYCN* non-amplified SK-N-SH xenografts. In vivo studies evaluating the effect of eflornithine on the prevention or delay of *MYCN* non-amplified neuroblastoma, which are the most relevant to the proposed clinical indication, were not located in the literature search as of March 1, 2023.

There are also published literature findings supporting that eflornithine can prevent or delay tumor formation in mouse models of other cancers including lymphoma, pancreatic cancer, intestinal tumors, skin cancer, and prostate cancer (Nilsson et al. 2005, Mohammed et al. 2014, LoGiudice et al. 2018, Alexiou et al. 2017, Kadmon 1992, Meyskens et al. 1999). The *MYC* oncogene is a central driver in B cell lymphoma and is also involved in the oncogenesis of pancreatic cancer, colon cancer, and prostate cancer (Nilsson et al. 2005, Wang et al. 2021).

Overall, the available pharmacology data from various investigators demonstrate that eflornithine inhibits ODC and polyamine synthesis, thereby restoring balance to the LIN28/Let-7 metabolic pathway involved in regulation of cancer stem cells. Eflornithine is primarily cytostatic rather than cytotoxic in neuroblastoma. Eflornithine induced in vitro senescence and suppressed neurosphere formation in *MYCN*-amplified and *MYCN* non-amplified neuroblastoma cells. Treatment with eflornithine suppressed tumor-initiating *MYCN*-amplified neuroblastoma cells in vivo, thereby preventing or delaying tumor formation and improving event-free survival in mice who have no initial evidence of disease. Eflornithine also prevented/delayed tumor formation in a well-established transgenic mouse model (TH-*MYCN*) of neuroblastoma. In general, most of the published literature identified in the FDA's literature-based assessment were consistent with the studies and published literature provided by the Applicant and support that eflornithine is cytostatic in neuroblastoma.

### Secondary Pharmacology

The molecular mechanism of action of DFMO in limiting polyamine synthesis also has clinical applications unrelated to those of a cancer chemotherapeutic. While not directly related to a cellular or immune mechanism of a cancer therapeutic, many *in vitro* and *in vivo* studies pertaining to DFMO's mechanism of action supporting the approvals of an IV administered

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injectable formulation for the treatment of *Trypanosoma brucei gambiense* infection (also known as West African trypanosomiasis or West African Sleeping Sickness), and a topical cream formulation for the treatment of unwanted facial hair in women are described in their respective reviewer approval packages (ORNIDYL 1990, [VANIQA, 2018](#)).

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment.

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Safety Pharmacology

The effects of DFMO on the cardiovascular system were investigated in anesthetized dogs. After IV injection of DFMO at 500 mg/kg to dogs (10 min infusion), a transient decrease in blood pressure (~ 19%), myocardial contractility (~ 41%), and heart rate (~ 10%) were noted (ORNIDYL 1990). There have been no reports of serious adverse effects on the central nervous system nor the respiratory system.

DFMO has been safely used (ex-US, distributed by WHO) for three decades for the FDA-approved African sleeping sickness indication, applicable to both adults and children, at substantially higher doses than proposed in the current marketing application. Therefore, no additional sponsored pharmacodynamic or safety pharmacology studies have been conducted or were considered warranted by the current Applicant.

The FDA's Assessment:

The FDA acknowledges the Applicant's assessment and agrees that it is appropriate to rely on FDA's previous findings of safety pharmacology for the RLD Ornidyl.

**5.4. ADME/PK**

The PK/ADME properties of DFMO have evaluated in *in vitro* and *in vivo* studies and are described in the Ornidyl NDA as well as in the scientific literature. The Applicant investigated DFMO's potential to induce or inhibit cytochrome 450 enzymes or act as a substrate or inhibitor of the major drug transporters. Below is a tabular listing of ADME studies supporting this application along with their locations in the NDA.

**Absorption** – Summarized and Discussed in 2.6.4.3 from ORNIDYL 1990, Romijn 1987, Jansson 2008, Haeghele 1981.

DFMO is well absorbed in preclinical species. As DFMO is not metabolized, absorption characteristics were determined from <sup>14</sup>C-plasma concentration data after administration of a single dose of <sup>14</sup>C-DFMO at 75 mg/kg, by IV and orally (PO) to rats and to dogs. The absolute bioavailability of oral DFMO, based on AUC, ranged from 78% in the rat to 100% in the dog. DFMO administration at 200 mg/kg, subcutaneously (SC) to mice or PO to rats, resulted in maximum organ levels at 1 hr in uterus, plasma, liver, and spleen in mice, or spleen and testes in rat. At 6 hr, levels were undetectable. A serum t<sub>1/2</sub> of 17 minutes was noted in mice, while the maximum serum level in rats was seen at 30 minutes with a t<sub>1/2</sub> of 23 minutes. IP administration of <sup>14</sup>C-DFMO (10-2000 mg/kg) to BALB/C nude mice resulted in similar rapid and biphasic rate of clearance from serum with a t<sub>1/2</sub> α of 14 minutes and t<sub>1/2</sub> β of 2.1 hr and from muscle, liver, or

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>kidney with a <math>t_{1/2} \alpha</math> of 30-60 min and <math>t_{1/2} \beta</math> of 2.1 hr. Serum drug concentrations were dose proportional.</p> <p>To provide a comparison of PK profiles after oral administration, DFMO was administered at 10 mg/kg to several species. <math>C_{max}</math> occurred at 1 hr in rat (5.6 nM/mL), 2 hr in rabbit and dog <math>C_{max}</math> (23.9 and 57.1 nM/mL), 5 hr in monkey (24.2 nM/mL), and 4 hr in human (25.5 nM/mL), with a <math>t_{1/2}</math> of 1.4 hr in rat, 2 hr in rabbit, 1.8 hr in dog, and 5.9 hr in primate. The half-life in the rat was estimated after a higher oral dose (200 mg/kg) to obtain a more accurate representation of the elimination profile. Half-life in human was reported to range from 3.3-3.5 h after an IV dose of 5 mg/kg as well as after an oral dose of 10-20 mg/kg.</p> |
| <p><b>Distribution</b> – Summarized and Discussed in 2.6.4.4 from ORNIDYL 1990.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <p>DFMO does not bind significantly to plasma proteins of mouse, rat, or human, or to purified bovine serum albumin.</p> <p>An autoradiographic study of DFMO administered IV at 100 mg/kg with 50 mCi/kg to pregnant mice on GD 17 showed high levels in kidney, blood, lungs, and skin after 5 min and lower levels in heart, liver, spleen, small intestine, and placenta, but none in brain, feces, or fetus. Over time, distribution decreased in lungs and increased in small intestine, urine, and bile, with a low level in the fetus. At 2 hr elimination was almost complete and at later timepoints radioactivity was no longer detected.</p>                                                                                                                                                                                                                  |
| <p><b>Metabolism</b>– Summarized and Discussed in 2.6.4.5 and 2.6.4.7 from ORNIDYL 1990, 2011RXP-UWM-001, 2011IND-UWM-002, 2011INH, UWM-003, <a href="#">Saulnier Sholler 2015</a>.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p>Analysis of plasma, urine, liver and kidney, bile and urine samples from rat and dog after IV and PO administration have shown that DFMO is not metabolized and is excreted unchanged via the renal route. A CYP-450 study demonstrated that there is no hepatic metabolism of DFMO.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <p><b>Excretion</b>– Summarized and Discussed in 2.6.4.6 from <a href="#">ORNIDYL 1990</a>.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p>In general, species with shorter elimination half-lives (<math>t_{1/2}</math>) excreted relatively more DFMO during 24 hr after oral dosing of 10 mg/kg than species with longer half-lives; total excretion in rat was 82%, dog 42%, non-human primate 23%, and human 46%. After oral dosing of <math>^{14}\text{C}</math>-DFMO at 200 mg/kg to rats, 87% of the administered radioactivity was recovered within 48 hr of dosing.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p><b>Summary PK parameters from pharmacokinetic studies</b> – Detailed in Tables 5 and 6 of 2.6.7 from 104-Week carcinogenicity studies in mice and rats (Studies IITRI L06297 and SRI 9118.01.01)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p><b>Mouse:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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| Sex                                          | Male |      |       |       | Female |      |       |       |
|----------------------------------------------|------|------|-------|-------|--------|------|-------|-------|
| Daily Dose (mg/kg/day)                       | 0    | 100  | 300   | 1000  | 0      | 100  | 300   | 1000  |
| Number of Toxicity Animals                   | 50   | 50   | 50    | 50    | 50     | 50   | 50    | 50    |
| Number of Toxicokinetic Animals <sup>a</sup> | 5    | 5    | 5     | 5     | 5      | 5    | 5     | 5     |
| <b>Toxicokinetics<sup>b</sup>:</b>           |      |      |       |       |        |      |       |       |
| Month 3, C <sub>p</sub> (mg /mL)             | NA   | 2.48 | 3.94  | 10.52 | NA     | 0.86 | 4.76  | 10.99 |
| Month 16, C <sub>p</sub> (mg /mL)            | NA   | BDL  | 2.61  | 7.56  | NA     | BDL  | BDL   | 4.73  |
| Month 18, C <sub>p</sub> (mg /mL)            | NA   | 6.45 | 18.32 | 59.35 | NA     | 5.04 | 21.91 | 33.23 |

| Sex                                          | Male |      |     |     | Female |      |      |     |
|----------------------------------------------|------|------|-----|-----|--------|------|------|-----|
| Daily Dose (mg/kg/day)                       | 0    | 150  | 300 | 600 | 0      | 150  | 300  | 600 |
| Number of Toxicity Animals                   | 60   | 60   | 60  | 60  | 50     | 50   | 50   | 50  |
| Number of Toxicokinetic Animals <sup>a</sup> | 10   | 10   | 10  | 10  | 10     | 10   | 10   | 10  |
| <b>Toxicokinetics<sup>b</sup>:</b>           |      |      |     |     |        |      |      |     |
| Month 6, C <sub>max</sub> (mg/mL)            | NA   | 69.5 | 138 | 228 | NA     | 49.1 | 91.6 | 209 |
| Month 12, C <sub>max</sub> (mg/mL)           | NA   | 74.5 | 134 | 197 | NA     | 74.9 | 142  | 254 |
| Month 18, C <sub>max</sub> (mg/mL)           | NA   | 90.0 | 136 | 217 | NA     | 80.3 | 133  | 272 |
| Month 24, C <sub>max</sub> (mg/mL)           | NA   | 107  | 154 | 192 | NA     | 109  | 170  | 247 |

**Rat:**

**Integrative summary table of C<sub>max</sub> and AUC parameters across toxicology studies (general, reproductive, and carcinogenicity, if conducted).**

DFMO is not metabolized and therefore no metabolites were examined or quantified. AUC calculations were not performed for the carcinogenicity studies. C<sub>max</sub> summary data are listed in the previous section.

**Tabulation of any exposure margins used in proposed labeling.** – Summarized and discussed in 2.6.6.3, Love 1993

Animal to human safety margins, based on dose levels adjusted for body surface area, at the NOEL in key repeat dose toxicity studies and the maximum recommended clinical daily dose of DFMO HCl monohydrate salt at  $1500 \pm 500$  mg/m<sup>2</sup>/day are summarized in the table below. Dose limiting toxicities that determined the NOEL values in rats, dogs, and monkeys, consisted, in varying degrees across the nonclinical species included in the toxicity studies, of GI upset

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resulting in severe diarrhea and electrolyte imbalance, intestinal lesions, leukopenia, thrombocytopenia, and bone marrow depression. Safety margins in rat and primate clear the clinical maximum recommended daily dose. The dog appears to be the most sensitive species and dose limiting toxicities, consisting mostly of GI upset and intestinal lesions, reduced body weight gain, decreased reticulocyte count, and anti-estrogenic effects, resulted in a safety margin of <1, which may be acceptable in this high-risk pediatric cancer patient population. GI toxicity (nausea, diarrhea, and flatus) has also been noted in NCI-sponsored DFMO clinical trials at a daily dose of 500 mg/m<sup>2</sup>/day.

**Animal-to-Human Safety Margins at Recommended Clinical Regimen of Oral DFMO HCl Monohydrate at 1500 ± 500 mg/m<sup>2</sup>/day**

| Toxicity Study                         | NOEL (mg/kg) | Dose (mg/m <sup>2</sup> /day) <sup>e</sup> |            | Animal-to-Human Safety Margin |
|----------------------------------------|--------------|--------------------------------------------|------------|-------------------------------|
|                                        |              | Animal                                     | Human      |                               |
| 52-Week Oral Rat Study <sup>a</sup>    | 400          | 2400                                       | 1500 ± 500 | 1.2-2.4                       |
| 2-Week Oral Dog Study <sup>b,c</sup>   | 40           | 800                                        | 1500 ± 500 | 0.4-0.8                       |
| 4-Week Oral Primate Study <sup>d</sup> | 200          | 2400                                       | 1500 ± 500 | 1.2-2.4                       |

NOEL = no-observed-effect-level

<sup>a</sup> Crowell, 1994

<sup>b</sup> Ornidyl Pharmacology Review

<sup>c</sup> A NOEL was not identified in longer duration oral toxicity studies in dogs

<sup>d</sup> Ornidyl Pharmacology Review

<sup>e</sup> All dose levels are given as HCl monohydrate salt concentrations

**The FDA's Assessment:**

The FDA acknowledges the Applicant's assessment and agrees that it is appropriate to rely on FDA's previous findings of ADME/PK for the RLD Ornidyl. Consistent with the proposed route of administration of IWILFIN, the FDA's review focused on oral administration of eflornithine. The FDA generally agrees with the oral nonclinical ADME/PK data summarized by the Applicant. Literature references describing clinical data (i.e., Haegele et al. 1981, Saulnier Sholler et al. 2015) were not reviewed by the pharmacology/toxicology team and thus the results from these publications were not confirmed. Human metabolism/PK drug interaction studies

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evaluating drug transporters and cytochrome 450 enzymes were reviewed by FDA's Clinical Pharmacology team. Toxicokinetic data from the mouse and rat carcinogenicity studies was previously reviewed by the FDA under another NDA (See 5.5.3). The FDA did not review the Applicant's summary of animal-to-human safety margins for general toxicology studies because they are not pertinent to the IWILFIN prescribing information. The Applicant did not conduct a nonclinical PK bridging study comparing IV Ornidyl and oral eflornithine nor is it possible because Ornidyl is no longer manufactured.

## 5.5. Toxicology

Most of the general toxicity studies supporting this application were previously submitted to the Ornidyl NDA. Tabular presentation of the toxicity highlights were not feasible. In lieu of tabular presentations, toxicology sections are presented here in brief with guidance to the specific NDA sections for more information.

### 5.5.1. General Toxicology

The toxicological profile of DFMO has been characterized in rodents, dogs, and primates in single-dose acute and repeat-dose subchronic and chronic toxicity studies. A standard genotoxicity battery including *in vitro* and *in vivo* of studies was conducted, and carcinogenicity studies were completed in mice and rats. Teratogenicity studies were performed in rat and rabbit, and peri- and postnatal reproductive toxicity studies were carried out in the rat. Major DFMO-related adverse effects observed in the nonclinical safety studies appear to be consistent with DFMO's pharmacological mechanisms of action, and were observed in rapidly proliferating and maturing tissues, such as intestinal epithelium, bone marrow, and embryonic tissues, and various formed elements in the blood.

Toxicology support for the DFMO NDA to treat HRNB is relying on FDA's previous findings of safety supporting the approval of Ornidyl ([ORNIDYL 1990](#)), combined with nonclinical data supporting the development of DFMO as an anti-cancer therapeutic by NCI (IND (b) (4)), and reviews of relevant data in the public domain. Many of these studies are considered legacy studies with unknown GLP-status.

#### Acute Toxicity

Single-dose toxicity studies with oral, IV, and IP administration of DFMO in mice and rats resulted in an LD<sub>50</sub> greater than 5000 mg/kg after oral administration in mice and rats, 1035 and 2134 mg/kg after IV administration in mice and rats, respectively, and 3000 mg/kg after IP administration in mice and rats. A DFMO dose of 960 mg/kg/day (40 mg/kg/hr for 24 hr) by IV administration to dogs was well tolerated.

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## Repeat-Dose Toxicity

The repeat dose oral toxicity of DFMO was evaluated in mice, rats, dogs, and monkeys with a duration of up to 3 months in mice (data from Ornidyl NDA review discussed in 4.2 Nonclinical Overview), 52 weeks in rats, 52 weeks in dogs, and 3 months in monkeys. The duration of IV toxicity studies was up to 2 weeks in dogs and 2 weeks in monkeys. Major test article related findings were reversible and related to disturbances in the GI system and in formed elements of the blood.

Dietary DFMO administration to mice for up to 3 months with dose levels up to 3000 mg/kg/day (9000 mg/m<sup>2</sup>/day) was well tolerated with exception of a 7% decrease in final body weight at the high dose.

In the rat, DFMO added to diet or drinking water at dose levels up to 2000 mg/kg (12000 mg/m<sup>2</sup>/day) for up to 3 months was well tolerated with exception of a decrease in body weight gain, while higher dose levels resulted in reversible GI disturbances with decreased erythrocyte and platelet counts.

A 52-week oral chronic toxicity study in rats with dose levels up to 1600 mg/kg/day resulted in dose-related reduced body weight gain associated with reduced food consumption, increased platelets, alopecia, skin abrasions and dermatitis, liver necrosis, and gastric inflammation. The NOEL was identified at 400 mg/kg/day (2400 mg/m<sup>2</sup>/day).

Two-week oral administration of DFMO to dogs resulted in a NOEL of 40 mg/kg/day (800 mg/m<sup>2</sup>/day) while higher dose levels of 400 mg/kg/day for a dosing period of 5 weeks resulted in GI disturbances and weight loss. Divided oral daily doses in dogs of 50 mg/kg q4hr (300 mg/kg/day) for 2 weeks caused emesis, GI upset, and weight loss, while 600 mg/kg/day resulted in mortality of 2/4 dogs and more severe GI disturbances. Correlative pathological lesions indicated GI mucosal hemorrhages and villus atrophy with esophageal inflammation presumably due to repeated emesis at 600 mg/kg/day.

A subchronic 13-week oral toxicity study administered DFMO, with and without tamoxifen to female Beagle dogs, with one dose group receiving DFMO alone at 100 mg/kg/day (2000 mg/m<sup>2</sup>/day). Histopathology in the DFMO-only dose group on tissues determined abnormal at necropsy showed reduced reticulocyte counts, intestinal crypts, reproductive tract lesions, and ovarian lesions, such as ovarian atrophy, associated with reduced ovarian weight, reduced number of corpora lutea and antral follicles. A NOEL for DFMO could not be identified.

Chronic oral administration of DFMO for 52 weeks to dogs by capsule at doses up to 200 mg/kg/day (4000 mg/m<sup>2</sup>/day) resulted in dose-related reduced body weight gain and reduced food consumption at the high dose, and conjunctivitis, hyperkeratosis, alopecia, and cystic

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intestinal crypts at all dose levels (50, 100, 200 mg/kg/day; or 1000, 2000, 4000 mg/m<sup>2</sup>/day). A NOEL was not determined.

DFMO by IV administration at dose levels at or above 300 mg/kg/day resulted in more prominent signs, such as emesis, diarrhea, anorexia, weight loss, and death associated with bone marrow hypoplasia. Removal of dogs from treatment prior to moribundity resulted in recovery.

Oral administration of DFMO to cynomolgus monkeys for 3 months at dose levels up to 800 mg/kg/day (given in 2 divided doses) indicated a NOEL at the low dose level of 200 mg/kg/day (2400 mg/m<sup>2</sup>/day) with higher doses resulting in chronic diarrhea and/or mortality and villous atrophy or mucosal degeneration in mid- (400 mg/kg/day) and high-dose animals.

#### The FDA's Assessment:

Due to the proposed route of administration for IWILFIN, FDA's review of general toxicology studies focused on the 52-week oral toxicology studies evaluating the API, eflornithine, conducted in Charles River CD rats and Beagle dogs as described in Crowell et al. (1994). FDA generally agreed with the Applicant's summary of the 52-week oral toxicology studies. Other general toxicology data summarized by the Applicant was not reviewed and thus cannot be verified. The Applicant did not submit study reports for the 52-week oral studies to the NDA; however, they submitted a literature publication (Crowell et al. 1994) describing these studies to support continuous daily dosing of eflornithine. FDA's assessment of the 52-week oral toxicology studies based on data provided in Crowell et al. (1994) is below. GLP status was not specified; however, both studies evaluated sufficient animal numbers and contained standard toxicity endpoints, thus enabling a substantive review of the literature publication. In addition, target organ toxicity was identified in rats and dogs. Toxicokinetics were not conducted in either study.

There were no drug-related mortalities in either 52-week toxicology study. In the rat study, 25 animals/sex/group received 0, 400, 800, or 1600 mg/kg eflornithine via oral gavage. Treatment with  $\geq 800$  mg/kg eflornithine resulted in mild to moderate alopecia, abrasions, and necrotic dermatitis; skin abscesses; trace to moderately severe chronic dermatitis; and trace to mild histologic liver necrosis. There was an increase in the incidence and severity of histologic glandular inflammation in the stomach of rats dosed with  $\geq 400$  mg/kg eflornithine compared to controls. There was an up to 26% statistically significant decrease in mean body weight in rats dosed with 1600 mg/kg eflornithine compared to controls, which correlated with reduced food consumption. Treatment with  $\geq 800$  mg/kg eflornithine resulted in increased mean platelets (up

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to 58%) and leukocytes (up to 56%) and decreased mean hemoglobin (up to 9%) and MCV (up to 4%) compared to controls. Treatment with 1600 mg/kg eflornithine also resulted in decreased mean glucose (up to 16%) and urinary pH compared to controls.

In the 52-week dog study, 4 animals/sex/group received 0, 50, 100, or 200 mg/kg eflornithine orally via capsules. Treatment with  $\geq 50$  mg/kg eflornithine resulted in mild to moderate alopecia, thickened conjunctiva, and mucoid conjunctivitis; and mild skin hyperkeratosis and cystic crypts in the duodenum. Treatment with  $\geq 100$  mg/kg eflornithine resulted in decreased mean cholesterol (up to 45%) and body weight (up to 21%; males only) compared to controls. Increased prothrombin time (up to 11%) and decreased total protein (up to 11%) were seen in male dogs dosed with  $\geq 100$  mg/kg eflornithine compared to controls. Treatment with 200 mg/kg eflornithine resulted in decreased mean red blood cell parameters up to 16% in male dogs compared to controls.

### 5.5.2. Genetic Toxicology

#### The Applicant's Position:

DFMO was negative for mutagenic activity in the Ames reverse mutation assay with and without rat liver S9, did not exhibit clastogenic effects in the in vitro CHO assay with or without metabolic activation, and did not result in an increased incidence of micronucleated cells in the *in vivo* mouse micronucleus assay (Kelloff 1994, ORNIDYL 1990, VANIQA 2018).

#### The FDA's Assessment:

The FDA agrees that it is appropriate to rely on FDA's previous findings of genetic toxicology for the RLD Ornidyl. However, we note that only mutagenic activity was included for Ornidyl. Kelloff et al. (1994) reports the eflornithine was not clastogenic in the in vitro CHO assay and in vivo micronucleus assay; however, this publication does not contain any experimental details.

### 5.5.3. Carcinogenicity

#### The Applicant's Position:

These carcinogenicity study tables are adapted from data presented in 2.6.7. Fully tabulated study summaries can be found there.

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**Table 3: A 104-Week Carcinogenicity Study of a-Difluoromethylornithine (DFMO) in Mice**

|                                                                                            |      |                                                               |      |       |        |                         |      |       |
|--------------------------------------------------------------------------------------------|------|---------------------------------------------------------------|------|-------|--------|-------------------------|------|-------|
| Test Article: DFMO                                                                         |      |                                                               |      |       |        |                         |      |       |
| Report Title: A 104-Week Carcinogenicity Study of a-Difluoromethylornithine (DFMO) in Mice |      |                                                               |      |       |        |                         |      |       |
| Species/Strain: Mouse (B <sub>6</sub> C <sub>3</sub> F <sub>1</sub> )                      |      | Duration of Dosing: At least 104 consecutive weeks            |      |       |        | Study No.: IITRI L06297 |      |       |
| Initial Age: 4 to 5 weeks                                                                  |      | Method of Administration: Oral, admixed in the diet           |      |       |        | Location: 4.2.3.4.1.1   |      |       |
| Vehicle/Formulation: In diet                                                               |      |                                                               |      |       |        |                         |      |       |
| Date of First Dose: 23 January 1997 (all animals)                                          |      | Treatment of Controls: Group 1 received untreated rodent chow |      |       |        | GLP Compliance: Yes     |      |       |
| Basis for High-Dose Selection: Data not provided in study report                           |      |                                                               |      |       |        |                         |      |       |
| No Observed Effect Levels (NOEL) for Neoplasia: 1000 mg/kg                                 |      |                                                               |      |       |        |                         |      |       |
| Special Features: None                                                                     |      |                                                               |      |       |        |                         |      |       |
| Sex                                                                                        | Male |                                                               |      |       | Female |                         |      |       |
| Daily Dose (mg/kg/day)                                                                     | 0    | 100                                                           | 300  | 1000  | 0      | 100                     | 300  | 1000  |
| Number of Toxicity Animals                                                                 | 50   | 50                                                            | 50   | 50    | 50     | 50                      | 50   | 50    |
| Number of Toxicokinetic Animals <sup>a</sup>                                               | 5    | 5                                                             | 5    | 5     | 5      | 5                       | 5    | 5     |
| Toxicokinetics <sup>b</sup> :                                                              |      |                                                               |      |       |        |                         |      |       |
| Month 3, C <sub>p</sub> (mg /mL)                                                           | NA   | 2.48                                                          | 3.94 | 10.52 | NA     | 0.86                    | 4.76 | 10.99 |
| Month 16, C <sub>p</sub> (mg /mL)                                                          | NA   | BDL                                                           | 2.61 | 7.56  | NA     | BDL                     | BDL  | 4.73  |

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{Eflornithine [DFMO]}

|                                                                                            |      |                                                               |       |       |        |                         |                |       |
|--------------------------------------------------------------------------------------------|------|---------------------------------------------------------------|-------|-------|--------|-------------------------|----------------|-------|
| Test Article: DFMO                                                                         |      |                                                               |       |       |        |                         |                |       |
| Report Title: A 104-Week Carcinogenicity Study of a-Difluoromethylornithine (DFMO) in Mice |      |                                                               |       |       |        |                         |                |       |
| Species/Strain: Mouse (B <sub>6</sub> C <sub>3</sub> F <sub>1</sub> )                      |      | Duration of Dosing: At least 104 consecutive weeks            |       |       |        | Study No.: IITRI L06297 |                |       |
| Initial Age: 4 to 5 weeks                                                                  |      | Method of Administration: Oral, admixed in the diet           |       |       |        | Location: 4.2.3.4.1.1   |                |       |
| Vehicle/Formulation: In diet                                                               |      |                                                               |       |       |        |                         |                |       |
| Date of First Dose: 23 January 1997 (all animals)                                          |      | Treatment of Controls: Group 1 received untreated rodent chow |       |       |        | GLP Compliance: Yes     |                |       |
| Basis for High-Dose Selection: Data not provided in study report                           |      |                                                               |       |       |        |                         |                |       |
| No Observed Effect Levels (NOEL) for Neoplasia: 1000 mg/kg                                 |      |                                                               |       |       |        |                         |                |       |
| Special Features: None                                                                     |      |                                                               |       |       |        |                         |                |       |
| Sex                                                                                        | Male |                                                               |       |       | Female |                         |                |       |
| Daily Dose (mg/kg/day)                                                                     | 0    | 100                                                           | 300   | 1000  | 0      | 100                     | 300            | 1000  |
| Number of Toxicity Animals                                                                 | 50   | 50                                                            | 50    | 50    | 50     | 50                      | 50             | 50    |
| Number of Toxicokinetic Animals <sup>a</sup>                                               | 5    | 5                                                             | 5     | 5     | 5      | 5                       | 5              | 5     |
| Month 18, C <sub>p</sub> (mg /mL)                                                          | NA   | 6.45                                                          | 18.32 | 59.35 | NA     | 5.04                    | 21.91          | 33.23 |
| Noteworthy Findings:                                                                       |      |                                                               |       |       |        |                         |                |       |
| Died or Sacrificed Moribund                                                                | 7    | 6 <sup>c</sup>                                                | 9     | 9     | 6      | 10                      | 9 <sup>d</sup> | 10    |
| Number of Animals at Terminal Sacrifice -Week 104                                          | 43   | 44                                                            | 41    | 41    | 44     | 40                      | 41             | 40    |

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{Eflornithine [DFMO]}

|                                                                                                   |             |            |                                                                      |             |               |                                |            |             |
|---------------------------------------------------------------------------------------------------|-------------|------------|----------------------------------------------------------------------|-------------|---------------|--------------------------------|------------|-------------|
| <b>Test Article: DFMO</b>                                                                         |             |            |                                                                      |             |               |                                |            |             |
| <b>Report Title: A 104-Week Carcinogenicity Study of a-Difluoromethylornithine (DFMO) in Mice</b> |             |            |                                                                      |             |               |                                |            |             |
| <b>Species/Strain:</b> Mouse (B <sub>6</sub> C <sub>3</sub> F <sub>1</sub> )                      |             |            | <b>Duration of Dosing:</b> At least 104 consecutive weeks            |             |               | <b>Study No.:</b> IITRI L06297 |            |             |
| <b>Initial Age:</b> 4 to 5 weeks                                                                  |             |            | <b>Method of Administration:</b> Oral, admixed in the diet           |             |               | <b>Location:</b> 4.2.3.4.1.1   |            |             |
| <b>Vehicle/Formulation:</b> In diet                                                               |             |            |                                                                      |             |               |                                |            |             |
| <b>Date of First Dose:</b> 23 January 1997 (all animals)                                          |             |            | <b>Treatment of Controls:</b> Group 1 received untreated rodent chow |             |               | <b>GLP Compliance:</b> Yes     |            |             |
| <b>Basis for High-Dose Selection:</b> Data not provided in study report                           |             |            |                                                                      |             |               |                                |            |             |
| <b>No Observed Effect Levels (NOEL) for Neoplasia:</b> 1000 mg/kg                                 |             |            |                                                                      |             |               |                                |            |             |
| <b>Special Features:</b> None                                                                     |             |            |                                                                      |             |               |                                |            |             |
| <b>Sex</b>                                                                                        | <b>Male</b> |            |                                                                      |             | <b>Female</b> |                                |            |             |
| <b>Daily Dose (mg/kg/day)</b>                                                                     | <b>0</b>    | <b>100</b> | <b>300</b>                                                           | <b>1000</b> | <b>0</b>      | <b>100</b>                     | <b>300</b> | <b>1000</b> |
| <b>Number of Toxicity Animals</b>                                                                 | <b>50</b>   | <b>50</b>  | <b>50</b>                                                            | <b>50</b>   | <b>50</b>     | <b>50</b>                      | <b>50</b>  | <b>50</b>   |
| <b>Number of Toxicokinetic Animals<sup>a</sup></b>                                                | <b>5</b>    | <b>5</b>   | <b>5</b>                                                             | <b>5</b>    | <b>5</b>      | <b>5</b>                       | <b>5</b>   | <b>5</b>    |
| <b>Survival to Terminal Sacrifice - Week 104 (%)</b>                                              | 86          | 88         | 82                                                                   | 82          | 88            | 80                             | 82         | 80          |
| <b>No Observed Effect Levels (NOEL) for Neoplasia:</b> 1000 mg/kg                                 |             |            |                                                                      |             |               |                                |            |             |
| <b>Special Features:</b> None                                                                     |             |            |                                                                      |             |               |                                |            |             |
| <b>Sex</b>                                                                                        | <b>Male</b> |            |                                                                      |             | <b>Female</b> |                                |            |             |
| <b>Daily Dose (mg/kg/day)</b>                                                                     | <b>0</b>    | <b>100</b> | <b>300</b>                                                           | <b>1000</b> | <b>0</b>      | <b>100</b>                     | <b>300</b> | <b>1000</b> |
| <b>Number of Toxicity Animals</b>                                                                 | <b>50</b>   | <b>50</b>  | <b>50</b>                                                            | <b>50</b>   | <b>50</b>     | <b>50</b>                      | <b>50</b>  | <b>50</b>   |

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{Eflornithine [DFMO]}

|                                                                            |          |                |          |          |          |          |                |          |
|----------------------------------------------------------------------------|----------|----------------|----------|----------|----------|----------|----------------|----------|
| <b>Number of Toxicokinetic Animals<sup>a</sup></b>                         | <b>5</b> | <b>5</b>       | <b>5</b> | <b>5</b> | <b>5</b> | <b>5</b> | <b>5</b>       | <b>5</b> |
| <b>Toxicokinetics<sup>b</sup>:</b>                                         |          |                |          |          |          |          |                |          |
| <b>Month 3, C<sub>p</sub> (µg /mL)</b>                                     | NA       | 2.48           | 3.94     | 10.52    | NA       | 0.86     | 4.76           | 10.99    |
| <b>Month 16, C<sub>p</sub> (µg /mL)</b>                                    | NA       | BDL            | 2.61     | 7.56     | NA       | BDL      | BDL            | 4.73     |
| <b>Month 18, C<sub>p</sub> (µg /mL)</b>                                    | NA       | 6.45           | 18.32    | 59.35    | NA       | 5.04     | 21.91          | 33.23    |
| <b>Noteworthy Findings:</b>                                                |          |                |          |          |          |          |                |          |
| <b>Died or Sacrificed Moribund</b>                                         | 7        | 6 <sup>c</sup> | 9        | 9        | 6        | 10       | 9 <sup>d</sup> | 10       |
| <b>Number of Animals at Terminal Sacrifice –Week 104</b>                   | 43       | 44             | 41       | 41       | 44       | 40       | 41             | 40       |
| <b>Survival to Terminal Sacrifice –Week 104 (%)</b>                        | 86       | 88             | 82       | 82       | 88       | 80       | 82             | 80       |
| <b>Clinical Observations (most frequently observed; number of animals)</b> |          |                |          |          |          |          |                |          |
| Alopecia                                                                   | 30       | 34             | 39       | 40       | 28       | 32       | 29             | 26       |

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| Histopathology: Number of Animals with Neoplastic Lesions |                               |   |   |    |    |   |   |    |
|-----------------------------------------------------------|-------------------------------|---|---|----|----|---|---|----|
| Number evaluated                                          |                               |   |   |    |    |   |   |    |
| Lung (Number evaluated)                                   | 50                            | - | - | 50 | 50 | - | - | 49 |
| Adenocarcinoma, alveolar cell                             | 2                             | - | - | 6  | 2  | - | - | 2  |
| Adenoma, alveolar cell                                    | 3                             | - | - | 5  | 1  | - | - | 7  |
| Hematopoietic cell tumor (Number evaluated)               | 11                            | - | - | 8  | 20 | - | - | 20 |
| Lymphoma, FCC                                             | 6                             | - | - | 8  | 13 | - | - | 10 |
| Lymphoma, lymphoblastic                                   | 2                             | - | - | 0  | 6  | - | - | 4  |
| Erythroid leukemia                                        | -                             | - | - | -  | 0  | - | - | 1  |
| Histiocytic sarcoma                                       | 1                             | - | - | 0  | 1  | - | - | 5  |
| Noteworthy Findings:                                      |                               |   |   |    |    |   |   |    |
| Gross Pathology                                           | No treatment-related findings |   |   |    |    |   |   |    |
| Organ Weight                                              | No treatment-related findings |   |   |    |    |   |   |    |
| Histopathology – Incidence Non-Neoplastic Lesions         |                               |   |   |    |    |   |   |    |
|                                                           | No treatment-related findings |   |   |    |    |   |   |    |

Statistical significance based on actual data (not on percent difference): \*\* P < .01

BDL=below detection limit; C<sub>p</sub>= Plasma concentration; NA=not applicable

<sup>a</sup> Blood samples were taken from the first 5 surviving satellite animals (n=35/sex/group). Satellite animals were used for clinical pathology and TK evaluations.

<sup>b</sup> A single blood sample was taken in the morning during Month 3 and 18, and, inadvertently, in the afternoon during Month 16.

<sup>c</sup> Includes one accidental death

<sup>d</sup> Includes three accidental deaths

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{Eflornithine [DFMO]}

**Table 4: 104-Week Oral Carcinogenicity Study with DFMO in Fischer-344 Rats**

|                                                                                   |  |                                                                       |      |     |     |                           |      |      |     |
|-----------------------------------------------------------------------------------|--|-----------------------------------------------------------------------|------|-----|-----|---------------------------|------|------|-----|
| Test Article: DFMO                                                                |  |                                                                       |      |     |     |                           |      |      |     |
| Report Title: 104-Week Oral Carcinogenicity Study with DFMO in Fischer-344 Rats   |  |                                                                       |      |     |     |                           |      |      |     |
| Species/Strain: Rat (Fischer-344)                                                 |  | Duration of Dosing: 104 consecutive weeks                             |      |     |     | Study No.: SRI 9118.01.01 |      |      |     |
| Initial Age: 7 to 8 weeks                                                         |  | Method of Administration: Oral gavage                                 |      |     |     | Location: 4.2.3.4.1.2     |      |      |     |
|                                                                                   |  | Vehicle/Formulation: 0.5% carboxymethylcellulose in deionized water   |      |     |     |                           |      |      |     |
| Date of First Dose: 03 December 1996 (all animals)                                |  | Treatment of Controls: 0.5% carboxymethylcellulose in deionized water |      |     |     | GLP Compliance: Yes       |      |      |     |
| Basis for High-Dose Selection: Data not provided in study report                  |  |                                                                       |      |     |     |                           |      |      |     |
| No Observed Effect Levels (NOEL) for Neoplasia: Data not provided in study report |  |                                                                       |      |     |     |                           |      |      |     |
| Special Features: None                                                            |  |                                                                       |      |     |     |                           |      |      |     |
| Sex                                                                               |  | Male                                                                  |      |     |     | Female                    |      |      |     |
| Daily Dose (mg/kg/day)                                                            |  | 0                                                                     | 150  | 300 | 600 | 0                         | 150  | 300  | 600 |
| Number of Toxicity Animals                                                        |  | 60                                                                    | 60   | 60  | 60  | 50                        | 50   | 50   | 50  |
| Number of Toxicokinetic Animals <sup>a</sup>                                      |  | 10                                                                    | 10   | 10  | 10  | 10                        | 10   | 10   | 10  |
| Toxicokinetics <sup>b</sup> :                                                     |  |                                                                       |      |     |     |                           |      |      |     |
| Month 6, C <sub>max</sub> (µg/mL)                                                 |  | NA                                                                    | 69.5 | 138 | 228 | NA                        | 49.1 | 91.6 | 209 |
| Month 12, C <sub>max</sub> (µg/mL)                                                |  | NA                                                                    | 74.5 | 134 | 197 | NA                        | 74.9 | 142  | 254 |
| Month 18, C <sub>max</sub> (µg/mL)                                                |  | NA                                                                    | 90.0 | 136 | 217 | NA                        | 80.3 | 133  | 272 |
| Month 24, C <sub>max</sub> (µg/mL)                                                |  | NA                                                                    | 107  | 154 | 192 | NA                        | 109  | 170  | 247 |
| Number of Animals at Start Study                                                  |  | 60                                                                    | 60   | 60  | 60  | 50                        | 50   | 50   | 50  |
| Number of Animals Died or Sacrificed Moribund                                     |  | 22                                                                    | 24   | 22  | 27  | 18                        | 16   | 14   | 19  |
| Number of Animals at Terminal Sacrifice -Week 104                                 |  | 38                                                                    | 36   | 38  | 33  | 32                        | 34   | 36   | 31  |
| Survival to Terminal Sacrifice -Week 104 (%)                                      |  | 63                                                                    | 60   | 63  | 55  | 64                        | 68   | 72   | 62  |

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{Eflornithine [DFMO]}

| Clinical Observations (most frequently observed; number of animals) |                               |      |        |        |    |    |    |    |
|---------------------------------------------------------------------|-------------------------------|------|--------|--------|----|----|----|----|
| Alopecia                                                            | 0                             | 2    | 3      | 11     | 6  | 6  | 5  | 5  |
| Sores/ulcers                                                        | 12                            | 6    | 7      | 8      | 1  | 4  | 5  | 6  |
| Ptosis                                                              | 18                            | 16   | 22     | 28     | 19 | 27 | 30 | 26 |
| Head tilt                                                           | 17                            | 18   | 27     | 23     | 7  | 11 | 7  | 10 |
| Tissue masses                                                       | 16                            | 13   | 10     | 8      | 6  | 10 | 9  | 6  |
| Gross Pathology                                                     | No treatment-related findings |      |        |        |    |    |    |    |
| Organ Weight                                                        |                               |      |        |        |    |    |    |    |
| Number Evaluated                                                    | 38                            | 35   | 38     | 33     | NA | NA | NA | NA |
| Testes (pair)                                                       |                               |      |        |        |    |    |    |    |
| Organ weight (absolute)                                             | 4.18 g                        | -6.3 | -22.4* | -28.5* | -  | -  | -  | -  |
| Organ/body weight ratio                                             | 11.2                          | -8   | -22.6* | -23.0* | -  | -  | -  | -  |
| Histopathology: Non-Neoplastic Lesions <sup>c</sup>                 |                               |      |        |        |    |    |    |    |
| Lung (Number evaluated)                                             | 60                            | 60   | 60     | 60     | 50 | 50 | 50 | 50 |
| Histiocytic cellular infiltrate                                     | 8                             | 11   | 25     | 30     | 7  | 8  | 11 | 16 |
| Hyperplasia, alveolar epithelium                                    | 4                             | 3    | 7      | 3      | 1  | 2  | 1  | 1  |
| Congestion                                                          | 2                             | 4    | 4      | 8      | 6  | 5  | 9  | 5  |
| Hemorrhage                                                          | 3                             | 8    | 3      | 6      | 2  | 1  | 1  | 1  |
| Edema                                                               | 1                             | 0    | 6      | 0      | 1  | 2  | 3  | 1  |
| Foreign body                                                        | 5                             | 4    | 2      | 3      | 0  | 1  | 0  | 0  |
| Suppurative inflammation                                            | 1                             | 1    | 2      | 0      | 1  | 1  | 0  | 0  |
| Granulomatous inflammation                                          | 4                             | 4    | 3      | 4      | 0  | 0  | 1  | 0  |
| Pancreas (Number evaluated)                                         | 60                            | 60   | 60     | 60     | 50 | 50 | 50 | 50 |
| atrophy, acinar cell                                                | 12                            | 19   | 14     | 17     | 2  | 8  | 6  | 9  |
| Focal hyperplasia, acinar cell                                      | 0                             | 1    | 2      | 0      | 0  | 0  | 0  | 0  |
| Cytoplasmic alteration, acinar cell                                 | 1                             | 2    | 0      | 1      | 0  | 1  | 0  | 0  |
| Hemorrhage                                                          | 0                             | 0    | 0      | 0      | 1  | 0  | 0  | 0  |

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{Eflornithine [DFMO]}

|                           |    |    |    |    |    |    |    |    |
|---------------------------|----|----|----|----|----|----|----|----|
| Hyperplasia, islet cell   | 1  | 4  | 2  | 2  | 0  | 0  | 0  | 0  |
| Edema                     | 0  | 0  | 0  | 1  | 0  | 0  | 0  | 0  |
| Cyst                      | 1  | 0  | 1  | 1  | 0  | 0  | 0  | 0  |
| Skin (Number evaluated)   | 60 | 36 | 34 | 60 | 49 | 22 | 18 | 50 |
| Hyperplasia, epidermis    | 1  | 12 | 11 | 5  | 1  | 2  | 2  | 1  |
| Hyperkeratosis            | 1  | 1  | 0  | 0  | 0  | 1  | 0  | 0  |
| Ulcer                     | 6  | 12 | 14 | 16 | 0  | 3  | 2  | 3  |
| Chronic inflammation      | 2  | 1  | 4  | 3  | 1  | 2  | 1  | 0  |
| Hemorrhage                | 0  | 1  | 0  | 0  | 0  | 0  | 0  | 0  |
| Edema                     | 0  | 0  | 0  | 1  | 1  | 0  | 0  | 0  |
| Epithelial inclusion cyst | 1  | 0  | 0  | 0  | 0  | 0  | 1  | 0  |

BDL=below detection limit; Cmax= Maximum plasma concentration; NA=not applicable; MCV=mean corpuscular volume; nRBC=nucleated red blood cells; RBC=red blood cells; WBC=white blood cells

Statistical significance based on actual data (not on percent difference): \*P < .05; \*\* P < .01

a A single blood sample was taken from the first 10 surviving rats used for collection of blood samples for clinical chemistry analyses

b A single blood sample was taken at 1-2 hours after dosing at 6, 12, and 18 months and at study termination prior to necropsy

c Complete histopathological evaluation was performed on control and high dose rats as well as low and mid dose rats that died on study. Based on possible drug-related lesions in the initial evaluation, spleen, lungs, and pancreas from all male and female animals in 150 and 300 mg/kg/day dose groups, including those from the scheduled sacrifice, were subsequently also evaluated

A 104-week carcinogenicity study in male and female B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> mice (IITRI #L06297, Study 3) with oral administration of DFMO admixed with the diet at dose levels of 0, 100, 300, and 1000 mg/kg/day, did not result in treatment-related neoplastic or non-neoplastic histopathological lesions.

- o Except for a slight, but statistically significant reduction in male body weights, no treatment-related effects were seen on any parameter evaluated including survival, female body weights, food consumption, clinical pathology, and organ weights.
- o There was no indication of a carcinogenic effect in any organ in male or female B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> mice after 104 weeks of DFMO dosing up to 1000 mg/kg/day.

In a 104-week carcinogenicity study in male and female Fischer-344 rats (SRI #9118.01.01), DFMO was administered via oral gavage at dose levels of 0, 150, 300, and 600 mg/kg/day.

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{Eflornithine [DFMO]}

DFMO had no impact on the overall survival (OS) of rats and sufficient numbers of animals survived to the terminal sacrifice to adequately evaluate carcinogenicity.

- Slight reductions in body weight gain for both sexes, consistent with the observations made in mice. The primary signs of toxicity associated with DFMO administration included an increased incidence of alopecia in male rats and an increased incidence of ptosis in both male and female rats.
- Increased incidences in mononuclear cell leukemia, islet adenoma, and squamous cell carcinomas were observed in treated relative to control animals and were considered potentially test article-related; however only the increased incidence in mononuclear cell leukemia was considered biologically relevant.
- DFMO was not considered carcinogenic in the rat at doses levels up to 600 mg/kg/day.

#### The FDA's Assessment

The FDA acknowledges the Applicant's summary of the 104-week mouse and rat carcinogenicity studies and generally agrees with the conclusions, including the provided  $C_{max}$  values (AUC was not measured). The results of these studies were previously reviewed by Dr. Alexander H. Putman and discussed with the FDA Executive Carcinogenicity Assessment Committee (ECAC) on June 1, 2021, under another NDA. The carcinogenicity studies were conducted over 20 years ago by contract research organizations contracted by the National Cancer Institute, and the ECAC was not involved in the study design of either study. Dr. Putman's review of the 104-week carcinogenicity studies is summarized below.

There were no eflornithine-related neoplasms in mice (Study #L06297/N01-CN-25506) or rats (Study #9118.01.01/N01-CN-65028) at doses up to 1000 mg/kg/day and 600 mg/kg/day, respectively, under the conditions of these studies; however, confirmatory statistical analyses could not be conducted because the Applicant did not submit tumor.xpt files. In the 104-week mouse study, histopathological findings were only examined in control and high dose mice, so a dose-response relationship could not be established. The ECAC did not concur that the 104-week carcinogenicity study in mice was adequate because of an insufficient basis for dose selection and inadequate histopathology. Thus, the nonclinical team recommends that data from the mouse carcinogenicity study not be included in the IWILFIN label. The ECAC did not concur that data from male rats in the 104-week study were adequate because of insufficient dose justification and lack of adverse body weight or other findings. The ECAC concurred that data from female rats in the 104-week study were adequate due to adverse body weight findings (up to 8%

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{Eflornithine [DFMO]}

decrease in body weight at 600 mg/kg/day) and tumor data. Thus, the lack of drug-related neoplasms in female rats was included in Section 13.1 of the IWILFIN label.

#### 5.5.4. Reproductive and Developmental Toxicology

The reproductive toxicity studies supporting this application were previously submitted to the Ornidyl NDA. In lieu tabular presentations, toxicology sections are presented here in brief with guidance to the specific NDA sections for more information. Reproductive toxicology is fully discussed in 2.6.6.

Oral teratogenicity studies were conducted in rats and rabbits during the period of organogenesis (Kirchner 1999).

- Rats were administered DFMO by oral gavage at 30, 80, or 200 mg/kg/day on GD 6-17 with dams sacrificed on GD 20.
  - Maternal toxicity was not observed during the study.
  - Developmental toxicity consisting of decreased fetal weights and increased incidence of skeletal variations was observed at 200 mg/kg/day.
  - No fetal skeletal malformations or visceral anomalies were noted at any dose.
  - The maternal NOEL for the rat was 200 mg/kg/day (1200 mg/m<sup>2</sup>/day) and the fetal NOEL was 80 mg/kg/day (480 mg/m<sup>2</sup>/day).
- Rabbits were administered DFMO by oral gavage at 15, 45, or 135 mg/kg/day on GD 7-20 with dams sacrificed on GD 29.
  - Maternal toxicity was not noted at any dose.
  - Developmental toxicity, such as increased early resorption (nonsignificant), decreased implantation sites, decreased viable fetuses, and reduced fetal weights, was observed at the high dose.
  - No fetal skeletal malformations or external and visceral anomalies were noted.
  - The maternal NOEL for the rabbit was 135 mg/kg/day (1620 mg/m<sup>2</sup>/day) and the fetal NOEL was 45 mg/kg/day (540 mg/m<sup>2</sup>/day).

An oral peri- and postnatal reproductive toxicity study was performed with administration of DFMO in drinking water.

- Rats were administered at 0.1, 0.3, or 1.0% (average dose levels for first weeks of treatment were 167, 480, and 1329 mg/kg/day, corresponding to 1002, 2880, and 7974 mg/m<sup>2</sup>/day) during the last week of gestation and continuing to weaning.

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{Eflornithine [DFMO]}

- Significant maternal toxicity, consisting of reduced body weights and food and water consumption, was seen at the mid and high dose, but without adverse effects on maternal reproductive parameters.
- Pup weights were also significantly reduced at the mid and high dose levels, continuing throughout the growth period in female pups and for 5 weeks in male pups.
- A reduced fertility index was seen in F<sub>1</sub> offspring in the high dose group.
- The NOEL was considered to be at the low dose with 0.1% DFMO in drinking water (167 mg/kg/day, or 1002 mg/m<sup>2</sup>/day) ([ORNIDYL 1990](#)).

The FDA's Assessment (all data presented by the FDA):

Fertility and Early Embryonic Development

No new studies were submitted to the NDA. Stand-alone fertility or early embryonic development studies were not previously reviewed under the Ornidyl NDA and are not needed to support the use of eflornithine in the proposed indication per ICH S9.

Embryo-Fetal Development

The rat and rabbit embryofetal development studies summarized in Kirchner et al. (1999) were not included in the original Ornidyl submission; however, the Applicant submitted study reports for these GLP-compliant studies for which they have the right of reference to the NDA. The Applicant also submitted dose range-finding embryofetal development studies to the NDA. FDA generally agrees with the Applicant's assessment of the embryofetal studies in rats and rabbits, although one pregnant dam in the rat study dosed with 200 mg/kg eflornithine exhibited severe hydronephrosis in the right kidney. FDA's assessment of the GLP-compliant studies is below.

**Study title/ number: Oral Developmental Toxicity Study of DFMO in Rats / NO1-CN-55110-MAO/USWM-DF0-TOX-0005**

Key Study Findings

- There was no maternal toxicity except one rat dosed with 200 mg/kg eflornithine exhibited severe hydronephrosis in the right kidney
- Treatment with 200 mg/kg eflornithine resulted in decreased fetal body weights and an increase in the incidence of skeletal variations
- Eflornithine was not teratogenic and did not affect embryo-fetal survival at doses up to

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*Version date: July 2021 (ALL NDA/ BLA reviews)*

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{Eflornithine [DFMO]}

200 mg/kg

GLP compliance: Yes

#### Methods

Dose and frequency of dosing: 0, 30, 80 and 200 mg/kg once daily from Gestation Day (GD) 6 to 17

\*Doses were selected based on a dose range-finding study (#USWM-DF0-TOX-0006; 0, 50, 125, 300, 800, 2000 mg/kg/day) in pregnant rats. Rats dosed with 300 mg/kg eflornithine exhibited increased early resorptions and post-implantation loss compared to controls concomitant with decreased numbers of viable fetuses and fetal weight. Rats dosed with  $\geq 800$  mg/kg eflornithine exhibited complete early resorption resulting in 100% post-implantation loss and no viable fetuses.

Route of administration: Oral gavage

Formulation/Vehicle: Deionized distilled water

Species/Strain: Rat / CrI:CD<sup>®</sup> BR CD<sup>®</sup>

Number/Sex/Group: 25 females/group

Satellite groups: None

Study design: Time-mated female rats (mating confirmed by vaginal plug on GD 0) were received on GD 1, 2, or 3 and eflornithine was given once daily on GD 6-17. Rats were euthanized on GD 20.

Deviation from study protocol affecting interpretation of results: No

#### **Observations and Results**

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Version date: July 2021 (ALL NDA/ BLA reviews)

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

{Eflornithine [DFMO]}

| Parameters                        | Major findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mortality                         | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Clinical Signs                    | No drug-related findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Body Weights and Food Consumption | No drug-related findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Gravid Uterine Weights            | Unremarkable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Necropsy findings                 | <i>Gross Pathology</i><br><br>One rat (#985) dosed with 30 mg/kg eflornithine exhibited a fluid-filled pancreatic cyst. One rat (#994) dosed with 80 mg/kg eflornithine exhibited multiple abscesses adhered to the right lung. One rat (#1165) dosed with 200 mg/kg eflornithine exhibited severe hydronephrosis in the right kidney.<br><br><i>Cesarean Section Data</i><br><br>Treatment with 200 mg/kg eflornithine resulted in an ~10% statistically significant decrease in mean fetal body weights compared to controls. |

| Cesarean Section Findings (Embryo-fetal development Study; Rats) |           |           |           |           |
|------------------------------------------------------------------|-----------|-----------|-----------|-----------|
| Dose (mg/kg)                                                     | 0         | 30        | 80        | 200       |
| # Mated females                                                  | 25        | 25        | 25        | 25        |
| # Pregnant (%)                                                   | 23 (92%)  | 22 (88%)  | 22 (88%)  | 23 (92%)  |
| # Dams with live fetuses (%)                                     | 23 (100%) | 22 (100%) | 22 (100%) | 23 (100%) |
| Mean # corpora lutea                                             | 15.1      | 13.3      | 13.6      | 13.6      |
| Mean # implantation sites                                        | 12.4      | 12.7      | 12.7      | 12.8      |
| Mean % pre-implantation loss                                     | 15.3%     | 3.9%      | 5.7%      | 4.9%      |
| Mean % post-implantation loss                                    | 8.3%      | 4.7%      | 5.8%      | 9.1%      |
| Mean % total implantation loss                                   | 22.1%     | 8.4%      | 11.2%     | 13.6%     |

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{Eflornithine [DFMO]}

|                                             |      |      |      |       |
|---------------------------------------------|------|------|------|-------|
| Mean # early resorptions                    | 1    | 0.6  | 0.7  | 1     |
| Mean # late resorptions                     | 0    | 0    | 0    | 0     |
| Mean # dead (nonviable) fetuses             | 0    | 0    | 0    | 0.1   |
| Mean # live (viable) fetuses                | 11.4 | 12.1 | 12   | 11.7  |
| Mean fetal body weight (g): Male            | 3.85 | 3.81 | 3.76 | 3.41* |
| Female                                      | 3.55 | 3.63 | 3.58 | 3.25* |
| Litter                                      | 3.7  | 3.72 | 3.65 | 3.34* |
| Mean fetal sex ratio (% males) <sup>§</sup> | 53.4 | 50.4 | 43.7 | 49.8  |

\* , P ≤ 0.05 vs. controls; Mean % implantation loss were calculated by Applicant [% pre-implantation loss = (# of corpora lutea - # of implants) / # of corpora lutea x 100; % post-implantation loss = (# of implants - # of live fetuses) / # of implants x 100; % total implantation loss = (# of corpora lutea - # of live fetuses) / # of corpora lutea x 100]; Other (%) values were calculated on a litter basis

<sup>§</sup> : Calculated by Reviewer based on individual fetal sex data

|                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Necropsy findings | There were no eflornithine-related fetal malformations or external/visceral variations.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Offspring         | There was an increase in the incidence of skeletal variations (presence of a 14th rudimentary rib, 14th full rib, and 27th presacral vertebrae) at 200 mg/kg compared to controls. Historical control data was not provided for the testing facility, but the Applicant cited historical control data for the rat strain at a different facility (MARTA/MTA Historical Control Data, 1996). Although the presence of a 14 <sup>th</sup> rudimentary rib was also increased at the 30 and 80 mg/kg dose levels compared to controls, the incidence (based on % litter) was within the historical control range of CrI:CD® BR CD® mice. |

## Fetal Malformations and Variations (Embryo-fetal development Study; Rats)

| Dose (mg/kg)                  | 0   | 30  | 80  | 200 |
|-------------------------------|-----|-----|-----|-----|
| # Fetuses examined externally | 262 | 266 | 263 | 268 |

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{Eflornithine [DFMO]}

| Dose (mg/kg)                                                        | 0                     | 30       | 80       | 200        |
|---------------------------------------------------------------------|-----------------------|----------|----------|------------|
| # Fetuses examined viscera                                          | 132                   | 129      | 135      | 133        |
| # Fetuses examined skeletally                                       | 130                   | 137      | 128      | 135        |
| # of Litters examined                                               | 23                    | 22       | 22       | 23         |
| Total # fetuses with malformations (% of litters)                   | 2 <sup>§</sup> (8.7%) | 1 (4.5%) | 1 (4.5%) | 1 (4.3%)   |
| Total # fetuses with variations (% of litters)                      | 61 (87%)              | 60 (86%) | 65 (86%) | 106 (100%) |
| <b>Skeletal malformations: # of fetuses affected (% of litters)</b> |                       |          |          |            |
| Vertebral anomaly with associated rib anomaly                       | 0 (0%)                | 0 (0%)   | 1 (4.5%) | 0 (0%)     |
| Costal cartilage anomaly                                            | 0 (0%)                | 0 (0%)   | 0 (0%)   | 1 (4.3%)   |
| Total # with skeletal malformations (% of litters)                  | 0 (0%)                | 0 (0%)   | 1 (4.5%) | 1 (4.3%)   |
| <b>Skeletal variations: # of fetuses affected (% of litters)</b>    |                       |          |          |            |
| 14 <sup>th</sup> full ribs                                          | 0 (0%)                | 0 (0%)   | 0 (0%)   | 9 (22%)*   |
| 14 <sup>th</sup> rudimentary ribs                                   | 0 (0%)                | 6 (18%)* | 5 (18%)* | 60 (91%)*  |
| Cervical arches- reduced ossification                               | 0 (0%)                | 0 (0%)   | 0 (0%)   | 1 (4.3%)   |
| 27 presacral vertebrae                                              | 0 (0%)                | 0 (0%)   | 0 (0%)   | 55 (74%)*  |

% per litter calculated by Reviewer = (Total # of litters with malformation or variation / Total # of litters) x 100;

§: Includes 2 control rats (2 litters) with external malformations not shown in this Table; ^: Includes 1 control rat (1 litter) with a visceral malformation not shown in this Table

|                       |              |
|-----------------------|--------------|
| <b>Toxicokinetics</b> | Not assessed |
|-----------------------|--------------|

**Study title/ number: Oral Developmental Toxicity Study of DFMO in Rabbits / NO1-CN-55110-MAO/USWM-DF0-TOX-0003**

#### Key Study Findings

- Treatment with 135 mg/kg eflornithine resulted in reduced gravid uterine weight
- Eflornithine resulted in abortions in one rabbit at 15 mg/kg and one rabbit at 135 mg/kg

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{Eflornithine [DFMO]}

- Treatment with 135 mg/kg eflornithine resulted in a slight decrease in implantation sites and live fetuses; increased pre-implantation and post-implantation loss; increased early resorptions; and decreased fetal weights
- Eflornithine was not teratogenic at doses up to 135 mg/kg. There was a slight increase in unossified talus (skeletal variation) at 135 mg/kg compared to controls.

GLP compliance: Yes

### Methods

|                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dose and frequency of dosing: | 0, 15, 45, and 135 mg/kg once daily from Gestation Day (GD) 7 to 20<br><br>*Doses were selected based on a dose range-finding study (#USWM-DF0-TOX-0004; 0, 30, 60, 120, 240, 500 mg/kg/day) in pregnant rabbits. Reduced fetal body weights were observed at doses $\geq$ 120 mg/kg. Treatment with 240 mg/kg resulted in increased early/late resorptions, post-implantation loss, and dead fetuses compared to controls and decreased live fetuses. Treatment with 500 mg/kg resulted in complete early resorptions, 100% post-implantation loss, and no live fetuses. |
| Route of administration:      | Oral gavage                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Formulation/Vehicle:          | Deionized distilled water                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Species/Strain:               | Rabbit / New Zealand White                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Number/Sex/Group:             | 20 females/group                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Satellite groups:             | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Study design:                 | Time-mated female rabbits (mating presumed on GD 0) were received on GD 1, 2, or 3 and eflornithine was given once daily on GD 7-20. Rabbits were euthanized on GD 29.                                                                                                                                                                                                                                                                                                                                                                                                    |

{Eflornithine [DFMO]}

Deviation from study protocol affecting interpretation of results: No

## Observations and Results

| Parameters                        | Major findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mortality                         | <p>There were no mortalities due to eflornithine-induced toxicity.</p> <p>One rabbit (#422) dosed with 15 mg/kg eflornithine and one rabbit (#480) dosed with 135 mg/kg eflornithine aborted their litters and were subsequently euthanized on GD26 and GD18, respectively. Blood was observed in their cage pans. One rabbit (#439) dosed with 15 mg/kg eflornithine delivered prematurely and was subsequently euthanized on GD29.</p>                                                                         |
| Clinical Signs                    | Unremarkable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Body Weights and Food Consumption | Unremarkable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Gravid Uterine Weights            | There was a statistically significant 23% decrease in mean uterine weight in rabbits dosed with 135 mg/kg eflornithine compared to controls, which correlated with decreased fetal weight.                                                                                                                                                                                                                                                                                                                       |
| Necropsy findings                 | <p><i>Gross Pathology</i></p> <p>No drug-related findings</p> <p><i>Cesarean Section Data</i></p> <p>One rabbit dosed with 15 mg/kg eflornithine and one rabbit dosed with 135 mg/kg eflornithine aborted their litters. These findings were not dose-dependent, but did occur at the high dose level, so a relationship to eflornithine cannot be definitively ruled out.</p> <p>Treatment with 135 mg/kg eflornithine resulted in a slight decrease in implantation sites and live fetuses, increased pre-</p> |

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{Eflornithine [DFMO]}

|                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |            |          |          |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|----------|----------|
|                                                                     | implantation and post-implantation loss, and increased early resorptions. These findings were not statistically significant compared to controls. Additional analyses of individual data conducted by the FDA reviewer demonstrated that although there was not a substantial difference in the number of eflornithine treated-dams with pre- and post-implantation losses compared to controls, the magnitude of pre- and post-implantation loss was higher in dams dosed with 135 mg/kg eflornithine compared to controls. Treatment with 135 mg/kg eflornithine also resulted in an up to 17% statistically significant decrease in mean fetal body weights compared to controls. |            |          |          |
| Cesarean Section Findings (Embryo-fetal development Study; Rabbits) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |            |          |          |
| Dose (mg/kg)                                                        | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 15         | 45       | 135      |
| # Mated females                                                     | 20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 20         | 20       | 20       |
| # Pregnant (%)                                                      | 19 (95%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 17 (85%)   | 19 (95%) | 19 (95%) |
| # Premature delivery/abortion                                       | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 2          | 0        | 1        |
| # Examined at cesarean section                                      | 20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 18         | 20       | 19       |
| # Dams with live fetuses (%)                                        | 19 (95%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 17 (94.4%) | 19 (95%) | 18 (95%) |
| Mean # corpora lutea                                                | 9.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 9.8        | 9.3      | 9.5      |
| Mean # implantation sites                                           | 8.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 8.6        | 8.4      | 7.9      |
| Mean % pre-implantation loss                                        | 6.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 13.6%      | 9.4%     | 16.8%    |
| Mean % post-implantation loss                                       | 2.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 4.9%       | 3.4%     | 12.8%    |
| Mean % total implantation loss                                      | 8.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 17.7%      | 12.5%    | 28.1%    |
| Mean # early resorptions                                            | 0.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 0.1        | 0.3      | 0.7      |
| Mean # late resorptions                                             | 0.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 0.4        | 0        | 0.3      |
| Mean # total resorptions                                            | 0.3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 0.5        | 0.3      | 1.1      |
| Mean # dead (nonviable) fetuses                                     | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0          | 0        | 0        |
| Mean # live (viable) fetuses                                        | 8.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 8.1        | 8.1      | 6.8      |

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{Eflornithine [DFMO]}

|                                             |       |       |       |        |
|---------------------------------------------|-------|-------|-------|--------|
| Mean fetal body weight (g): Male            | 37.93 | 39.42 | 37.75 | 32.83* |
| Female                                      | 39.18 | 35.59 | 36.55 | 32.44* |
| Litter                                      | 38.28 | 38.7  | 37.26 | 32.6*  |
| Mean fetal sex ratio (% males) <sup>§</sup> | 57.8  | 53.3  | 59.7  | 54.6   |

\*,  $P \leq 0.05$  vs. controls; Mean % implantation loss were calculated by Applicant [% pre-implantation loss = (# of corpora lutea - # of implants) / # of corpora lutea x 100; % post-implantation loss = (# of implants - # of live fetuses) / # of implants x 100; % total implantation loss = (# of corpora lutea - # of live fetuses) / # of corpora lutea x 100]; Other (%) values were calculated on a litter basis

<sup>§</sup> : Calculated by Reviewer based on individual fetal sex data

|                   |                                                                                                                                                                                                                                                                                                                                  |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Necropsy findings | There were no eflornithine-related fetal malformations. There was a slight increase in skeletal variations (i.e., talus unossified) at 135 mg/kg compared to controls. Skeletal variation is likely secondary to decreased fetal body weight. The Applicant did not provide or reference historical control data for comparison. |
| Offspring         |                                                                                                                                                                                                                                                                                                                                  |

## Fetal Malformations and Variations (Embryo-fetal development Study; Rabbits)

| Dose (mg/kg)                                                     | 0          | 15         | 45         | 135        |
|------------------------------------------------------------------|------------|------------|------------|------------|
| # Fetuses examined                                               | 155        | 138        | 154        | 130        |
| # of Litters examined                                            | 19         | 17         | 19         | 18         |
| Total # fetuses with malformations (% of litters)                | 4 (21%)    | 5 (24%)    | 7 (32%)    | 1 (5.6%)   |
| Total # fetuses with variations (% of litters) <sup>^</sup>      | 130 (100%) | 109 (100%) | 125 (100%) | 102 (100%) |
| <b>Skeletal variations: # of fetuses affected (% of litters)</b> |            |            |            |            |
| 12 <sup>th</sup> rudimentary ribs                                | 0 (0%)     | 0 (0%)     | 0 (0%)     | 1 (5.6%)   |
| 25 presacral vertebrae                                           | 0 (0%)     | 0 (0%)     | 0 (0%)     | 1 (5.6%)   |
| Talus unossified                                                 | 1 (5.3%)   | 0 (0%)     | 0 (0%)     | 3 (17%)    |

% per litter calculated by Reviewer = (Total # of litters with malformation or variation / Total # of litters) x 100;

<sup>^</sup>: Includes non-drug-related variations not included in this table; <sup>§</sup>: Includes malformations in control rabbits not included in this table

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{Eflornithine [DFMO]}

|                       |              |
|-----------------------|--------------|
| <b>Toxicokinetics</b> | Not assessed |
|-----------------------|--------------|

Since eflornithine induced more severe embryofetal toxicity at higher dose levels in dose range-finding embryofetal development studies, pertinent findings from these studies relevant for labeling are reviewed below. Toxicokinetics was not evaluated in these studies.

**Study title/ number: Oral Dose Range-Finding Developmental Toxicity Study of DFMO in Rats / NO1-CN-55110-MAO/USWM-DF0-TOX-0006**

Time-mated female CD® rats (5/group) were administered 0, 50, 125, 300, 800, or 2000 mg/kg eflornithine once daily via oral gavage during GD 6-17 and were euthanized on GD 20. Fetal examination was limited to weight, sex, and gross external alterations. Eflornithine induced maternal toxicity characterized by reduced body weight and food consumption at dose levels  $\geq$  800 mg/kg/day. Rats dosed with  $\geq$  300 mg/kg/day eflornithine exhibited reduced uterine and fetal body weights; increased early resorptions and post-implantation loss; and decreased numbers of viable fetuses (Table 5). Treatment with 800 mg/kg/day eflornithine resulted in 100% post-implantation loss and no viable fetuses.

**Table 5: Cesarean Section Findings in Dose Range-Finding Embryo-fetal Development Study in Rats**

| Dose (mg/kg)                   | 0        | 50       | 125      | 300     | 800      | 2000     |
|--------------------------------|----------|----------|----------|---------|----------|----------|
| # Mated females                | 5        | 5        | 5        | 5       | 5        | 5        |
| # Pregnant (%)                 | 5 (100%) | 5 (100%) | 5 (100%) | 4 (80%) | 5 (100%) | 5 (100%) |
| Uterine weight (g)             | 75.6     | 57.3*    | 68.7     | 29.4*   | 2.9*     | 0.5*     |
| Mean # corpora lutea           | 15       | 11.8     | 14.4     | 11      | 14.4     | 12.8     |
| Mean # implantation sites      | 13.6     | 10.6     | 12.6     | 10      | 11.8     | 11.4     |
| Mean % pre-implantation loss   | 8.7%     | 11.7%    | 11%      | 6.2%    | 15.7%    | 11.4%    |
| Mean % post-implantation loss  | 1.4%     | 3.3%     | 6.2%     | 40.9%*  | 100%*    | 100%*    |
| Mean % total implantation loss | 10.1%    | 14.8%    | 16.4%    | 43.9%*  | 100%*    | 100%*    |
| Mean # early resorptions       | 0.2      | 0.4      | 0.8      | 5.2*    | 11.8*    | 11.4*    |

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{Eflornithine [DFMO]}

| Dose (mg/kg)                                  | 0     | 50    | 125   | 300   | 800 | 2000 |
|-----------------------------------------------|-------|-------|-------|-------|-----|------|
| # Mated females                               | 5     | 5     | 5     | 5     | 5   | 5    |
| Mean # late resorptions                       | 0     | 0     | 0     | 0     | 0   | 0    |
| Mean # dead fetuses                           | 0     | 0     | 0     | 0     | 0   | 0    |
| Mean # live (viable) fetuses                  | 13.4  | 10.2* | 11.8  | 4.8*  | 0*  | 0*   |
| Mean fetal body weight (g): Male              | 3.91  | 3.74  | 3.79  | 2.93* | NA  | NA   |
| Female                                        | 3.53  | 3.53  | 3.59  | 2.9*  |     |      |
| Mean fetal sex ratio (% males) <sup>§</sup>   | 34%   | 54.9% | 64.6% | 39%   | NA  | NA   |
| Number of fetuses with variations (anomalies) | 2 (0) | 1 (0) | 1 (0) | 1 (1) | NA  | NA   |

\*, P ≤ 0.05 vs. controls; NA = Not applicable; § : Calculated by Reviewer

Mean % implantation loss were calculated by Applicant [% pre-implantation loss = (# of corpora lutea - # of implants) / # of corpora lutea x 100; % post-implantation loss = (# of implants - # of live fetuses) / # of implants x 100; % total implantation loss = (# of corpora lutea - # of live fetuses) / # of corpora lutea x 100]; Other (%) values were calculated on a litter basis

**Study title/ number: Oral Dose Range-Finding Developmental Toxicity Study of DFMO in Rabbits / NO1-CN-55110-MAO/USWM-DF0-TOX-0004**

Time-mated female New Zealand White rabbits (5/group) were administered 0, 30, 60, 120, 240, or 500 mg/kg eflornithine once daily via oral gavage during GD 7-20 and were euthanized on GD 29. Fetal examination was limited to weight, sex, and gross external alterations. Eflornithine did not induce substantial maternal toxicity. Treatment with ≥ 120 mg/kg/day eflornithine resulted in reduced fetal body weights (Table 6). Rabbits dosed with ≥ 240 mg/kg/day eflornithine exhibited reduced uterine weight; increased early resorptions, post-implantation loss,

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{Eflornithine [DFMO]}

and dead fetuses; and decreased live fetuses. Treatment with 500 mg/kg/day eflornithine resulted in 100% post-implantation loss and no viable fetuses.

**Table 6: Cesarean Section Findings in Dose Range-Finding Embryo-fetal Development Study in Rabbits**

| Dose (mg/kg)                                  | 0        | 30       | 60       | 120      | 240      | 500      |
|-----------------------------------------------|----------|----------|----------|----------|----------|----------|
| # Mated females                               | 5        | 5        | 5        | 5        | 5        | 5        |
| # Pregnant (%)                                | 5 (100%) | 5 (100%) | 5 (100%) | 5 (100%) | 5 (100%) | 5 (100%) |
| Uterine weight (g)                            | 530.5    | 480.7    | 472.7    | 435.5    | 162.4*   | 13.59*   |
| Mean # corpora lutea                          | 11.2     | 11.2     | 11.6     | 11       | 10.8     | 8        |
| Mean # implantation sites                     | 10       | 9.2      | 10.2     | 10.4     | 9.8      | 8        |
| Mean % pre-implantation loss                  | 11.4%    | 17.9%    | 12.7%    | 5.6%     | 8.7%     | 0%       |
| Mean % post-implantation loss                 | 3.3%     | 4%       | 4.7%     | 1.8%     | 75.1%*   | 100%*    |
| Mean % total implantation loss                | 14.8%    | 20.1%    | 16.4%    | 7.4%     | 75.7%*   | 100%*    |
| Mean # early resorptions                      | 0        | 0.2      | 0.2      | 0.2      | 4.6      | 8*       |
| Mean # late resorptions                       | 0        | 0        | 0        | 0        | 1.2      | 0        |
| Mean # dead fetuses                           | 0.4      | 0        | 0.2      | 0        | 1.4      | 0        |
| Mean # live (viable) fetuses                  | 9.6      | 9        | 9.8      | 10.2     | 2.6*     | 0*       |
| Mean fetal body weight (g): Male              | 38.3     | 38.7     | 35.6     | 30.3*    | 27*      | NA       |
| Female                                        | 40.1     | 38.3     | 35.3     | 31.6*    | 29.2*    |          |
| Mean fetal sex ratio (% males) <sup>§</sup>   | 55%      | 51%      | 51%      | 41%      | 38%      | NA       |
| Number of fetuses with variations (anomalies) | 0 (0)    | 0 (0)    | 0 (0)    | 0 (0)    | 0 (0)    | 0 (0)    |

\*,  $P \leq 0.05$  vs. controls; NA = Not applicable; <sup>§</sup>: Calculated by Reviewer

Mean % implantation loss were calculated by Applicant [% pre-implantation loss = (# of corpora lutea - # of implants) / # of corpora lutea x 100; % post-implantation loss = (# of implants - # of live fetuses) / # of implants x 100; % total implantation loss = (# of corpora lutea - # of live fetuses) / # of corpora lutea x 100]; Other (%) values were calculated on a litter basis

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#### Prenatal and Postnatal Development

No new studies were submitted to the NDA. The FDA agrees that is appropriate to rely on FDA's previous findings of prenatal and postnatal development toxicity (oral studies) for ORNIDYL.

#### **5.5.5. Other Toxicology Studies**

##### The Applicant's Position:

Not applicable.

##### The FDA's Assessment:

The FDA agrees with the Applicant's Position.

X

X

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Emily F. Wearne, PhD  
Primary Reviewer

Claudia P. Miller, PhD  
Supervisor

## 6. CLINICAL PHARMACOLOGY

### 6.1. Executive Summary

#### The FDA's Assessment:

The Applicant submitted the current 505(b)(2) NDA 215500 for Iwilfin® (eflornithine hydrochloride, DFMO) Tablets for the proposed indication to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma (HRNB) who have completed multiagent, multimodality therapy. The reference drug, Ornidy1® (eflornithine hydrochloride) for Injection, was approved in 1990 for the treatment of West African sleeping sickness.

The Applicant submitted a single externally controlled trial comprised of data from Study 3(b), a multi-center, open-label, single arm trial of eflornithine monotherapy 750 mg/m<sup>2</sup> ( $\pm$  250 mg/m<sup>2</sup>) BID for up to 2 years in pediatric patients with HRNB in remission after immunotherapy, compared to an external control arm constructed from patients enrolled on Study ANBL0032, a multi-center, open-label, randomized trial of immunotherapy plus standard up-front therapy vs. up-front therapy alone. A total of 90 eflornithine-treated patients who met the criteria for the comparison and had complete data for specified clinical covariates were matched (1:3) using propensity scores to 270 ANBL0032 control patients for a comparison of outcomes. The Applicant's primary analysis resulted in a HR for EFS of 0.48 (95% CI: 0.27, 0.85) and 0.32 (95% CI: 0.15, 0.70) for OS, favoring the eflornithine arm.

The proposed dosage was selected based on PK, safety and efficacy results from an earlier publication and results from a Phase 1 dose-escalation study where dosages of 500, 7500, 1000, and 1500 mg/m<sup>2</sup> BID were evaluated. The safety profile with the tested dose is acceptable given the low incidence of Grade 3 AEs (i.e., hypoacusis, increased ALT/AST, diarrhea) and Grade 4 AEs (one event of hypoglycemia). A small number of patients experienced hearing loss which largely recovered with dose interruption and reduction. An interim analysis from the ongoing Study 14 provided additional safety and pharmacokinetic (PK) data for eflornithine for the treatment of pediatric patients with HRNB in remission.

A non-compartmental analysis (NCA) of PK data from patients (N = 190) in Study 14, suggested that age (1 year to 19 years), body surface area (0.4 m<sup>2</sup> to 2.0 m<sup>2</sup>), sex, and race (White, Black or African American, Asian, American Indian or Alaska native, Native Hawaiian or other Pacific

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Islander) had no clinically meaningful effects on the PK exposure to eflornithine. A limited exposure-response (E-R) analysis for safety found no correlation between the eflornithine PK exposure based on the BSA-based dosage and its safety profile. These data and analyses support the proposed BSA-based dosing regimen. A post-marketing requirement (PMR) will be issued to request the applicant to conduct a renal impairment study in patients with moderate to severe renal impairment to inform dosage adjustment as a post-marketing requirement.

### 6.1.1. Recommendations

The Clinical Pharmacology review team has reviewed the information contained in NDA 215500. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and/or comments are summarized in Table 7 and an outstanding Clinical Pharmacology issue to be conveyed to the Applicant through a post-marketing requirement (PMR) is summarized in Table 8 below.

**Table 7. The Key Clinical Pharmacology Review Issues, Recommendations and Comments**

| <b>Review Issue</b>                                                  | <b>Recommendations and Comments</b>                                                                                                                                                                                                                                                       |
|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pivotal or supportive evidence of effectiveness</b>               | The primary evidence of efficacy and safety is provided by Study 3(b) conducted in pediatric patients with HRNB in remission. Both EFS and OS favor eflornithine. The interim analysis of the ongoing Study 14 provided supportive evidence of safety in the intended patient population. |
| <b>General dosing instructions</b>                                   | The proposed eflornithine dosing regimen is $576 \pm 192$ mg/m <sup>2</sup> (free base) or $750 \pm 250$ mg/m <sup>2</sup> (salt form) BID                                                                                                                                                |
| <b>Dosing in patient subgroups (intrinsic and extrinsic factors)</b> | The effect of intrinsic and extrinsic factors (including effects of age, body size, sex, race, food, and administered dose) on eflornithine PK were evaluated in Study 14 with no relationships identified.                                                                               |
| <b>Drug Interactions</b>                                             | Based on the in vitro studies, no drug-drug interaction (DDI) potential for eflornithine                                                                                                                                                                                                  |
| <b>Labeling</b>                                                      | FDA labeling revisions per FDA labeling guidance have been provided.                                                                                                                                                                                                                      |

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**Table 8. Outstanding Clinical Pharmacology Issues**

| Key Issue(s) to be Addressed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Rationale                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Conduct a clinical pharmacokinetic trial to determine an appropriate dosage of DFMO to minimize a potential serious risk of increased drug toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing.” found at <a href="https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing-and">https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing-and</a></p> | <p>Eighty percent of systemically available DFMO is excreted in urine unchanged. The effect of moderate or severe renal impairment on the exposure of DFMO is unknown and requires a clinical study to ensure safe use of the drug in the intended population. The results will inform dosage adjustment if needed for this specific patient population.</p> |

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

#### Pharmacokinetics

The PK characteristics of orally administered DFMO have been reported in the scientific literature. DFMO peak plasma concentrations are reached within a range of 3.4-6 hr after administration of an oral tablet in adults and 2.5-3.75 hr in children with dose-linear plasma concentrations. Griffin et al. showed linear PK after oral DFMO at dose levels up to 3.75 g/m<sup>2</sup>, above which dose a plateau in exposure was observed. Volume of distribution ranged from 0.30 to 0.35 L/kg and total body clearance from 1.2 to 2.5 mL/min/kg (Haegle 1981, Study 14 PK Report, Section 8.4). The terminal t<sub>1/2</sub> was reported to range from 3.5 hr to 4 hr. DFMO exposure after administration of an oral tablet (0.5 g/m<sup>2</sup>) was shown to be bioequivalent to that of an oral solution (0.5 g/m<sup>2</sup>) in normal volunteers.

Additionally, the Applicant has characterized the pharmacokinetic (PK) parameters of DFMO in 1) a food effect study conducted in healthy volunteers, USWM-FE-1001, and 2) the intended patient population utilizing data from Studies 3b and 14.

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Below are summary tables describing the clinical pharmacokinetics of DFMO. Full discussions and data can be found in 2.7.2.2.2.

**Table 9: Summary of Clinical Pharmacokinetics**

| Study Design and Treatment                                                                                                                                                                                                                                                                                                                                            |                  | PK Parameters |                                |       |                  |                |                     |     |          |      |                |                |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------------|--------------------------------|-------|------------------|----------------|---------------------|-----|----------|------|----------------|----------------|--|
| Study Number: NMTRC003b (Study 3b)                                                                                                                                                                                                                                                                                                                                    |                  |               |                                |       |                  |                |                     |     |          |      |                |                |  |
| Primary Objective: To evaluate preventative activity of DFMO as a single agent in patients that are in remission based on event free survival                                                                                                                                                                                                                         |                  |               |                                |       |                  |                |                     |     |          |      |                |                |  |
| PK Objective: To evaluate the PK of a new source of DFMO drug product (DP Source 2) in a minimum of 10 patients, as compared to the original source (DP Source 1)                                                                                                                                                                                                     |                  |               |                                |       |                  |                |                     |     |          |      |                |                |  |
| Design: Phase II, open-label, single-arm study of DFMO as a chemopreventative treatment in HRNB patients in remission after standard up-front treatment or following treatment for refractory or relapsed disease. Plasma PK samples were collected at predose and 0.5, 1, 3, and 6 hours after dosing each formulation (administered as the same dose <sup>a</sup> ) |                  |               |                                |       |                  |                |                     |     |          |      |                |                |  |
| Population: HRNB patients in remission; 12 patients evaluated for PK. Sex: 8 M/4 F; Mean age: 4.4 years; Age range: 3-6 years                                                                                                                                                                                                                                         |                  |               |                                |       |                  |                |                     |     |          |      |                |                |  |
| Treatment:<br>DFMO 250 mg IR tablets (dosed based on BSA):<br>Target dose of 750 mg/m <sup>2</sup> BID (actual dose: 500 to 1000 mg/m <sup>2</sup> BID)                                                                                                                                                                                                               | C <sub>max</sub> |               | AUC <sub>6</sub>               |       | T <sub>max</sub> |                | CL <sub>ss</sub> /F |     | Vd/F     |      | t <sub>½</sub> |                |  |
|                                                                                                                                                                                                                                                                                                                                                                       | Gmean (µg/mL)    | GCV %         | Gmean (h•µg/mL)                | GCV % | Median (h)       | Min to Max (h) | Mean (L/h)          | CV% | Mean (L) | CV % | Median (h)     | Min to Max (h) |  |
| DP Source 1 (n=10)                                                                                                                                                                                                                                                                                                                                                    | 10.1             | 51.0          | 40.1                           | 52.2  | 3                | 1 to 6         | -                   | -   | -        | -    | -              | -              |  |
| DP Source 2 (n=12)                                                                                                                                                                                                                                                                                                                                                    | 10.5             | 58.0          | 41.9                           | 57.5  | 3                | 1 to 6         | -                   | -   | -        | -    | -              | -              |  |
| Study Number: NMTRC014 (Study 14)                                                                                                                                                                                                                                                                                                                                     |                  |               |                                |       |                  |                |                     |     |          |      |                |                |  |
| Primary Study Objective: To evaluate efficacy of DFMO as a single agent in preventing relapse in patients with HRNB who are in remission based upon event free survival                                                                                                                                                                                               |                  |               |                                |       |                  |                |                     |     |          |      |                |                |  |
| PK Objective: To describe PK of DFMO in pediatric patients                                                                                                                                                                                                                                                                                                            |                  |               |                                |       |                  |                |                     |     |          |      |                |                |  |
| Design: Phase II, open-label, single agent, multicenter study. PK samples collected at 1, 91, and 181 days (at predose and 45 minutes, 3 hours, and 6 hours postdose)                                                                                                                                                                                                 |                  |               |                                |       |                  |                |                     |     |          |      |                |                |  |
| Population: Patients with HRNB in remission; 441 projected patients. As of cut-off date: 221 PK Evaluable patients and 171 PK Finisher patients (Sex: 96 M/75 F; Mean age: 5.59 years; Age range: 1-19 years)                                                                                                                                                         |                  |               |                                |       |                  |                |                     |     |          |      |                |                |  |
| Treatment                                                                                                                                                                                                                                                                                                                                                             | C <sub>max</sub> |               | AUC <sub>12</sub> <sup>b</sup> |       | T <sub>max</sub> |                | CL/F                |     | Vz/F     |      | t <sub>½</sub> |                |  |

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| Study Design and Treatment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | PK Parameters    |          |                        |          |                  |                         |                     |          |              |          |                |                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|----------|------------------------|----------|------------------|-------------------------|---------------------|----------|--------------|----------|----------------|----------------------|
| DFMO 250 mg IR tablets (dosed based on BSA):<br>750 ± 250 mg/m <sup>2</sup> BID for 730 days; (Strata 1, 2, 3, and 4) OR<br>2500 mg/m <sup>2</sup> BID (Stratum 1B) (no PK available)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Gmean<br>(µg/mL) | GCV<br>% | Gmean<br>(h•µg/<br>mL) | GCV<br>% | Median<br>(h)    | Min<br>to<br>Max<br>(h) | Gmean<br>(L/h)      | GCV<br>% | Gmean<br>(L) | GCV<br>% | Median<br>(h)  | Min to<br>Max<br>(h) |
| Day 1 PK Finisher Patients (N=171, n varies with parameter)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 13.6             | 65.7     | 82.4                   | 55.8     | 3.0              | 0.0 to<br>6.3           | 4.8                 | 51.1     | 20.0         | 68.2     | 2.7            | 1.2 to<br>49.8       |
| Day 91 PK Finisher Patients (N=171, n varies with parameter)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 16.6             | 58.3     | 98.0                   | 55.7     | 3.0              | 0.9 to<br>6.1           | 4.6                 | 57.4     | 18.3         | 75.8     | 2.8            | 0.8 to<br>11.4       |
| Day 181 PK Finisher Patients (N=171, n varies with parameter)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 16.9             | 56.4     | 101.8                  | 53.5     | 3.0              | 0.0 to<br>6.0           | 4.6                 | 55.6     | 18.2         | 67.2     | 2.8            | 1.0 to<br>6.6        |
| <b>Study Number: USWM-FE1-1001</b><br><b>Primary Study Objective:</b> To evaluate the relative bioavailability of intact (i.e. “whole”) DFMO tablets administered under fasted conditions to that of intact DFMO tablets administered under fed conditions and of intact tablets administered under fasted conditions to that of crushed DFMO tablets mixed into standard pudding (approximately 2 tablespoons) and administered under fasted conditions<br><b>Design:</b> Phase 1, open-label, single-center, multiple-dose, randomized, 3-treatment, 4-sequence crossover food effect study; DFMO administered BID for 10 days as described below. PK samples collected on Days 6, 8, 10, and 11 (predose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours postdose)<br><b>Population:</b> Healthy adult participants; 17 participants were included in the study; 16 completed and evaluated for PK. Sex: 14 M/3 F; Mean age: 32 years; Age range: 22-45 years |                  |          |                        |          |                  |                         |                     |          |              |          |                |                      |
| Treatment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | C <sub>max</sub> |          | AUC <sub>12</sub>      |          | T <sub>max</sub> |                         | CL <sub>ss</sub> /F |          | Vd/F         |          | t <sub>½</sub> |                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Gmean<br>(µg/mL) | GCV<br>% | Gmean<br>(h•µg/<br>mL) | GCV<br>% | Median<br>(h)    | Min<br>to<br>Max<br>(h) | Gmean<br>(L/h)      | GCV<br>% | Gmean<br>(L) | GCV<br>% | Median<br>(h)  | Min to<br>Max<br>(h) |
| Intact tablets DFMO 1500 mg (6 × 250 mg) BID for 10 days; fasted condition (n=16)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 20.0             | 34.9     | 117.8                  | 27.0     | 2.5              | 2.0 to<br>6.0           | 9.8                 | 27.0     | 38.3         | 32.4     | 2.8            | 2.2 to<br>3.4        |

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| Study Design and Treatment                                                                            | PK Parameters |      |       |      |     |            |      |      |      |      |     |            |
|-------------------------------------------------------------------------------------------------------|---------------|------|-------|------|-----|------------|------|------|------|------|-----|------------|
| Intact tablets DFMO 1500 mg (6 × 250 mg) BID for 10 days; fed condition (n=16)                        | 18.6          | 12.8 | 114.7 | 12.5 | 3.0 | 2.0 to 4.1 | 10.1 | 12.6 | 37.8 | 17.7 | 2.6 | 2.2 to 3.2 |
| Crushed tablets DFMO 1500 mg (6 x 250 mg) mixed with pudding BID for 10 days; fasted condition (n=16) | 20.5          | 14.4 | 118.0 | 18.1 | 2.5 | 2.0 to 3.0 | 9.8  | 18.1 | 37.4 | 23.6 | 2.7 | 2.2 to 3.1 |

AUC<sub>6</sub> = area under the concentration-time curve from time 0 to 6 hours postdose; AUC<sub>12</sub> = area under the concentration-time curve from time 0 to 12 hours postdose; BID = twice daily; BSA = body surface area; CL/F and CL<sub>ss</sub>/F = apparent total body clearance; C<sub>max</sub> = maximum observed drug concentration; CPP = Cancer Prevention Pharmaceuticals; CV = coefficient of variation; F = female; GCV=geometric coefficient of variation; Gmean = geometric mean; HRNB = high-risk neuroblastoma; IR = immediate-release; KCP = KC Pharma, LLC; M = male; max = maximum; min = minimum; n = number of observations; N = number in population; PK = pharmacokinetic(s); t<sub>1/2</sub> = elimination half-life; T<sub>max</sub> = time of maximum observed drug concentration; Vz/F, V<sub>d</sub>/F = apparent volume of distribution

<sup>a</sup> 11 patients in Study 3b received the same dose for both formulations, while 1 patient received a dose of 500 mg for the CPP formulation and 750 mg for the KCP formulation since they had an increase in BSA between the 2 observation periods.

<sup>b</sup> AUC<sub>12</sub> was estimated as described in the NMTRC014 PK Report, Section 8.4.1.1.

Note: For Study USWM-FE-1001, GCV calculations were not included in the USWM-FE-1001 PK Report, and therefore these values were calculated by the Applicant using Listing 7.3-6 of the USWM-FE-1001 PK Report.

Source: NMTRC 003B Clinical Study Report and 3b DFMO Pharmacokinetics and Comparative Bioavailability Report, Table 1 and Table 3; Study NMTRC014 PK Report, Table 8, Table 18, and Table 10.3.2; USWM-FE1-1001 Clinical Study Report, Table 7 and Table 8; USWM-FE1-1001 PK Report Amendment 1, Table 7.1-2

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Details on the study designs and summaries of individual study results are provided in Section 2.7.2

- NMTRC003b (referred to as Study 3b): A Phase II preventative study of DFMO as a single agent in patients with HRNB in remission.
- NMTRC014 (referred to as Study 14): A Phase II, open-label, single agent, multicenter, study designed to evaluate safety, efficacy, and PK of maintenance DFMO for patients with HRNB in remission. This study is currently ongoing, and an interim analysis of PK data from 221 patients is summarized (as described in Section 2.7.2.2.2.).
- USWM-FE1-1001: A Phase I, single center, multiple-dose, open-label, randomized, 3-treatment, 4-sequence crossover food-effect study of DFMO.

Clinical pharmacology is supported by these studies as follows:

- PK parameters of DFMO have been characterized in the intended patient population utilizing data from Studies 3b and 14, which provide support for the DFMO dosing regimen of  $750 \pm 250$  mg/m<sup>2</sup> BID for 2 years.
- The effect of food on DFMO PK parameters was investigated in USWM-FE1-1001.
- The bioavailability of DFMO administered as crushed tablets as compared to intact tablets was evaluated in healthy participants in Study USWM-FE1-1001 and findings were supported in pediatric HRNB patients in Study 14.
- The relationship between systemic DFMO exposure and corrected QT (QTc) intervals was evaluated in Study 14.
- DFMO exposures as associated with clinical chemistry data indicative of renal and hepatic function were evaluated in Study 14.
- The effect of intrinsic and extrinsic factors (including effects of age, body size, sex, race, food, and administered dose) on DFMO PK were evaluated in Study 14 with no relationships identified.

### Pharmacodynamics

Evaluations of Study 14 PK data included evaluation of pharmacodynamics as follows:

- In Study 14, a single electrocardiogram (ECG) was performed at Screening and additional ECGs were collected in triplicate (3 ECGs in a row) at 1 single time point that coincided with the 3-hour postdose PK sample on PK Days 1, 91, and 181 (the 3-hour time point is the time of C<sub>max</sub> in most patients). QT interval corrected by Fridericia's formula (QTcF) values from triplicate ECGs at each time point were averaged and plotted against the DFMO concentration in the corresponding PK sample.

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- For both absolute and change from Baseline QTcF analysis, the slope of the regression line is flat to slightly negative, supporting that there is no apparent QTcF prolongation risk with DFMO treatment at therapeutic levels. Additionally, very few QTcF intervals were observed over 450 msec and no intervals over 500 msec occurred. No increases of >60 msec from Baseline were observed.
- QTcF and change from Baseline are also presented by individual PK day (NMTRC014, Appendix 16.5, Figure 30, Figure 31, and Figure 32) for Days 1, 91, and 181, respectively.
- No clear relationships between exposure and response for safety or efficacy were identified in a limited analysis of interim data from Study 14, although such analyses were limited to outcomes reported within the first 180 days of therapy which coincided with PK sampling. To further investigate, dose category and outcomes were assessed within the more mature dataset of Study 3b as discussed in Section 8.1.1 below.

## Special Populations

### Hepatic Impairment

Hepatic impairment is not expected to be a common comorbidity in the HRNB population following up-front treatment. In support of this characterization of the intended patient population, the inclusion criteria in both Studies 3b and 14 required patients to have adequate hepatic function defined as AST and ALT levels <10x the upper limit of normal (ULN). In Study 3b, patients were also required to have serum bilirubin level  $\leq 2.0$  mg/dL to be eligible for the study. The eligibility criteria allowed for some level of impairment, as an AST or ALT level at 10x ULN would be the equivalent of a Grade 3 AE (which the Common Terminology Criteria for Adverse Events defines as >5 to 20x ULN [if normal at baseline] for AST and ALT). There were no documented screen fails based on these criteria in either Study 3b or within the HRNB patients included in the Study 14 interim PK report. However, collection of screen fail information was not required per protocol in Study 14 until approximately midway through the study.

Available absorption, distribution, metabolism, excretion (ADME) information on DFMO pharmacology supports that DFMO is not highly metabolized, therefore, hepatic impairment would not be expected to alter DFMO exposure. Due to the inclusion criteria applied in Studies 3b and 14 the Applicant would have limited ability to collect exposure data in patients with impaired liver function in these studies even if hepatic impairment was more common. However, an assessment of hepatic function vs. DFMO exposure has been performed on data from Study 14. The Applicant examined DFMO exposure, as quantified by AUC<sub>6</sub>, for its dependence on hepatic function, as quantified by ALT, AST, and bilirubin summarized in 2.7.2.3.4.

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## Renal Impairment

Renal clearance of DFMO is the main clearance pathway for DFMO with 80% of systemically available DFMO being recovered unchanged in the urine in healthy normal volunteers following IV and oral dosing. Despite harsh up-front medical treatment including treatment with drugs known to impair kidney function such as cisplatin, few HRNB patients have been found to have impaired renal function, even at the end of up-front treatment with first-line chemotherapies. The inclusion criteria in both Studies 3b and 14 protocols required patients to have adequate renal function. For Study 14, this was defined as creatinine clearance or radioisotope GFR  $\geq 70$  mL/min/1.73 m<sup>2</sup> or an allowed serum creatinine based on age and sex. For Study 3b, adequate renal function was based on serum creatinine based on age and sex.

There were no documented screen fails based on these criteria in either Study 3b or within the HRNB patients included in the Study 14 interim PK report. However, collection of screen fail information was not required per protocol in Study 14 until approximately midway through the study. Therefore, the Applicant would have limited ability to collect exposure data in patients with impaired renal functions in these studies even if renal impairment was common. However, a preliminary analysis of DFMO exposure (AUC<sub>6</sub>) vs. renal function has been performed on data from Study 14.

Described in 2.7.2.3.4, positive trends for AUC<sub>6</sub> to increase with increasing creatinine and BUN were observed, consistent with the apparent importance of renal clearance for DFMO elimination in healthy adults. The regression relationships indicate AUC<sub>6</sub> increased approximately 30% as creatinine increased from 20 µmol/L to 100 µmol/L, both creatinine values being within the normal range. Steady-state AUC<sub>6</sub> increased approximately 40% as the BUN increased from 2 mmol/L to 12.5 mmol/L, the normal range for BUN has been reported to be approximately 1.8 to 6.4 mmol/L ([PediaMCU 2022](#)). While few HRNB patients apparently have impaired renal function, even after harsh up-front treatments prior to starting maintenance treatments with DFMO, the drug should be used with caution in a patient that has moderate or severe renal impairment. Since the drug is hydrophilic and not extensively protein bound, it is expected to be cleared by dialysis.

### The Applicant's Position:

The pharmacokinetic and pharmacodynamic properties of 192 mg immediate release DFMO tablets have been well characterized. The Applicant has conducted one study in healthy adult volunteers, USWM-FE1-1001, and performed extensive PK analyses in the target HRNB patient population within a subset of patients in Study 3b and from an interim analysis of Study 14. The clinical pharmacology program is also supported by relevant published literature, and information associated with the Ornidyl NDA. The data generated by the clinical pharmacology

program characterizes the PK of DFMO in pediatric patients ranging from 1 year to 19 years of age. The results extend the understanding of DFMO PK in adults, as reported previously in published literature and the Orindyl NDA, to the pediatric patient population.

#### The FDA's Assessment:

The Applicant's PK characterization of eflornithine is generally acceptable.

The PK data in the intended patient population mainly come from Study 14. The Applicant analyzed the effect of intrinsic factors (including effects of age, body size, sex, race) on eflornithine PK exposure based on individual patient's exposure using the non-compartmental analysis (NCA). FDA's assessment confirmed that age, BSA, weight have no clinically meaning effects on eflornithine PK exposures (C<sub>max</sub> and AUC<sub>0-12h</sub>). The Applicant did not conduct a pop-PK analysis to evaluate the effect of intrinsic and extrinsic factors on eflornithine PK exposure.

FDA agrees with the Applicant's analysis of the results of food-effect study, USWM-FE-1001, which demonstrated that food has no clinically meaningful effect on the bioavailability of eflornithine intact tablets and crushed tablets. Therefore, both eflornithine intact tablets and crushed tablets can be administered without regard to food intake.

No moderate or severe hepatic or renally impaired patients were enrolled in the clinical studies. FDA agrees with the Applicant that hepatic impairment would not be expected to alter eflornithine exposure as 80% of systemically available eflornithine is excreted in urine unchanged. The Applicant will be required to conduct a clinical study to evaluate the effect of moderate and severe renal impairment on eflornithine exposure as a PMR.

The FDA QT-IRT review team's analysis of the QTc data using by-time as the primary analysis showed that eflornithine does not cause a mean increase in the QTc interval  $\geq 20$  msec at the proposed dosage, which is supported by the lack of QTc prolongation in nonclinical data and categorical analysis.

{Eflornithine [DFMO]}

**6.2.2. General Dosing and Therapeutic Individualization****6.2.2.1. General Dosing**Data:

DFMO immediate release (IR) tablets, contain 192 mg eflornithine free base (250 mg eflornithine HCl monohydrate salt) for oral administration. DFMO doses are presented in terms of the eflornithine HCl monohydrate salt, as this was the nomenclature used in the clinical protocols discussed and from which are presented herein. All 11 dose levels studied in the clinical program were achieved by administering multiple units of 192 mg eflornithine HCl monohydrate salt tablets. The recommended dose of oral DFMO is  $576 \pm 192 \text{ mg/m}^2$  BID free base ( $750 \pm 250 \text{ mg/m}^2$  BID), i.e.,  $1152 \pm 384 \text{ mg/m}^2$  per day free base ( $1500 \pm 500 \text{ mg/m}^2$  per day), for 2 years. A dose conversion table (Table 10) is provided below for reference.

**Table 10: DFMO Clinical Dosing Regimen**

| BSA (m <sup>2</sup> ) | Tablets to be Dispenses for Each Dose | Total Tablets Per Day | Dose mg/m <sup>2</sup> (eflornithine HCl) | Dose mg/m <sup>2</sup> (eflornithine free base) |
|-----------------------|---------------------------------------|-----------------------|-------------------------------------------|-------------------------------------------------|
| >1.5                  | Four (4) tablets orally twice a day   | Eight (8)             | 625 and down, BID                         | 480 and down, BID                               |
| 0.75 to 1.5           | Three (3) tablets orally twice a day  | Six (6)               | 500 to 1000, BID                          | 384 to 768, BID                                 |
| 0.5 to <0.75          | Two (2) tablets orally twice a day    | Four (4)              | 675 to 1000, BID                          | 518 to 768, BID                                 |
| 0.25 to <0.5          | One (1) tablet orally twice a day     | Two (2)               | 500 to 1000, BID                          | 384 to 768, BID                                 |
| <0.25                 | Not eligible for trial                |                       |                                           |                                                 |

The Applicant's Position:

Treating patients in this age range requires a dose that can adjust as they grow. Our dosing regimen, based on BSA, is adaptive and our data demonstrates that the recommended dosing regimen (used in both Study 3b and Study 14) is a safe and effective.

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#### The FDA's Assessment:

A single dosage of DFMO  $576 \pm 192 \text{ mg/m}^2$  (free base) or  $750 \pm 250 \text{ mg/m}^2$  (salt form) BID was studied in Studies 3(b) and 14 to support the NDA submission. The Applicant's justification for the proposed dosage includes the following aspects:

- Early published work in adult chemoprevention studies identified  $500 \text{ mg/m}^2/\text{day}$  as the lower end of clinical dose range.
- A Phase 1, dose escalation study in neuroblastoma patients (0-21 years of age) (Study NCT01059071) studied the following dosages:  $500 \text{ mg/m}^2$  BID (n = 4);  $750 \text{ mg/m}^2$  BID (n = 5);  $1000 \text{ mg/m}^2$  BID (n = 3) and  $1500 \text{ mg/m}^2$  BID (n = 9). There were no confirmed DLTs or study drug related SAEs, and MTD was not established.
- There was a lack of a clear dose response in the Phase 1 study to justify the selection of a higher dose.
- Data from an interim analysis of Study 14 supports the proposed dosing regimen.
- There were limited dose modifications and discontinuations due to tolerability challenges in Studies 3(b) and 14.

The Applicant's justifications for the proposed dosage appear reasonable. An information request (IR) was issued on February 24, 2023, requesting that the Applicant conduct pop-PK and E-R analyses for safety and efficacy by combining data from all completed and ongoing studies for eflornithine. The Applicant clarified that the only data they could include in the safety/efficacy analyses were from Studies 3(b) and 14 as they do not have rights to the study data associated with NMRTC002 at this time.

The Applicant's NCA results and limited E-R analysis for safety appear supporting the proposed dosage of  $750 \text{ mg/m}^2$  BID.

#### **6.2.2.2. Therapeutic Individualization**

##### Data:

Therapeutic individualization is needed in the proposed indication and determined by body surface area (BSA ( $\text{m}^2$ )) is discussed in 2.7.2, 2.7.3, and associated study reports in Module 5. Eligibility criteria required that participants' BSA be  $\geq 0.25 \text{ m}^2$ . The dosing maximum is eight tablets per day for BSA of  $>1.5 \text{ m}^2$ . Refer to **Table 10** for the Clinical Dosing Regimen by BSA. **Table 11** shows PK metrics from study 14 based on BSA and dose/BSA normalizations.

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Consistency in exposure supports this individualized dosing regimen allowing for consistency in exposures across patient age and size.

**Table 11: Summary of Geometric Mean DFMO Plasma Pharmacokinetic Parameters by HRNB Patient Age and PK Day, when Dosed Based on BSA, in PK Finisher Patients in Study 14**

|                | N<br>(171) | PK<br>Day 1                 | PK<br>Day 91                | PK<br>Day 181               | PK<br>Day 1                   | PK<br>Day 91                   | PK<br>Day 181                  | PK<br>Day 1                      | PK<br>Day 91                     | PK<br>Day 181                    |
|----------------|------------|-----------------------------|-----------------------------|-----------------------------|-------------------------------|--------------------------------|--------------------------------|----------------------------------|----------------------------------|----------------------------------|
|                | n          | C <sub>max</sub><br>(µg/mL) | C <sub>max</sub><br>(µg/mL) | C <sub>max</sub><br>(µg/mL) | AUC <sub>∞</sub><br>(h•µg/mL) | AUC <sub>12</sub><br>(h•µg/mL) | AUC <sub>12</sub><br>(h•µg/mL) | T <sub>max</sub><br>(h)          | T <sub>max</sub><br>(h)          | T <sub>max</sub><br>(h)          |
| Ages 1 to <6   | 113        | 13.55                       | 16.55                       | 16.41                       | 91.98                         | 93.83                          | 97.13                          | 3.076                            | 3.074                            | 2.937                            |
| Ages 6 to <12  | 48         | 14.74                       | 18.14                       | 20.01                       | 97.12                         | 114.7                          | 120.6                          | 3.285                            | 3.232                            | 2.925                            |
| Ages 12 to <17 | 9          | 9.901                       | 10.72                       | 10.60                       | 84.03                         | 75.17                          | 77.48                          | 3.814                            | 3.867                            | 3.159                            |
|                | n          | CL/F<br>(L/h)               | CL/F<br>(L/h)               | CL/F<br>(L/h)               | Vz/F<br>(L)                   | Vz/F<br>(L)                    | Vz/F<br>(L)                    | t <sub>½</sub><br>(h)            | t <sub>½</sub><br>(h)            | t <sub>½</sub><br>(h)            |
| Ages 1 to <6   | 113        | 4.361                       | 4.325                       | 4.297                       | 17.70                         | 16.75                          | 17.00                          | 2.814                            | 2.687                            | 2.790                            |
| Ages 6 to <12  | 48         | 5.703                       | 4.815                       | 4.706                       | 24.83                         | 20.80                          | 18.50                          | 3.018                            | 3.058                            | 2.796                            |
| Ages 12 to <17 | 9          | 7.709                       | 8.728                       | 8.743                       | 36.71                         | 51.33                          | 40.51                          | 3.301                            | 4.272                            | 3.206                            |
|                | n          | Age<br>(years)              | Age<br>(years)              | Age<br>(years)              | BSA<br>(m <sup>2</sup> )      | BSA<br>(m <sup>2</sup> )       | BSA<br>(m <sup>2</sup> )       | Dose/BSA<br>(mg/m <sup>2</sup> ) | Dose/BSA<br>(mg/m <sup>2</sup> ) | Dose/BSA<br>(mg/m <sup>2</sup> ) |
| Ages 1 to <6   | 113        | 3.774                       | 4.039                       | 4.298                       | 0.6335                        | 0.6563                         | 0.6771                         | 810.7                            | 802.4                            | 799.6                            |
| Ages 6 to <12  | 48         | 7.491                       | 7.749                       | 8.008                       | 0.8741                        | 0.8964                         | 0.9227                         | 815.7                            | 802.0                            | 799.2                            |
| Ages 12 to <17 | 9          | 13.62                       | 13.87                       | 14.11                       | 1.415                         | 1.449                          | 1.493                          | 602.4                            | 588.4                            | 589.5                            |

AUC<sub>∞</sub> = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC<sub>12</sub> = area under the plasma concentration-time curve from time zero to 12 hours postdose; BSA = body surface area; CL/F = apparent total body clearance; C<sub>max</sub> = maximum observed drug concentration; HRNB = high-risk neuroblastoma; n = number of observations; N = number in population; PK = pharmacokinetic; t<sub>½</sub> = terminal elimination half-life; T<sub>max</sub> = time of maximum observed drug concentration; Vz/F = apparent volume of distribution

Note: Age groups are expressed in years.

Source: NMTRC014 PK Report, Table 29 and Table 30

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{Eflornithine [DFMO]}

In Study 3b, 98% of the Stratum 1 patients had a BSA  $< 1.5\text{m}^2$ , the highest dosing category. Thus, there could be up to a 2-fold difference in actual dose received for patients in the upper end of a BSA-based dosing category compared to a patient at the low end of the range of the next BSA-based dosing category. For example, if a patient BSA =  $0.45\text{m}^2$  they would receive 1 tablet BID or 500 mg total daily dose, whereas a patient with a slightly higher BSA of  $0.5\text{m}^2$  would fall into the next dose category and receive 2 tablets BID or 1000 mg total daily dose. A post-hoc analysis was performed investigating the association of BSA adjusted dose versus outcome. Discussed in full in the Study 3 CSR in Module 5 and in Module 2.7.4.2.4, results show no differences in BSA normalized dose and their clinical outcomes or safety indices.

A specific dose adjustment is not recommended for patients with renal or hepatic impairment.

#### The Applicant's Position:

DFMO dosing is based on BSA, resulting in smaller subjects in a given BSA range receiving a higher dose of DFMO per  $\text{m}^2$ . At the time of a dose increase, the patient's weight-adjusted dose would be towards the upper end of the possible dose range ( $2000\text{ mg}/\text{m}^2$ ). To explore the potential impact of total exposure on occurrence of AEs, AE data are also presented by exposure-adjusted AE incidence rates by study and dose (ISS Table 14.3.1.11.1) and by BSA-adjusted dose (2.7.4 Table 23).

The overall duration of exposure was similar between the  $<1500\text{ mg}/\text{m}^2$  and the  $\geq 1500\text{ mg}/\text{m}^2$  groups across both studies ( $1500\text{ mg}/\text{m}^2$ ) pooled (293.8 versus 298.9 years), as well as within Study 14 (236.9 versus 241.7 years) and within Study 3b (56.9 versus 57.2 years). The Applicant anticipates that findings of higher incidence of overall AEs in Study 3b, and higher incidence of certain events (e.g., hypoacusis, ALT increased), in the  $<1500\text{ mg}/\text{m}^2$  dose group likely do not represent true dose-response relationship or a higher risk of these events occurring with lower doses of DFMO. Additional investigations into the clinical findings that trigger such events (e.g., anemia and other hematologic findings, changes in liver function tests and other clinical chemistry testing, and hypoacusis) generally do not suggest any trends between higher blood concentrations of DFMO and changes in these parameters at the indicated dose level of  $1500\text{ mg}/\text{m}^2$ . Further, available data from patients who were administered a higher dose ( $5000\text{ mg}/\text{m}^2$ ) suggest that higher doses may be associated with certain hematologic changes including anemia.

#### The FDA's Assessment:

The Applicant is proposing four BSA-based dosing bands:  $>1.5\text{ m}^2$ , 8 tablets/day;  $0.75$  to  $1.5\text{ m}^2$ , 6 tablets/day;  $0.5$  to  $<0.75\text{ m}^2$ , 4 tablets/day; and  $0.25$  to  $<0.5\text{ m}^2$ , 2 tablets/day. The Applicant conducted limited E-R analysis for safety both in the initial NDA submission [Figure 16 (A)] and in the 120-day safety update (including higher dose data from Study 14) [Figure 16 (B)]. In

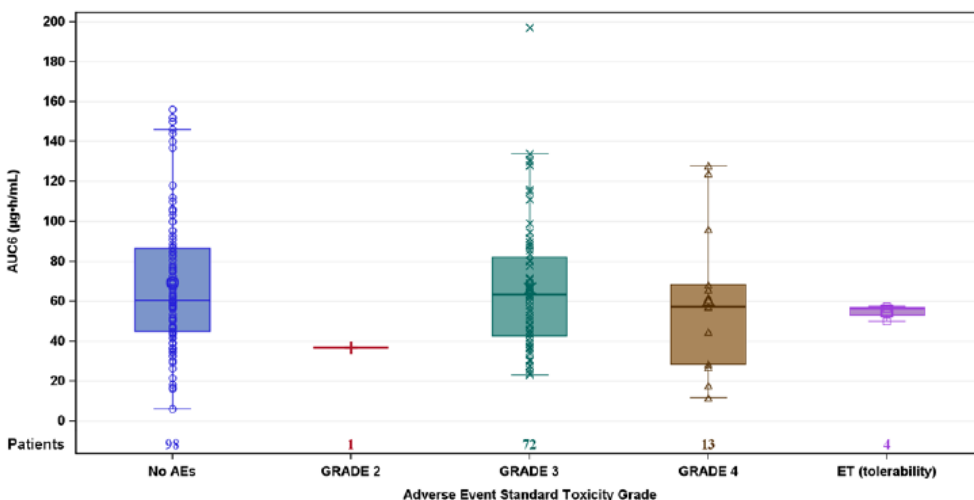
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{Eflornithine [DFMO]}

these analyses, the Applicant compared the exposure (AUC<sub>0-6h</sub>) to different categories of AEs (no AEs, Grade 2, 3, and 4 AEs, and tolerability) and concluded that with or without including higher dose data, AEs are not correlated with eflornithine exposure. A similar pattern was observed with the safety analysis on C<sub>max</sub> (data not shown). These analyses suggest that the difference in BSA-based dosing may not have a clinically meaningful impact on the overall safety profile.

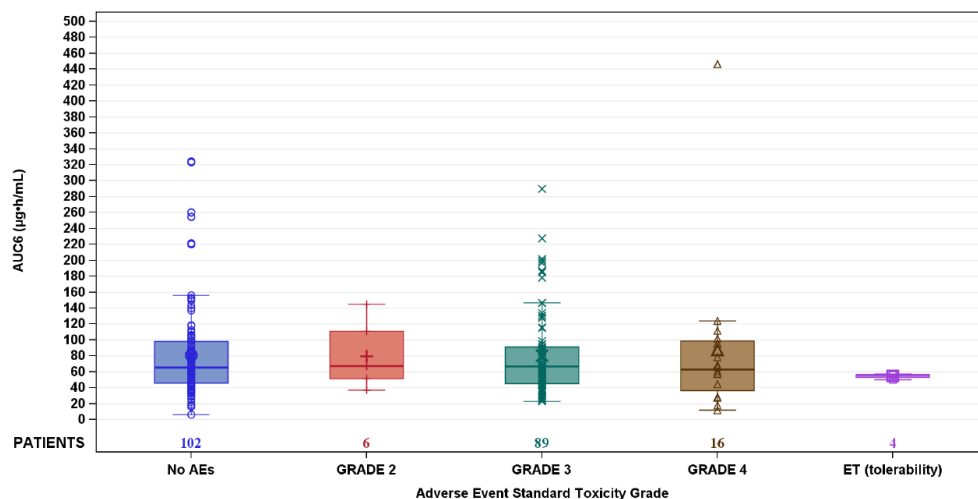
Although the Applicant's proposed BSA-based dosing did not correlate with Grade 3 anemia [Figure 17 (A)] based on the safety analysis in the NDA submission; Grade 4 anemia appeared to be associated with higher exposure, especially when the higher dose data was included in the Update safety analysis [Figure 17 (B)].



(A)

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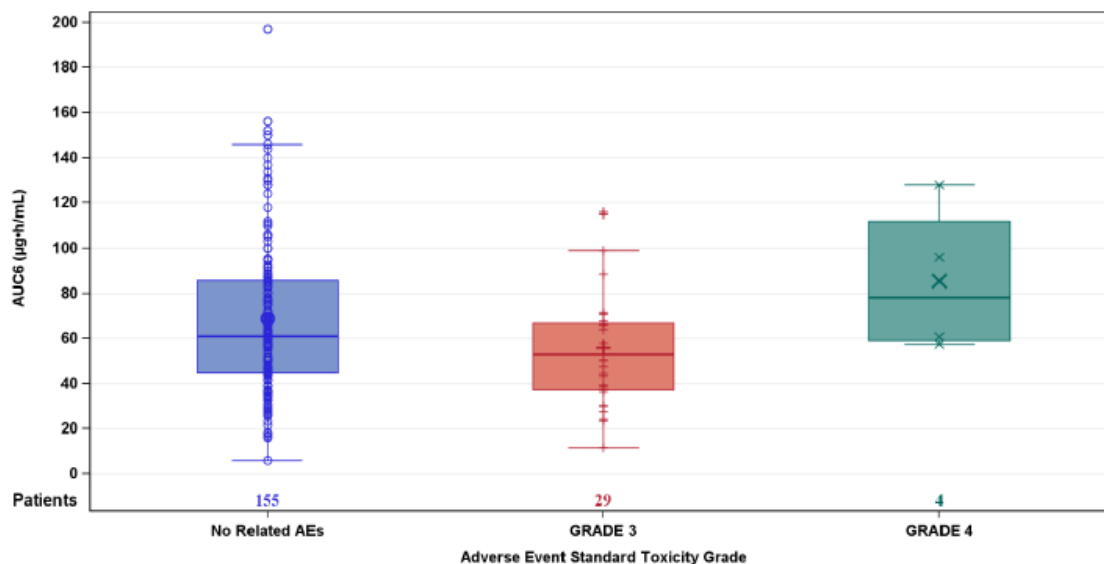
{Eflornithine [DFMO]}



(B)

**Figure 16. Exposure (AUC<sub>0-6h</sub>) on Day 91 versus AE category. (A) Safety vs exposure data in NDA submission (without Stratum 1b data from Study 14); (B) Safety vs exposure data in 120-day safety report (including Stratum 1b data from Study 14)**

(Source of the data: Clinical Information Amendment received on March 9, 2023)



(A)

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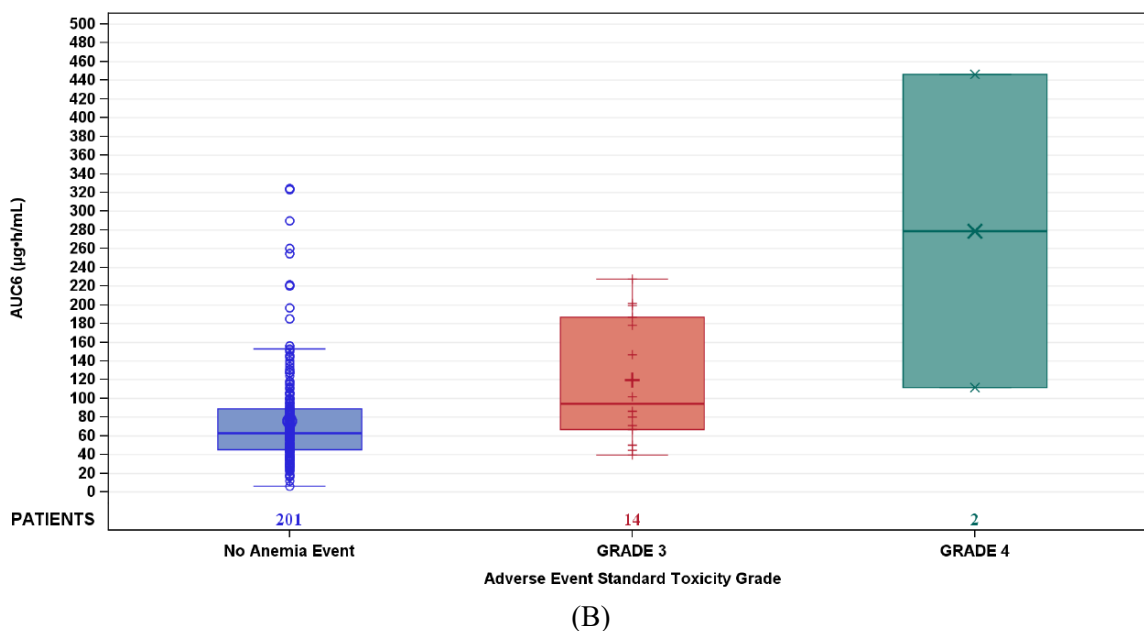


**Figure 17. Exposure (AUC<sub>0-6h</sub>) on Day 91 versus Anemia. (A) Safety vs exposure data in the initial NDA submission; (B) Safety vs exposure data in 120-day safety report (including Stratum 1b data from Study 14)**

**(Source of the data: Clinical Information Amendment received on March 9, 2023)**

### 6.2.2.3. Outstanding Issues

Data:

None

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The following outstanding issue will be included in a PMR:

- 1) Conduct a renal impairment study to inform an appropriate dosage in renally impaired patients.

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### 6.3. Comprehensive Clinical Pharmacology Review

#### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Pharmacology and pharmacokinetics are extensively discussed in 2.7.2 and the Study 14 PK Report in Module 5.3.5.2. DFMO is an irreversible inhibitor of ODC, a critical enzyme in the production of polyamines from arginine via ornithine. Doses in this section are presented in terms of the salt; 250 mg of eflornithine hydrochloride is equivalent to 192 mg of eflornithine. DFMO has been in use since the 1980s and a study describing its PK in humans appeared in 1981 (Haegele 1981). In that study, DFMO had an oral bioavailability of approximately 54%-58%. Following IV administration, approximately 80% of the drug was collected unchanged in the urine within 24 hours. The median T<sub>max</sub> was at 4 hours and the t<sub>1/2</sub> was observed to be 3.3 hours after both oral and IV dosing. Total body clearance was 1.20 mL/min/kg (5.0 L/h for a 70 kg person) and the volume of distribution was 24 L for a 70 kg person (Haegele 1981). Carbone, 2000 compared the bioavailability of tablets to an oral solution in 10 healthy participants and found them to produce bioequivalent exposures and had similar t<sub>1/2</sub>. In their study T<sub>max</sub> occurred at 3.4-3.9 hours and the t<sub>1/2</sub> were 3.5-3.9 hours.

The Applicant conducted a multiple-dose food effect study (USWM-FE1-1001) in healthy adult subjects using an intensive PK sample collection schedule over the 12-hour BID dosing interval. The dosing regimen, 750 ± 250 mg/m<sup>2</sup>, was administered as 1500 mg (6 tablets) twice daily for 10 days. The plasma PK of DFMO was followed after oral administration of whole (intact) tablets under fasting conditions, after administration of whole tablets following a high fat breakfast, and after administration of crushed tablets mixed in pudding under fasting conditions. Results from this study indicate that a high fat meal does not affect the oral bioavailability of DFMO tablets, and that similar PK profiles and oral bioavailability are obtained whether the tablets are taken whole (intact) or crushed and mixed in pudding. This study also demonstrated that with repeated BID dosing, the trough plasma DFMO concentrations just predose the evening dose (end of the daytime dosing interval), averaged 70% of the trough concentration just prior to that morning dose, consistent with a modest diurnal fluctuation in DFMO clearance.

In the Study 14 PK analyses, estimation of the additional DFMO concentration at the end of the dosing interval enabled the calculation of standard non-compartmental PK parameters. A sensitivity analysis indicated that the exposure parameters of C<sub>max</sub>, AUC and CL/F were relatively insensitive to realistic variations in the estimated value of C<sub>12</sub>, whereas t<sub>1/2</sub> and V<sub>z</sub>/F

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were more sensitive. Uncertainty in the  $t_{1/2}$  estimates (2.4–4 h) are not expected to be clinically significant given the typically short  $t_{1/2}$  of DFMO.

Dose proportionality holds for DFMO exposures over the 2-fold range in dose/ $m^2$  utilized in this study. There was an approximately 20%-24% increase in maximum exposure ( $C_{max}$ ) and total exposure ( $AUC_{12}$ ) between first dose and steady state. The short  $t_{1/2}$  of DFMO (between 2 and 4 hours in more than 70% of the pediatric patients) means that with BID dosing, near steady-state concentrations are achieved by the second day of treatment.

Mean DFMO  $C_{max}$  concentrations at steady state were typically between 10 and 20  $\mu g/mL$ , or approximately 55-110  $\mu M$ . DFMO predose concentrations were approximately 14%-18% of the subsequent  $C_{max}$  when patients were dosed per protocol. Plasma concentration declined from  $C_{max}$  by approximately 8-10-fold over the remainder of the dosing interval. DFMO concentrations at steady state remained above approximately 1  $\mu M$  over the entire dosing interval in more than 90% of patients given the protocol-specified doses and BID dosing regimen.

Clearance of DFMO is consistent with elimination being renal and associated with GFR.  $CL/F$  values standardized to 1.73  $m^2$  were in the range of 8.5 to 10.4 L/h based on allometric scaling across the entire pediatric population. Assuming the reported value from literature for oral bioavailability of 54%-58%, total body clearance DFMO is in the range of 75 to 100 mL/min/1.73  $m^2$ , a range consistent with DFMO clearance being approximately 80% of conventional 90-120 mL/min/1.73  $m^2$  range classified as normal renal function. DFMO clearance increased as expected with increasing age and body size.

Both DFMO  $CL/F$  and  $V_z/F$  increased with increasing age. Flat dosing with DFMO across the entire pediatric patient population would result in older and larger patients having substantially less exposure than the younger and smaller patients. Dosing based on BSA adequately compensated for the changes in clearance and volume of distribution differences across the pediatric age range and associated range of body sizes. The dosing algorithm utilized in this study kept mean DFMO plasma exposures within an approximately 2-fold range, consistent with the 2-fold range in BSA-normalized doses administered.

Covariates of sex and race do not appear to have systematic effects on DFMO PK parameters. Age has an effect on  $CL/F$  and  $V_z/F$  that coincides with the increase in body size that generally accompanies increasing age, and that effect can be compensated by dosing based on BSA.

#### The Applicant's Position:

DFMO PK in the pediatric patients were predictable, consistent over prolonged treatment intervals, dose proportional, not sensitive to the form of administration of the immediate release

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tablet, and closely correlated with patient BSA. DFMO PK in the pediatric patient population was generally consistent with previous reports for the molecule in healthy adult populations, the main difference being dose adjustment associated with body size differences, expected in the pediatric population still undergoing development and growth.

Study 14 PK/PD analyses included characterization of PK parameters and concentration-effect analyses on QTc and an assessment of the potential effect of renal and hepatic impairment on exposure showing no discernable relationships between exposure and adverse effect risk. In vitro data resulting from the Applicant's CYP450 drug interaction and transporter studies demonstrate that there are no likely effects of concomitant medications on DFMO exposure as DFMO has no effect on CYP induction/inhibition or transporters. Therefore, no warnings against concomitant medication use are recommended for final labeling.

#### The FDA's Assessment:

In Study 14 Stratum 1b, patients received a 2500 mg/m<sup>2</sup> BID dosing regimen of eflornithine, which is more than 3-fold higher on average than that in all other Strata and in Study 3(b). The corresponding PK exposures (C<sub>max</sub> and AUC) in Stratum 1b were 2.5 to 3-fold higher than that in all other strata (Table 12) after single dose (Day 1) and at steady state (Days 91 and 181).

**Table 12. Comparison of PK Exposure of Eflornithine: Stratum 1b vs All Strata Excluding 1b (FDA Reviewer compiled)**

| PK Day  | PK Parameter                  | Strata 1, 2, 3, and 4<br>(Day 1: N = 216<br>Day 91: N = 190<br>Day 181: N = 176) |     | Stratum 1b<br>(N=29) |     |
|---------|-------------------------------|----------------------------------------------------------------------------------|-----|----------------------|-----|
|         |                               | Mean                                                                             | %CV | Mean                 | %CV |
| Day 1   | C <sub>max</sub> (µg/mL)      | 16.2                                                                             | 61  | 53.4                 | 43  |
|         | AUC <sub>0-6h</sub> (h*µg/mL) | 54.5                                                                             | 59  | 164.9                | 39  |
| Day 91  | C <sub>max</sub> (µg/mL)      | 18.7                                                                             | 50  | 53.0                 | 63  |
|         | AUC <sub>0-6h</sub> (h*µg/mL) | 67.1                                                                             | 51  | 166.5                | 59  |
| Day 181 | C <sub>max</sub> (µg/mL)      | 19.3                                                                             | 50  | 48.0                 | 51  |
|         | AUC <sub>0-6h</sub> (h*µg/mL) | 70.3                                                                             | 49  | 163.4                | 50  |

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The Applicant analyzed the relationship between the change from baseline in QTcF and absolute QTcF versus DFMO concentration on Days 1, 91, and 181 using all PK data including Stratum 1b. As shown in **Figure 18** below, the slope of the regression line in both change from baseline in QTcF and absolute QTcF were slightly negative, suggesting no correlation between concentration and QTcF.

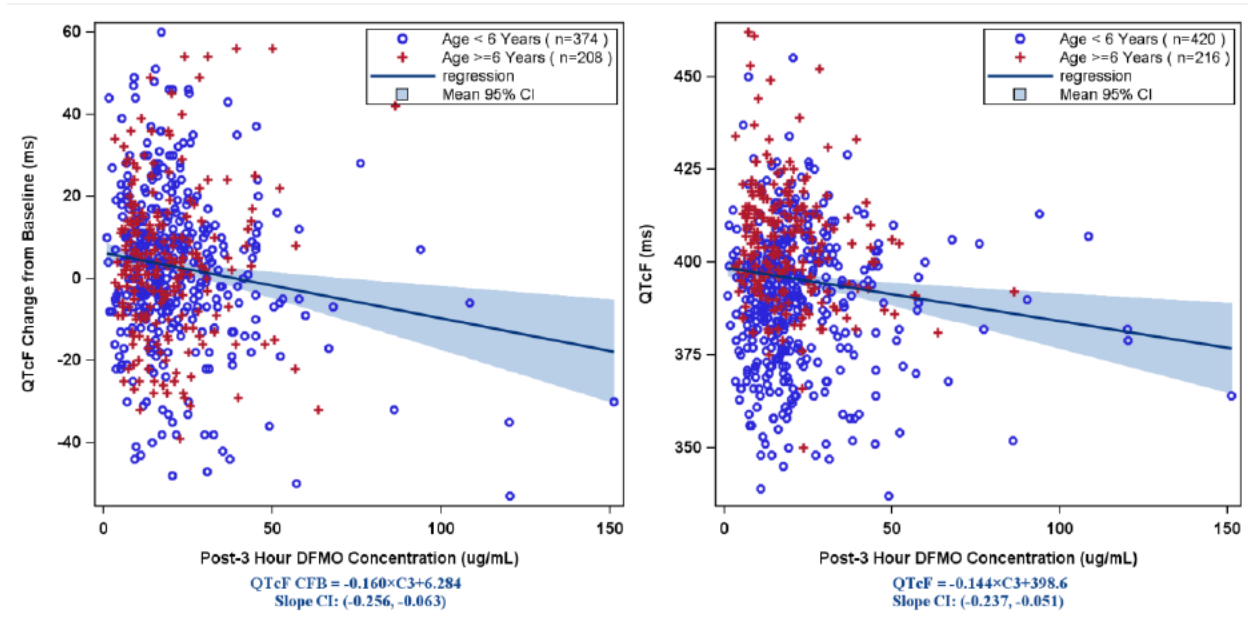


**Figure 18. Change from Baseline in QTcF (Left) and Absolute QTcF (Right) versus Eflornithine Concentrations at 3 Hours Post-dose on Days 1, 91 and 181 in HRNB Patients with QTcF and PK Data in Study 14 All Strata (Data source: 120-Day Safety Update Report)**

### 6.3.2. Clinical Pharmacology Questions

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

Data:

Not applicable.

The Applicant's Position:

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The clinical pharmacology program did not comprise specific supportive effectiveness evaluations.

**The FDA's Assessment:**

The Applicant did not conduct a pop-PK analysis. Instead, the Applicant conducted NCA analyses on each individual patient's PK data and concluded that the intrinsic and extrinsic factors did not affect the PK exposure.

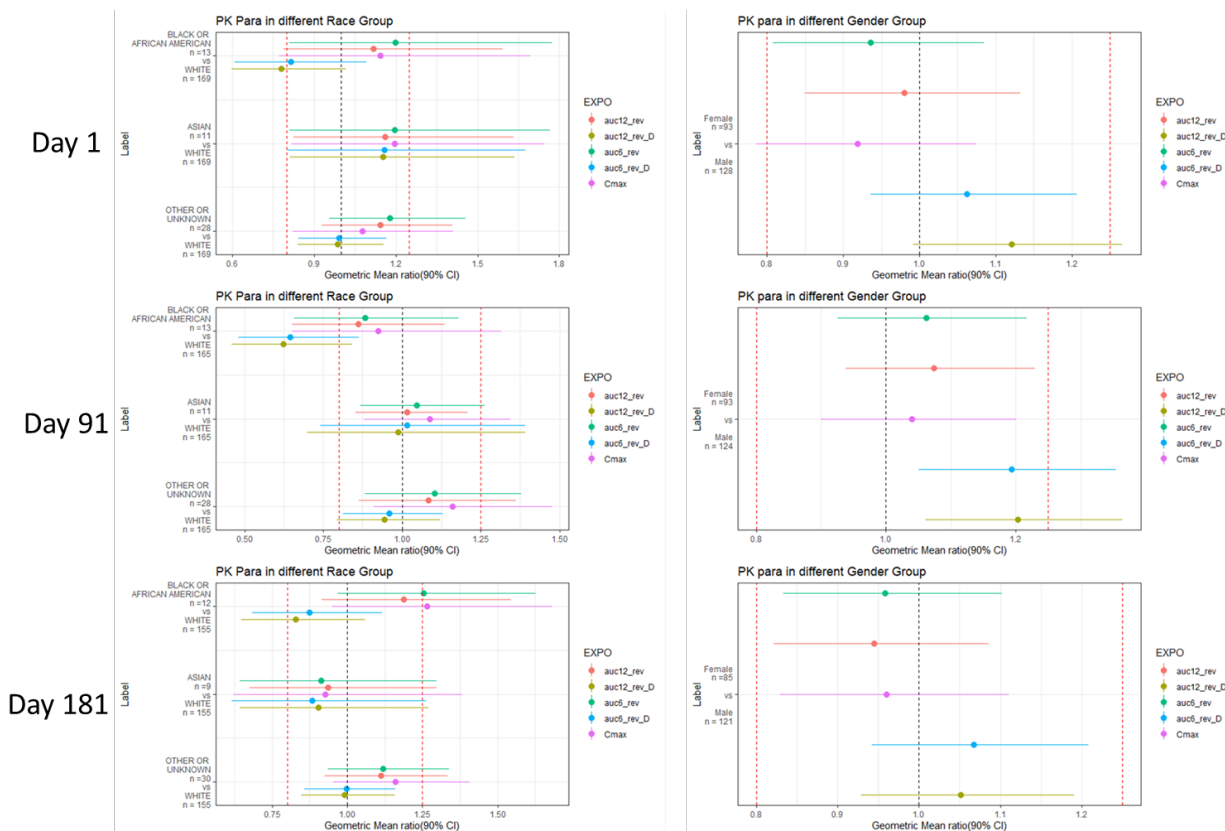
The Applicant proposed a BSA-based dosing regimen in pediatric patients. FDA repeated the Applicant's NCA analysis after removing patients who did not have at least 3 PK observations in elimination phase. Comparisons between eflornithine exposures (AUC0-6h, AUC0-12h and Cmax) and PK parameters (CL/F, BSA normalized CL/F and Vz/F) in different race and sex groups are shown in Figure 19 and Figure 20. On Day 91, Black or African American patients showed higher CL/F, lower dose normalized AUC0-6h and dose normalized AUC0-12h compared to White patients; however, the difference in geometric mean ratios (GMRs) on treatment days were less than 20%.

The relationships between PK parameters (CL/F, AUC0-12h, Cmax) and intrinsic factors (bodyweight, BSA, age) are shown in Figure 21, suggesting a slightly positive trend between BSA/Age/Weight with CL/F (CLobs/F for Day 1, CLss/F for Days 91 and 181). However, no clear relationships were observed between age, BSA, weight and eflornithine PK exposures (Cmax and AUC0-12h). The results should be interpreted with caution as bodyweight, BSA and age are highly correlated, and limited PK data were collected in the elimination phase.



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**Figure 19. Eflornithine exposures in different race and sex groups in NCA analysis.**

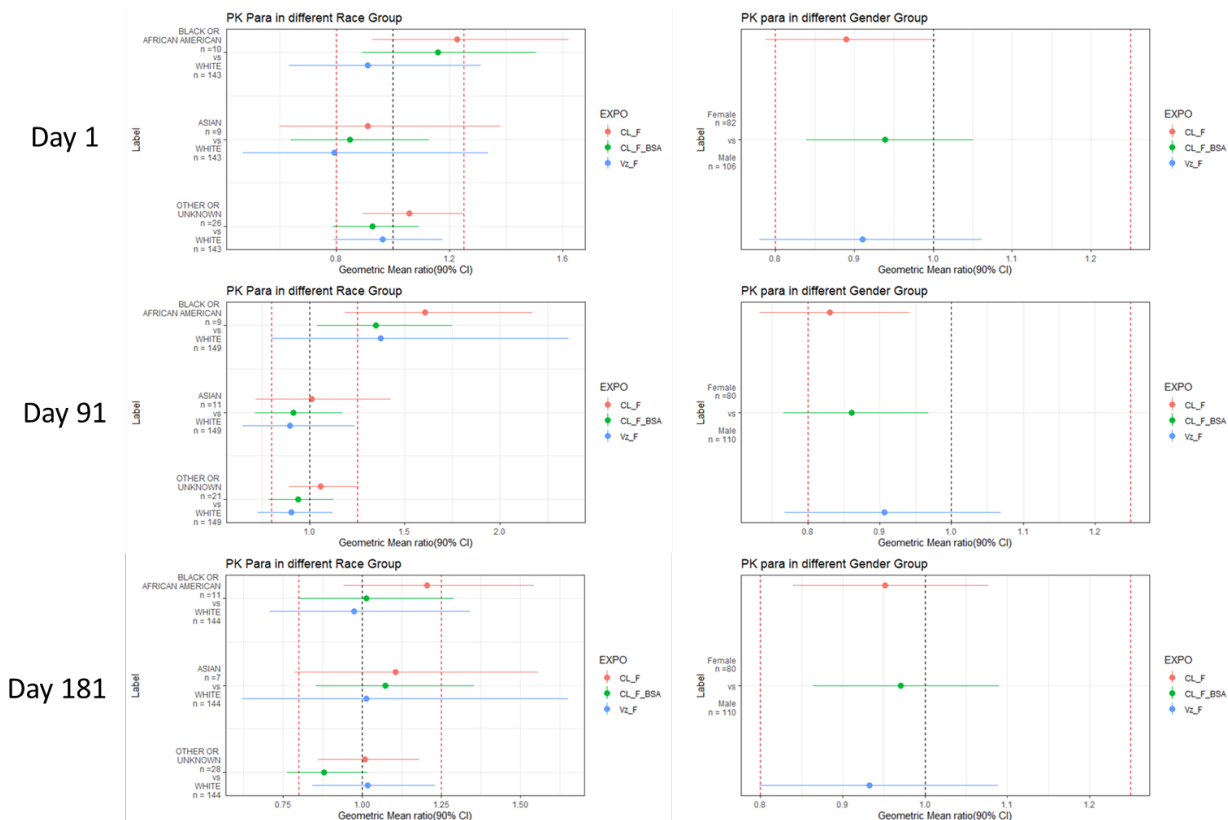


Source: FDA Reviewer's analysis.

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{Eflornithine [DFMO]}

**Figure 20. PK parameters of Eflornithine in different race and sex groups in NCA analysis.**

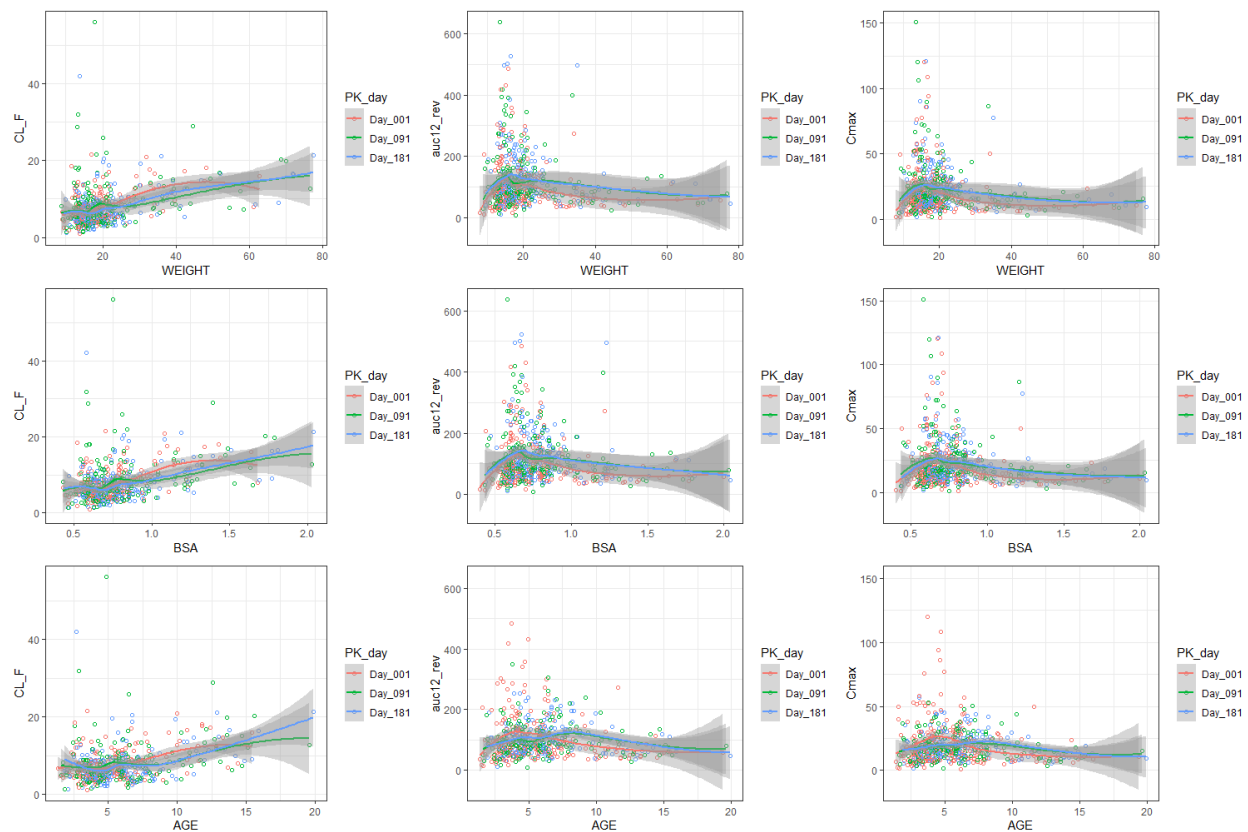


Source: FDA Reviewer's analysis.

**Figure 21. The relationships between clearance, AUC<sub>0-12h</sub>, or C<sub>max</sub> of Eflornithine and patients' bodyweight, BSA, age.**

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{Eflornithine [DFMO]}



Source: FDA Reviewer's analysis.

The Applicant conducted limited E-R analysis for safety. The safety profile as assessed in Study 14 was not correlated with the eflornithine exposure except for Grade 4 anemia. These analyses support the Applicant's proposed BSA-based dosage in pediatric patients from a safety perspective. No E-R analysis for efficacy was conducted since efficacy data is not yet available for Study 14. Taken together, the clinical pharmacology program supports the proposed dosage from a safety perspective.

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

Data:

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Discussed in 2.7.2.3.5, the dosing regimen was selected based on previous experience with DMFO in neuroblastoma patients and data from other indications. This includes a multicenter, Investigator-initiated dose escalation study in neuroblastoma patients (ages 0-21 years) (NCT01059071). A total of 21 patients were treated with DFMO, with 4 patients at 500 mg/m<sup>2</sup>, 5 patients at 750 mg/m<sup>2</sup>, 3 patients at 1000 mg/m<sup>2</sup>, and 9 patients at 1500 mg/m<sup>2</sup>. There were no confirmed DLTs (Saulnier Sholler 2015) or serious adverse events (SAEs) considered to be related to the study drug in any dose cohort.

This study provided early foundational support for the potential of DFMO to be an effective treatment in the most difficult to treat subset of HRNB patients. All 21 patients had refractory or relapsed/recurrent neuroblastoma. Of the 18 patients evaluable for efficacy (Response Evaluation Criteria in Solid Tumors), 1 patient had a partial response, 12 patients had stable disease, 5 had progressive disease. Three patients were evaluated by PET scans, of which 2 had a complete response of PET activity and one had a partial response. These 3 patients remained without disease progression in this study. As of the data cutoff for the study manuscript (Saulnier Sholler 2015), these 3 patients remained alive without progression of disease 2 years to 4.5 years after starting DFMO. These 3 surviving patients were enrolled in the 500 mg/m<sup>2</sup> (2 patients) and 1500 mg/m<sup>2</sup> (1 patient) dose cohorts. As such, response to treatment did not appear to be dependent on DFMO dose. The efficacy signal supporting DFMO as a potentially effective agent to prevent disease progression in multiply relapsed/refractory patients, together with an acceptable safety profile for chronic treatment, led to the evaluation for its use as a long-term maintenance extension treatment in HRNB patients considered to be in remission following upfront therapy. Although no DLTs or SAEs were associated with any of the Phase 1 evaluated dose levels, the dose of 750 mg/m<sup>2</sup> was selected for further evaluation in consideration of i) the lack of a clear dose response in the Phase 1 study to justify selection of a higher dose and ii) and to optimize tolerability for non-serious AEs for HRNB patients in remission where benefit/risk considerations are different than for those patients with active disease.

PK evaluations from study 14 show that drug concentrations returned to baseline levels around 12 hours postdose (Module 2.7.2.2.2.2). Thus, a BID dosing regimen is a natural fit and showed to be a successful and achievable dosing regimen with high compliance in our clinical studies.

#### The Applicant's Position:

A BSA adjusted BID dosing regimen is proper, achieves good patient compliance, and allows for proper drug exposure and pharmacodynamic effects.

#### The FDA's Assessment:

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FDA agrees with the Applicant's position. Refer to the FDA's Assessment in Section 6.2.2.2 above for FDA's assessment of the Applicant's proposed BSA-based dosage from a safety perspective.

**6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

Data:

No alternative dosing regimen is required for subpopulations based on demographic characteristics or special populations. No specific studies have been performed in impaired populations; however, analyses performed show no clear relationships between indicators of kidney/liver function and DFMO exposure within the available data.

The Applicant's Position:

No alternative dosing regimen are sought or required.

The FDA's Assessment:

FDA considers it to be premature to conclude that no alternative dosing regimens will be required. As stated in Section 6.2.2.3, FDA will require that the Applicant conduct a renal impairment study to inform an appropriate dosage recommendation in this specific population as a post-marketing requirement.

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

Data:

There are no clinically relevant food-drug or drug-drug interactions. In study USW-FE-1001, DFMO 192 mg immediate release tablet bioavailability was comparable between fed and fasted conditions as well as when tablets were administered intact vs. crushed in pudding. DFMO did not inhibit or induce any CYP450 enzymes or act as a substrate or inhibitor of the major drug transporters, thus no drug-drug interactions are expected.

The Applicant's Position:

There are no clinically relevant food-drug or drug-drug interactions.

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**The FDA's Assessment:**

FDA agrees with the Applicant's position. The statistical analysis results of food-effect study USWM-FE-1001 demonstrated that food has no effect on the bioavailability of eflornithine intact tablets and crushed tablets (Table 13). The crushed tablet had 16% higher exposure than the intact tablet, which is not considered clinically relevant. Therefore, both eflornithine intact tablets and crushed tablets can be administered without regard to food intake.

**Table 13. Statistical Analysis Results of Food-Effect Study USWM-FE-1001 (FDA Reviewer Compiled)**

| Treatment Ratio | GMR (%) (90% Confidence Intervals) (N=17) |                   |                  |
|-----------------|-------------------------------------------|-------------------|------------------|
|                 | AUC <sub>t</sub>                          | AUC <sub>12</sub> | C <sub>max</sub> |
| B/A             | 96 (87 – 105)                             | 96 (87 – 105)     | 91 (81 – 103)    |
| C/A             | 116 (101 – 134)                           | 116 (101 – 134)   | 118 (100 – 140)  |
| B/C             | 99 (89 – 110)                             | 99 (89 – 110)     | 91 (81 – 101)    |

A: Intact Tablets under fasted condition; B: Intact Tablets under fed condition; C: Crushed Tablets under fasted condition

X

X

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## 7. SOURCES OF CLINICAL DATA

### 7.1. Table of Clinical Studies

#### Data:

An Overview of the clinical studies supporting the efficacy and safety of DFMO is presented in [Table 8](#).

#### The Applicant's Position

The DFMO program consists of two studies in the HRNB patient population, Study 3b and Study 14, and one study in healthy adult volunteers, USWM8.-FE-1001.

Study 3b, analyzed as prospectively designed and in comparison to an external control database ANBL0032, constitutes the efficacy package supporting claims for the application. Study 3b reporting reflects a total of 141 patients enrolled under the investigational protocol. The protocol initiated as NMTRC003 and was converted to NMTRC003b at the time of a change in drug product supplier. The change to NMTRC003b also resulted in the creation of a separate study database and separate informed consent from that of NMTRC003. Outcome data for 100 of the 140 ITT population, comprising those patients that either transferred from NMTRC003 to NMTRC003b or directly enrolled in NMTRC003b, are reported in the NMTRC003b database. However, because the Applicant does not have access to the NMTRC003 database, Study 3b outcome data in the application for the remaining 40 patients (those patients that enrolled only under NMTRC003) are sourced from BCC001, a retrospective chart review of HRNB outcomes across BCC sites. [Figure 2](#) further clarifies the source of efficacy data for the Study 3b CSR.

Data collection under BCC001 included a comprehensive review of medical records enabling the capture of prior treatment history including DFMO treatment information, demographics and disease characteristics, and EFS and OS outcomes. BCC001 provided the complete data necessary for efficacy endpoint analyses as specified by both the Study 3b SAP and the comparisons to ANBL0032 discussed in Section [8.1.3](#).

All studies, including NMTRC003 and NMTRC003b were conducted under Dr. Sholler's Research IND and were routinely monitored according to GCP and SOPs. Extensive source record review and data cleaning were conducted to ensure the accuracy of the data in both NMTRC003b and BCC001. All databases are the property of the Sponsor-Investigator of the Research IND. As the commercial and regulatory partner to the Research IND holder, the Applicant had access to source records for NMTRC003b and BCC001, covering the patients' treatment history prior to, during and after completion of treatment in the DFMO trial. Additionally, the Applicant directly supported data management activities for the NMTRC003b

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and BCC001 databases, although the regulatory responsibility was maintained by the Sponsor-Investigator for the studies.

Study 3b and Study 14 together support safety in the intended patient population at the recommended dose. USWM-FE-1001 contributes clinical pharmacology information and supporting safety in healthy adult volunteers.



**Table 7: Listing of Clinical Trials Relevant to this NDA/BLA**

| <b>Trial Identity, NCT Number</b>                                   | <b>Trial Design</b>                               | <b>Regimen/<br/>Schedule/ Route</b>                                             | <b>Study Endpoints</b>                                                                                                                                                                                                                        | <b>Treatment Duration/<br/>Follow Up</b>                                                | <b>Number of Patients</b>                                                                                       | <b>Study Population</b>                                                                        | <b>Number of Centers and Countries</b>                             |
|---------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <b><i>Controlled Studies to Support Efficacy and Safety</i></b>     |                                                   |                                                                                 |                                                                                                                                                                                                                                               |                                                                                         |                                                                                                                 |                                                                                                |                                                                    |
| NMTRC003b (Study 3b)<br>NCT02395666 <sup>a</sup>                    | Single-arm, multi-center, open-label              | 750 ± 250 mg/m <sup>2</sup><br>BID DFMO (27 cycles of 28-day treatment periods) | <b>Primary Efficacy:</b><br>EFS at 2 years<br><br><b>Secondary Efficacy:</b><br>EFS at 4 years, OS at 2 years,<br><br>Safety and PK<br>Endpoints: Safety: vital signs, audiograms, adverse events and tolerability; PK; biological correlates | 2 years of DFMO treatment + 5 years of long term, off-therapy follow up (7 years total) | 141<br><br>Stratum 1: n=106<br>Stratum 2: n=35                                                                  | HRNB patients in remission after upfront (Stratum 1) or refractory/relapse (Stratum 2) therapy | 22 US sites                                                        |
| ANBL0032 database as an external control to Study 3b<br>NCT00026312 | Partially randomized, parallel, multicenter study | N/A. DFMO was not studied.                                                      | <b>Primary Endpoint:</b><br>EFS (3 year)<br><b>Key Secondary Endpoint:</b> EFS (3 years) comparison and OS (3 years)<br><br><b>Safety and PK Endpoints:</b> N/A                                                                               | 10 years of off-therapy long-term follow up                                             | 1440 (112 randomized to treatment without ch14.18; 1328 randomly or non-randomly assigned to ch14.18 treatment) | HRNB patients Following Myeloablative Therapy and Autologous Stem Cell Rescue                  | 197 sites (174 in US, 23 across Australia, New Zealand and Canada) |

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| <b><i>Study to Further Support Efficacy</i></b>                                                                    |                                                                                  |                                                                                                                                                 |                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                 |                                                                                                       |                                                                                                               |                                                  |
|--------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| W2218<br>NCT: N/A                                                                                                  | Blinded independent imaging review of EFS outcomes determinations from Study 3b. | DFMO PER COG population as defined by Study 3b vs. ANBL0032 SAP                                                                                 | <b>Primary:</b><br>determination of concordance between EFS outcome determinations made between local evaluator at site and blinded independent radiology reviewer.                                                                                       | On-treatment BICR Period: from eligibility assessment through the last protocol specified imaging timepoint (30 day follow-up visit following last dose of DFMO)<br><br>Full BICR period: from eligibility through the last timepoint available | 92                                                                                                    | DFMO PER COG analysis population, a subset of Study 3b treated HRNB patients                                  | N/A (images submitted to central imaging vendor) |
| <b><i>Studies to Support Safety</i></b>                                                                            |                                                                                  |                                                                                                                                                 |                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                 |                                                                                                       |                                                                                                               |                                                  |
| NMTRC014 (Study 14)<br>NCT02679144                                                                                 | Multi-center, open-label                                                         | Strata 1, 2, 3 and 4:<br><br>750 ± 250 mg/m <sup>2</sup> BID DFMO for 730 days<br><br>Stratum 1b: 2,500 mg/m <sup>2</sup> BID DFMO for 730 days | <b>Efficacy Endpoints:</b><br>N/A for application; single arm study contributing safety and PK data<br><br><b>Safety and PK Endpoints:</b> Safety (laboratory, vital signs, ECGs, audiograms, adverse events) and tolerability, PK, biological correlates | 2 years of DFMO treatment + 5 years of long term, off-therapy follow up (7 years total)                                                                                                                                                         | 280 out of 441<br>Stratum 1: 132<br>Stratum 1b: 21<br>Stratum 2: 50<br>Stratum 3: 29<br>Stratum 4: 48 | HRNB patients in remission after upfront (Strata 1/1b and 2) or relapse/refractory (Strata 3 and 4) treatment | 37 sites (33 in US and 4 in Canada)              |
| <b><i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i></b> |                                                                                  |                                                                                                                                                 |                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                 |                                                                                                       |                                                                                                               |                                                  |
| USWM-FE1-1001<br>NCT N/A                                                                                           | Single center, randomized,                                                       | 1500 mg BID approximately 12                                                                                                                    | PK and safety                                                                                                                                                                                                                                             | Dosing for 10 consecutive days                                                                                                                                                                                                                  | 17                                                                                                    | Healthy, normal, adult                                                                                        | Single center in US                              |

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                    |                                     |  |                                                      |  |            |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-------------------------------------|--|------------------------------------------------------|--|------------|--|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | multiple-dose, 3-treatment, 4-sequence crossover food-effect study | hours apart for 10 consecutive days |  | (up to 40 days inclusive of 30 day screening window) |  | volunteers |  |
| <p><sup>a</sup>Study 3b initiated as NMTRC003 (NCT01586260) and was later amended to NMTRC003b at the time of a change in drug product supplier. NMTRC003 is a predecessor study to NMTRC003b. Efficacy data for 40 patients treated in the predecessor study were sourced from BCC001, a retrospective chart review study conducted at BCC sites in HRNB patients. The data sources for Study 3b are described further in the Study 3b SAP, Study 3b CSR and in the following section of this document.</p> |                                                                    |                                     |  |                                                      |  |            |  |

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### The Applicant's Position

The DFMO program consists of two studies in the HRNB patient population, Study 3b and Study 14, and one study in healthy adult volunteers, USWM-FE-1001.

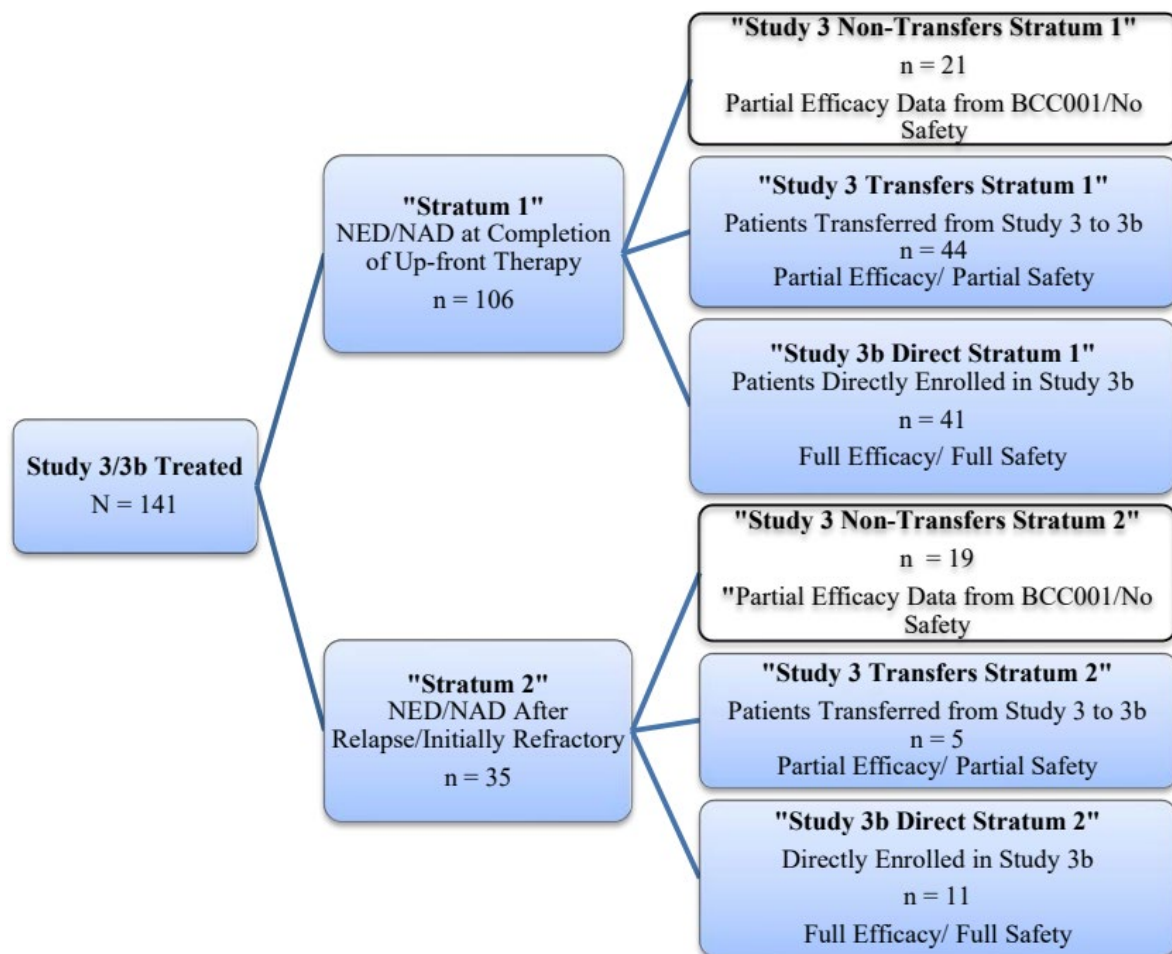
Study 3b, analyzed as prospectively designed and in comparison to an external control database ANBL0032, constitutes the efficacy package supporting claims for the application. Study 3b reporting reflects a total of 141 patients enrolled under the investigational protocol. The protocol initiated as NMTRC003 and was converted to NMTRC003b at the time of a change in drug product supplier. The change to NMTRC003b also resulted in the creation of a separate study database and separate informed consent from that of NMTRC003. Outcome data for 100 of the 140 ITT population, comprising those patients that either transferred from NMTRC003 to NMTRC003b or directly enrolled in NMTRC003b, are reported in the NMTRC003b database. However, because the Applicant does not have access to the NMTRC003 database, Study 3b outcome data in the application for the remaining 40 patients (those patients that enrolled only under NMTRC003) are sourced from BCC001, a retrospective chart review of HRNB outcomes across BCC sites. [Figure 2](#) further clarifies the source of efficacy data for the Study 3b CSR.

Data collection under BCC001 included a comprehensive review of medical records enabling the capture of prior treatment history including DFMO treatment information, demographics and disease characteristics, and EFS and OS outcomes. BCC001 provided the complete data necessary for efficacy endpoint analyses as specified by both the Study 3b SAP and the comparisons to ANBL0032 discussed in Section 8.1.3.

All studies, including NMTRC003 and NMTRC003b were conducted under Dr. Sholler's Research IND and were routinely monitored according to GCP and SOPs. Extensive source record review and data cleaning were conducted to ensure the accuracy of the data in both NMTRC003b and BCC001. All databases are the property of the Sponsor-Investigator of the Research IND. As the commercial and regulatory partner to the Research IND holder, the Applicant had access to source records for NMTRC003b and BCC001, covering the patients' treatment history prior to, during and after completion of treatment in the DFMO trial. Additionally, the Applicant directly supported data management activities for the NMTRC003b and BCC001 databases, although the regulatory responsibility was maintained by the Sponsor-Investigator for the studies.

Study 3b and Study 14 together support safety in the intended patient population at the recommended dose. USWM-FE-1001 contributes clinical pharmacology information and supporting safety in healthy adult volunteers.

**Figure 16: Study 3b Patient Data Sources**



**The FDA's Assessment:**

FDA agrees with the Applicant's overview of the clinical studies. Additional details regarding each study intended to support efficacy are included in Section 8.

## 8. STATISTICAL AND CLINICAL EVALUATION

### 8.1. Review of Relevant Individual Trials Used to Support Efficacy

Doses discussed in this section are presented in terms of the salt. Two-hundred fifty (250) mg eflornithine hydrochloride is equivalent to 192 mg eflornithine.

#### 8.1.1. NMTRC003b (Study 3b)

##### The Applicant's Description:

Study 3b is a phase 2, open label, single arm, multi-center, single agent study in HRNB patients prospectively designed to compare EFS outcomes in DFMO treated patients against published historical control rates from the literature. This study contributes efficacy, PK, and safety data within the application. The treatment period of Study 3b has completed and long-term follow up is ongoing.

High risk neuroblastoma patients in remission at the completion of initial upfront therapy (Stratum 1) or relapse/refractory therapy (Stratum 2) were eligible to enroll. Patients received DFMO treatment at a dose of 750 mg +/- 250 mg/m<sup>2</sup> BID, with daily dosing for two years. Patients were to be followed up for 5 years after completing DFMO for a total duration of 7 years on the study.

Study 3b outcomes are further compared to patient level data from the ANBL0032 database as an external control, serving as the pivotal efficacy data for the application. The comparison between Study 3b and ANBL0032 is presented separately under Section 8.1.7.

##### ***Trial Location:***

The study was conducted at 22 sites located in the US.

##### ***Choice of control group:***

Study 3b was designed as a single arm study for comparison to a published historical control rate. The study was philanthropically funded by a research consortium striving to rapidly make new treatments available to patients through investigational trials. The investigators were aware that the randomized portion of ANBL0032 took 9 years to enroll and follow 226 patients for the initial reporting of 2-year EFS results despite involvement of a higher number of COG affiliated sites than were available for NTMRC study participation at the time. Nearly a decade elapsed for only 114 children to receive randomized active treatment with a promising new agent,

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underscoring the timing considerations for the conduct of RCTs in rare diseases. Primarily, the goal to make therapy available to more patients in real time drove the decision to conduct the study as a single arm study in which all patients were assigned to DFMO treatment. The specific historical control rate was selected for each stratum based on EFS rates that represented the most recent information and/or advancement in HRNB therapy. The study initiated in 2012 for comparison to historical rates established in the most recent literature reports, 2010 for Stratum 1 and 2008 for Stratum 2.

Following the analysis of the study against the planned historical control rates, patient level data from ANBL0032 were obtained which served as an external control database of outcomes in HRNB patients receiving similar induction and consolidation regimens prior to study 3b entry and subsequent protocol-defined immunotherapy maintenance treatment. The choice of ANBL0032 as an external control is discussed in Section 8.1.3.

### Diagnostic Criteria

HRNB patients in remission based upon imaging were enrolled within 120 days of completion of multiagent, multimodality upfront (Stratum 1) or relapse/refractory (Stratum 2) therapy. Remission was operationally defined as patients achieving a disease response of at least PR (by CT or MRI) at the time of study entry and histologically negative bone marrow aspirate/biopsy. Patients were considered to have no evidence of disease if negative CT/MRI and MIBG scan (or PET for patients who have a history of MIBG non-avid disease). Patients were considered to have no active disease if they had stable residual tumor masses visible on CT/MRI provided the residual mass was either MIBG-negative or MIBG-positive without FDG-PET avidity, which was taken as evidence that the mass did not represent active disease and would otherwise not have received additional therapy after antibody therapy.

### Inclusion / Exclusion Criteria

**Table 8: Study 3b Key Inclusion / Exclusion Criteria:**

| Inclusion/Exclusion Criteria      | Study 3b                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Diagnosis                         | HRNB at the time of original diagnosis. Patients not originally diagnosed as high-risk but are later determined to be high-risk were not excluded.                                                                                                                                                                                                                   |
| Age at diagnosis                  | 0-21 years                                                                                                                                                                                                                                                                                                                                                           |
| Previous treatments               | Stratum 1: Patients that are in remission at the end of up-front therapy defined as chemotherapy (5-7 cycles), surgery as indicated, consolidation therapy as indicated, radiation therapy as indicated, anti-GD2 antibody therapy with retinoic acid up to 6 cycles.<br>Stratum 2: Subjects that are in remission after any previous relapse or refractory therapy. |
| Timing from previous treatment(s) | >30 days from completion of cytotoxic and antibody therapy and <120 days from previous therapy                                                                                                                                                                                                                                                                       |

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| Inclusion/Exclusion Criteria        | Study 3b                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End of Immunotherapy Disease Status | Disease status: neuroblastoma that is in remission.<br>Operationally, per the Sholler 2018 publication, remission was defined as disease status of at least PR (by CT or MRI) at the time of study entry and histologically negative bone marrow aspirate/biopsy. Patients were considered NED if negative CT/MRI and MIBG scan (or PET for patients who have a history of MIBG non-avid disease). Patients were considered NAD if they had stable residual tumor masses visible on CT/MRI provided the residual mass was either MIBG-negative or MIBG-positive without FDG-PET avidity, which was taken as evidence that the mass did not represent active disease and would otherwise not have received additional therapy after antibody therapy. |
| Performance Scale Score             | Lansky score $\geq 60\%$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Pervious anticancer treatments      | Anticancer Agents: Patients who are currently receiving other anticancer agents are not eligible. Patients must have fully recovered from the effects of prior chemotherapy (hematological and bone marrow suppression effects).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Hematological                       | ANC $> 500/\mu\text{l}$ + platelet count $> 50,000/\mu\text{l}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Renal                               | Adequate based on:<br>Serum creatinine based on age/gender according to Schwartz, 1985                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Hepatic                             | Adequate based on:<br>AST and ALT $< 10\times$ upper limit of normal<br>Serum bilirubin must be $\leq 2.0$ mg/dl                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

## Study Treatments

Enrolled patients, upon completion of Baseline assessments and confirmation of eligibility, received DFMO tablets ( $750 \pm 250$  mg/m<sup>2</sup> BID) for up to 2 years. If patients were unable to swallow tablets, DFMO could be chewed or crushed in a teaspoon and administered with a small amount of liquid.

## Assignment to treatment and Blinding

All patients were assigned to DFMO.

## Dose modification, dose discontinuation:

The protocol allowed for dose holds for any patient experiencing any toxicity specified below attributable to DFMO or any intolerable toxicity until toxicity reverted to  $\leq$  Grade 2 toxicity (with the exceptions below in Table 9). Upon resolution of the toxicity, DFMO dosing was reduced by removing one tablet per dose from their current dose. If a patient was currently taking one tablet per dose BID, their dose would be reduced to one tablet per day (QD). Patients were allowed to reduce their dose for subsequent toxicities as many times as they could until they reached one tablet per day dosing. If at that time the patient experienced another dose reducing toxicity, they were removed from protocol therapy.

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**Table 9: DFMO Dose Hold and Dose Reduction Criteria**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Grade 4 neutropenia or thrombocytopenia that persists for 7 days or longer <u>after holding study drug</u> . DFMO should be held as soon as a Grade 4 related neutropenia is discovered. Subject will only dose reduced if toxicity persists at a Grade 4 for longer than 7 days after the hold starts. If subject resolves before 7 days of hold they will resume at previous dose. If subject does not resolve after 14 days of a hold they will be discontinued from study.           |
| >10 X elevation of transaminases that persists for 7 days or longer <u>after holding study drug</u> . (DFMO should be held as soon as a 10X related elevation is discovered. Subject will only dose reduced if toxicity persists at >10X ULN or higher for longer than 7 days after the hold starts. If subject resolves before 7 days of hold they will resume at previous dose. If subject does not resolve to <10x ULN after 14 days of a hold they will be discontinued from study). |
| Any other Grade 3 non-hematologic toxicity, excluding alopecia, nausea, vomiting, and diarrhea that does not adequately respond to treatment.                                                                                                                                                                                                                                                                                                                                            |

Additionally, if there was no resolution of above toxicity by 14 days, DFMO was discontinued.

### **Administrative structure**

Prior to the study, the protocol was reviewed and approved by the Executive Committee of Beat Childhood Cancer Research Consortium (BCC). BCC along with Dr. Sholler was responsible for study oversight, vendor oversight, database development and maintenance, storage and distribution of clinical supplies to trial sites.

An independent Data Safety and Monitoring Board (DSMB) oversaw the conduct of the study. The members of the DSMB received database summaries, including AE reports, and met every 6 months. The DSMB was responsible for recommendations to the study committee regarding possible termination and/or early reporting of the study. DSMB review of safety data did not warrant any changes to the study.

### **Procedures and Schedule**

Table 10 describes the schedule of events and procedures.

During the 2-year on therapy portion of the study, visits occurred monthly, and imaging assessments for monitoring disease recurrence were required at approximately 3, 6, 9, 12, 18, and 24 months. Subjects were to be treated until disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, death, or discontinuation from the study treatment due to any other reason. During the off-therapy, long-term follow up, patient contact was required at approximately 6, 12, 18, 24, 36, 48, and 60 months from the end of DFMO treatment. Event free survival was assessed until disease progression, death, lost to follow-up, or withdrawal of study consent. Patients only withdrawing consent to continue DFMO treatment or who discontinued

treatment for a reason other than relapse were still followed for outcomes. Overall survival was assessed until patient withdrew study consent, died or was lost to follow-up. Subjects who withdrew from the study were not replaced, regardless of reason for withdrawal.

**Table 10: Study Design and Schedule of Assessments**

|                                                                               | Pre | Cycles 1 |       |        |        |              | Cycles 2-27    |       |        |        |                | Follow-Up |
|-------------------------------------------------------------------------------|-----|----------|-------|--------|--------|--------------|----------------|-------|--------|--------|----------------|-----------|
|                                                                               |     | Day 1    | Day 8 | Day 15 | Day 21 | End of Cycle | Day 1          | Day 8 | Day 15 | Day 21 | End of Cycle   |           |
| Informed consent                                                              | X   |          |       |        |        |              |                |       |        |        |                |           |
| Medical & surgical history, demographics<br>histologic evidence of malignancy | X   |          |       |        |        |              |                |       |        |        |                |           |
| Prior therapy for malignancy                                                  | X   |          |       |        |        |              |                |       |        |        |                |           |
| Physical examination                                                          | X   | X        |       | X      |        |              | X              |       |        |        |                | X         |
| Vital signs                                                                   | X   | X        |       | X      |        |              | X              |       |        |        |                | X         |
| ECOG performance/ Lansky play status                                          | X   |          |       |        |        |              | X              |       |        |        |                | X         |
| CBC and differential                                                          | X   |          |       | X      |        |              | X <sup>f</sup> |       |        |        |                | X         |
| Serum chemistries                                                             | X   |          |       | X      |        |              | X <sup>f</sup> |       |        |        |                | X         |
| CRP and ESR                                                                   | X   |          |       |        |        |              | X <sup>f</sup> |       |        |        |                |           |
| Pregnancy test                                                                | X   |          |       |        |        |              | X              |       |        |        |                |           |
| MIBG/CT/MRI Scan as needed                                                    | X   |          |       |        |        |              |                |       |        |        | X <sup>b</sup> | X         |
| Concomitant medications                                                       | X   | X        |       | X      |        |              | X              |       |        |        |                | X         |
| BSA calculation                                                               | X   |          |       |        |        |              | X              |       |        |        |                |           |
| Administration of DFMO                                                        |     | X        | X     | X      | X      | X            | X              | X     | X      | X      | X              |           |
| Dispense (and collect) drug dosing diary                                      |     | X        |       |        |        |              | X              |       |        |        |                | X         |

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|                                                      | Pre | Cycles 1 |       |        |        |              | Cycles 2-27    |       |        |        |                | Follow-Up      |
|------------------------------------------------------|-----|----------|-------|--------|--------|--------------|----------------|-------|--------|--------|----------------|----------------|
|                                                      |     | Day 1    | Day 8 | Day 15 | Day 21 | End of Cycle | Day 1          | Day 8 | Day 15 | Day 21 | End of Cycle   |                |
| <b>AE monitoring</b>                                 |     | X        |       | X      |        |              | X              |       |        |        |                | X              |
| <b>PK blood samples (Minimum 10 patients)</b>        |     |          |       |        |        |              | X <sup>c</sup> |       |        |        |                |                |
| <b>Urine for biological correlates</b>               | X   | X        |       | X      |        |              | X              |       |        |        |                |                |
| <b>Blood for biological correlates<sup>a</sup></b>   |     | X        |       | X      |        |              | X <sup>f</sup> |       |        |        |                |                |
| <b>Blood for Circulating tumor cells<sup>a</sup></b> |     | X        |       |        |        |              | X <sup>g</sup> |       |        |        |                |                |
| <b>Audiogram</b>                                     | X   |          |       |        |        |              |                |       |        |        | X <sup>d</sup> | X <sup>d</sup> |
| <b>Urine VMA/HVA</b>                                 | X   |          |       |        |        |              | X              |       |        |        |                |                |
| <b>Bone Marrow<sup>h</sup></b>                       | X   |          |       |        |        |              |                |       |        |        | X <sup>c</sup> | X <sup>c</sup> |

AE = adverse event; BSA = body surface area; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; DFMO = eflornithine HCL; ECOG = Eastern Cooperative Oncology Group; ESR = erythrocyte sedimentation rate; HVA = homovanillic acid; MIBG = an imaging test that uses metaiodobenzylguanidine as a tracer; MRI = magnetic resonance imaging; PK = pharmacokinetic; VMA = vanillylmandelic acid

Note: This schedule of events includes assessments to be conducted at study visits during DFMO administration and the 30-day follow-up visit. After the follow-up site visit, additional survival follow-up continued every 6 months for 2 years and then annually up to 5 years post-treatment or until death or loss to follow-up. This survival follow-up was conducted by contacting parents or the treating institution to confirm survival and patient status including remission status and date of death (if applicable) were recorded.

<sup>a</sup> Voluntary – additional informed consent was required. Section 9.5.7 (Study 3b CSR) provides additional details.

<sup>b</sup> End of Cycle 3, 6, 9, 13, 20, and at off protocol therapy (end of Cycle 27) or as clinically indicated.

<sup>c</sup> If concern for progression of disease (and/or if hematologic toxicity Grade 4).

<sup>d</sup> End of Cycle 6, 12, and off protocol therapy (and as clinically indicated).

<sup>e</sup> PK on the last day of prior DFMO and Day 2-5 of starting current DFMO. Samples were collected prior to administration of DFMO (time 0) and at the following times: 30 min, 1 hour, 3 hours, and 6 hours postdose.

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<sup>f</sup> Cycles 1-12, 14, 17, 21, 24, and off therapy (end of Cycle 27).

<sup>g</sup> Cycles 3, 6, 9, 12, 14, 17, 21, 24, and off therapy (end of Cycle 27).

<sup>h</sup> Standard of care bone marrow (separate consent required for additional research samples).

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**Dietary restrictions/instructions:**

Patients were encouraged to maintain a low polyamine diet during the two year dosing period of the study. A handout was provided to patients with foods they should avoid while they were on study, consistent with general recommendations for high risk neuroblastoma patients.

**Concurrent Medications, Treatment Compliance, Rescue medication:**

All concurrent medications for intercurrent medical conditions (i.e., typical childhood illnesses) were entered in the case report form and coded according to The World Health Organization Drug Reference List (WHODRL) dictionary and presented in the Study 3b CSR – Listing 16.2.4.7.

The Investigator or designee was responsible for maintaining complete and accurate logs for study drug receipt, dispensing and return/destruction when required. DFMO was stored at the investigational pharmacy at each institution. All drug records were periodically reviewed by the study monitor. Reconciliation of study drug was required for each patient.

DFMO was administered on an outpatient visit unless hospitalization is required for another reason. DFMO tablets and a “dosing diary” were provided to patients at each scheduled monthly clinic visit. Patients were requested to return any unused medication along with the dosing diary at each visit for review by the Investigator. At each visit, the Investigator or designee reviewed treatment compliance and if there were any concerns, captured the percentage of missed DFMO doses in text fields within a drug diary comments dataset (submitted within the application).

Rescue medication for relapse or secondary cancer was not allowed. DFMO was to be discontinued prior to treatment of relapse or secondary cancer.

**Subject completion, discontinuation, or withdrawal:**

Patients were to take DFMO for up to 2 years (DFMO treatment period) and after stopping DFMO, followed for overall survival and EFS at regular intervals for an additional 5 years. Patients could withdraw consent at any time. Discontinuation of DFMO therapy occurred if patient relapsed or had secondary cancer, experienced an intolerable toxicity, investigator discretion, or patient request. All DFMO treated patients regardless of therapy discontinuation status were included in the statistical analysis with the exception of one patient as discussed in the Patient Disposition section below.

**The FDA’s Assessment:**

FDA agrees with the Applicant’s description of Study 3(b) (NMTRC003(b); NCT02395666), an open-label, multicenter study of DFMO monotherapy at a dose of 500 to 1000 mg/m<sup>2</sup>

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administered twice daily as extended maintenance for up to 2 years for patients who completed standard of care up-front therapy including immunotherapy. The trial enrolled patients from June 2012 to February 2016 across 22 sites in the U.S. An independent Data Safety and Monitoring Board (DSMB) oversaw the conduct of the study.

Stratum 1 included patients who were in remission at the end of up-front therapy defined as chemotherapy (5-7 cycles), surgery as indicated, consolidation therapy as indicated, radiation therapy as indicated, or anti-ganglioside 2 (GD2) antibody therapy with retinoic acid up to 6 cycles. Stratum 2 included patients who were in remission after any previous relapse or refractory therapy. Stratum 1 enrolled 105 patients in remission after up-front therapy; Stratum 2 enrolled 35 patients who were in remission after any previous relapse or refractory therapy.

Remission was defined as patients achieving a disease response of at least partial response (by CT or MRI) at the time of study entry and histologically negative bone marrow aspirate/biopsy. Patients were considered to have no evidence of disease if negative CT/MRI and MIBG scan (or PET for patients who have a history of MIBG non-avid disease). Patients were considered to have no active disease if they had stable residual tumor masses visible on CT/MRI provided the residual mass was either MIBG-negative or MIBG-positive without FDG-PET avidity, which was taken as evidence that the mass did not represent active disease and would otherwise not have received additional therapy after antibody therapy.

Patients were treated until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, death, or discontinuation from the study treatment due to any other reason. Patients were followed up for 5 years after completing DFMO for a total duration of 7 years on the study. During the off-therapy, long-term follow up, patient contact was required at approximately 6, 12, 18, 24, 36, 48, and 60 months from the end of DFMO treatment.

## Study Endpoints

### The Applicant's Description:

The primary endpoint was to compare 2-year EFS rates to published historical rates for each of Stratum 1 and 2. The main secondary endpoint was to compare overall survival for Stratum 1 compared to published historical rates.

EFS was defined from the first date of DFMO administration until the first occurrence of relapse, progressive disease, secondary cancer, or death. If none of these events occurred, the patient was

censored at the last contact with the patient. Similarly, OS was defined from the first date of DFMO administration until the death from any cause or censored at the last contact date with patient.

The study endpoints EFS and OS are both recognized and accepted for oncology trials (FDA Guidance for Industry 2007). The goal of the study was to evaluate the efficacy of DFMO in reducing the risk of relapse, thus event-free survival is a direct measure of the patient outcome of interest. Patients with relapsed HRNB have poor prognosis with high mortality. Overall survival was assessed as a secondary endpoint to support EFS analyses; lowering the risk of relapse in a group of patients was expected to also reduce their risk of death.

#### The FDA's Assessment:

FDA agrees with the Applicant's description of the primary endpoint of EFS at 2 years. EFS was assessed until disease progression, death, loss to follow-up, or withdrawal of study consent. Patients only withdrawing consent to continue DFMO treatment or who discontinued treatment for a reason other than relapse were still followed for efficacy outcomes. Overall survival (OS) was assessed until patients withdrew study consent, died, or were lost to follow-up.

Patients in Stratum 1 were compared to a historical control rate of 70% based on clinical trial results from Study ANBL0032.

Patients in Stratum 2 were compared to a historical control rate of 10% based on median EFS times presented by Santana et al. (Cancer, June 15, 2008). As described in the Study 3(b) protocol, "for first and second recurrence times, a median first recurrence time of 8.7 months is equivalent to a 14.8% EFS at two years, and the median time to a subsequent second recurrence of 3.8 months is equivalent to an EFS rate of 1.3% at two years assuming an exponential time-to-event model. Assuming that two thirds of the relapse patient population will have had only a single relapse and that the other third of the patients will have had two or more relapses, then a weighted average of these two EFS rates (14.8% and 1.3%) equals 10.3%. A 10% historical EFS rate for two years was assumed for simplicity." (Source: NMTRC003 protocol, version 5.1, page 45) Refer to Section 8.1.5 for a discussion of the assumed historical EFS rate compared with recent publications.

While urine polyamine levels were collected as secondary endpoints, along with other biological correlates, these data were not submitted for the majority of patients in the application.



## **Statistical Analysis Plan and Amendments**

### The Applicant's Description:

The SAP was finalized prior to the locking of the database. There is only one version of the SAP.

### The FDA's Assessment:

FDA agrees there is one version of the Statistical Analysis Plan for Study 3(b), dated August 12, 2021. The SAP was submitted as Appendix 16.1.9 of the Clinical Study Report in Module 5.3.5.1 of the application.

## **Protocol Amendments**

### The Applicant's Description:

The original protocol and subsequent amendments (1-4), associated with the Study 3b predecessor study NMTRC003, are not available to the Applicant.

A review of the public record for the previous version of the NMTRC003 protocol at [clinicaltrials.gov](https://clinicaltrials.gov) permitted an assessment of key changes compared to the initial version of NMTRC003b. Study 3b initiated under Amendment 5 with new source of drug product and included one subsequent amendment, 5.1.

### **Amendment 5 (Study 3b: December 18, 2014)**

The primary reasons for this amendment from the predecessor study (NMTRC003) included the following:

- New source of drug product
- Addition of PK sub-study to evaluate comparative bioavailability of the drug product sources
- Increase DFMO therapy duration from 24 consecutive 28 day cycles to 27 consecutive 28 day cycles allowing full 2 years of DFMO therapy. At the time of the amendment no patient had reached 24 cycles thus no impact.
- Updated inclusion criterion "Disease Status: Neuroblastoma that is in remission" removing the parenthetical (defined as no evidence of disease >1 cm on radiologic assessment).

The removal of the parentheses providing specific measurement criteria for acceptable residual disease on imaging, if anything, permitted patients with more disease to enroll in later versions

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of the amendment. All patients were evaluated for remission status according to the operational remission definition in the (Saulnier Sholler 2018) paper and a subset of Study 3b patients were subsequently independently evaluated against these criteria by the Applicant's W2218 BICR study.

**Amendment 5.1 (Study 3b: February 18, 2015)**

The primary reason for this amendment was to revise the timing of required imaging from approximately every 3 cycles to every 6 cycles during the second year of DFMO therapy reducing burden on patients. The change in imaging frequency had no impact on analysis and left it to the investigator's discretion if additional, more frequent imaging should be performed if there was suspicion of relapse. The change in imaging frequency in the second year following up front treatment is also consistent with institutional standard protocols and the COG ANBL0032 study against which Study 3b was designed to be compared.

**The FDA's Assessment:**

FDA agrees that the protocol was initiated as Study NMTRC003 and was converted to Study NMTRC003b at the time of the change in drug product supplier. Study 3 was originally initiated with 250 mg eflornithine hydrochloride tablets provided by Cancer Prevention Pharmaceuticals (CPP). Amendment 5 (dated December 18, 2014) was initiated due to a change in source of study drug supply, from CPP to KC Pharma (KCP). The CMC review team determined that the Applicant "provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable." Further, they concluded that scientific bridging appeared to be established, and the clinical pharmacology team considered that the bioavailability between formulations was comparable.

The change to NMTRC003b also resulted in the creation of a separate study database and separate informed consent from that of NMTRC003. Outcome data for 100 of the 140 total patients, comprising those patients that either transferred from NMTRC003 to NMTRC003b or directly enrolled in NMTRC003b, were reported in the NMTRC003b database. However, because the Applicant did not have access to the NMTRC003 database, Study 3(b) outcome data in the application for the remaining 40 patients (those patients that enrolled only under NMTRC003) were sourced from the "BCC001 database," a retrospective chart review of HRNB outcomes across Beat Childhood Cancer Research Consortium (BCC) sites. Efficacy analyses of the primary efficacy population excluding patients who received the CPP formulation of DFMO were similar to the primary analysis results.

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### **8.1.2. Study 3b Study Results**

#### **Compliance with Good Clinical Practices**

##### The Applicant's Position:

Studies conducted by the Sponsor-Investigator within the DFMO clinical program were designed and monitored in accordance with Sponsor-Investigator procedures which comply with Good Clinical Practice (GCP) as required by the FDA. Study 3b sites were selected within the US. The studies were conducted in accordance with Good Clinical Practice (GCP) and the following CFRs: 21CFR Part 50 (protection of human subjects), 21CFR Part 54 (Financial Disclosure), 21CFR Part 56 (Institutional Review Boards) and 21CFR 312 the obligations of sponsors and investigators. Prior to enrollment written informed consent was obtained from the patient/guardian according to the regulatory regulations.

##### The FDA's Assessment:

FDA agrees with the Applicant's position.

#### **Financial Disclosure**

##### The Applicant's Position:

The Applicant submitted a financial disclosure certification document in Module 1.3.4. in accordance with 21 CFR 54. The document included 2 tables which provided a summation of the total number of investigators who participated in Studies 3b and 14 and a table listing the names of each investigator who participated in each study. Investigators had no disclosable interests. All investigators provided signed pre-study financial disclosure statements to the Sponsor-Investigator prior to participating and all were informed of their regulatory obligation to update one year after study concluded or if they left prior to study closure, one year from the date they were no longer a participating investigator.

##### The FDA's Assessment:

FDA agrees with the Applicant's position.

#### **Patient Disposition**

##### The Applicant's Position:

A total of 141 patients enrolled and received treatment with DFMO. The ITT population consists of all patients who received at least 1 dose of DFMO and did not have any important

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eligibility deviations. One patient (b) (6) who was enrolled on a compassionate use basis despite failing Lansky score eligibility criteria was prospectively excluded from the analysis population by written record at the time of enrollment. The ITT population (N=140) was the main population for analyses of subject disposition, demographics, baseline characteristics, and efficacy analyses. Disposition for the ITT population is presented in Table 11.

At the time of NDA submission all patients completed the protocol defined DFMO therapy (i.e., up to 2 years) with a total of 63 patients (Stratum 1 and 2) continuing in long-term follow-up. The most common reason for study discontinuation regardless of strata was death as a result of disease progression with < 10% from Stratum 1 versus ~ 46% from Stratum 2.

**Table 11: Patient Disposition for ITT Population**

| Variable, n(%)            | Stratum 1<br>(N=105) | Stratum 2<br>(N=35) |
|---------------------------|----------------------|---------------------|
| Discontinued Treatment    | (b) (4)              | 20 (57.1)           |
| Adverse Event             | 1 (1.0)              | 0                   |
| Relapse                   | 16 (15.2)            | 19 (54.3)           |
| Other                     | (b) (4)              | 1(2.9)              |
| Completed Study           | (b) (4)              | 7 (20.0)            |
| Discontinued Study        | (b) (4)              | 18 (51.4)           |
| Lost to Follow-up         | 3 (2.9)              | 2 (5.7)             |
| Death                     | (b) (4)              | 16 (45.7)           |
| Ongoing post DFMO therapy | 53 (50.5)            | 10 (28.6)           |

**The FDA's Assessment:**

FDA agrees that the ITT population in Study 3(b) included 140 patients.

During review of the NDA, FDA noted that there were errors in the patient disposition for the ITT population. The Applicant confirmed that errors were identified in the Stratum 1 column and re-submitted Table 12 below in a Clinical Information Amendment submitted by email on February 4, 2023.

In Stratum 1, 38% of patients completed the study, 11% discontinued the study (3% lost to follow-up), and 51% were ongoing in follow-up post-treatment completion.

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**Table 12.** Applicant's Revised Patient Disposition for ITT Population

| Variable, n(%)                                                | Stratum 1<br>[STRATA='Stratum 1']<br>(N=105) | Stratum 2<br>[STRATA='Stratum 2']<br>(N=35) |
|---------------------------------------------------------------|----------------------------------------------|---------------------------------------------|
| Discontinued Treatment<br>[EOTSTT='Discontinued Treatment']   | (b) (4) 22 (21.0)                            | 20 (57.1)                                   |
| Adverse Event<br>[DCTREAS='Adverse Event']                    | 1 (1.0)                                      | 0                                           |
| Relapse<br>[DCTREAS='Relapse']                                | 16 (15.2)                                    | 19 (54.3)                                   |
| Other<br>[DCTREAS=any option not Adverse Event<br>or Relapse] | (b) (4) 5 (4.8)                              | 1 (2.9)                                     |
| Completed Study<br>[EOSSTT='Completed']                       | (b) (4) 40 (38.1)                            | 7 (20.0)                                    |
| Discontinued Study<br>[EOSSTT='Discontinued']                 | (b) (4) 12 (11.4)                            | 18 (51.4)                                   |
| Lost to Follow-up<br>[DCSREAS='Death']                        | 3 (2.9)                                      | 2 (5.7)                                     |
| Death<br>[DCSREAS='Lost to Follow-Up']                        | (b) (4) 9 (8.6)                              | 16 (45.7)                                   |
| Ongoing post DFMO therapy<br>[EOSSTT='Ongoing']               | 53 (50.5)                                    | 10 (28.6)                                   |

Original table: [Assessment Aid Table 12](#)

Source: Clinical Information Amendment submitted by Applicant via email on February 4, 2023

**Protocol Violations/Deviations**The Applicant's Position:

The Sponsor-Investigator reviewed, assessed and classified protocol deviations in consultation as needed with members of the study team. Most protocol deviations were considered non-important or minor. Important protocol deviations were defined as those that may affect the subject's rights, safety or well-being, and/or the completeness, accuracy and reliability of the data. There was a total of 6 important protocol deviations identified during the 2 year treatment period, all within the Stratum 1 population. None of the protocol deviations reported in this study were considered to affect the patient's safety or wellbeing or the overall integrity of the study including the safety or efficacy conclusions.

- Delay in reporting serious adverse events to sponsor / IRB (1 subject)
- Eligibility (3 subjects)

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- two patients enrolled with exactly 120 days from date of last anticancer therapy versus < 120 days
- enrolled patient met exclusion criterion 1 with a Lansky score of 40 % versus <60%; Patient was allowed to enroll and data to be excluded for analysis.
- Protocol implementation (2 subjects)
  - Taking expired drug for 4.5 days
  - Missed MIBG assessment at end of cycle 3

**The FDA's Assessment:**

FDA agrees that the reported protocol deviations are unlikely to impact the safety or efficacy assessment. In addition to those listed above, other protocol deviations were primarily related to protocol implementation: patients seen outside visit window and missed assessments (primarily urine and inflammatory markers).

**Table of Demographic Characteristics**Data:

The general demographic characteristics for patients enrolled to Stratum 1 and Stratum 2 are presented in Table 13.

**Table 13: Study 3b ITT Population Demographic Characteristics by Strata**

| Demographic Parameters           | Strata            |                  |
|----------------------------------|-------------------|------------------|
|                                  | Stratum 1 (N=105) | Stratum 2 (N=35) |
| <b>Sex, n (%)</b>                |                   |                  |
| Female                           | 43 (41.0)         | 12 (34.3)        |
| Male                             | 62 (59.0)         | 23 (65.7)        |
| <b>Age at Baseline, n (%)</b>    |                   |                  |
| <6 years                         | 78 (74.3)         | 12 (34.3)        |
| ≥6 years                         | 27 (25.7)         | 23 (65.7)        |
| <b>Race, n (%)</b>               |                   |                  |
| American Indian or Alaska Native | 0                 | 2 (5.7)          |
| Asian                            | 1 (1.0)           | 0                |
| Black or African American        | 7 (6.7)           | 3 (8.6)          |

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| Demographic Parameters                     | Strata            |                  |
|--------------------------------------------|-------------------|------------------|
|                                            | Stratum 1 (N=105) | Stratum 2 (N=35) |
| White                                      | 90 (85.7)         | 29 (82.9)        |
| Unknown                                    | 2 (1.9)           | 1 (2.9)          |
| Multiple <sup>a</sup>                      | 5 (4.8)           | 0                |
| <b>BSA (m<sup>2</sup>)</b>                 |                   |                  |
| n (missing) <sup>b</sup>                   | 84 (21)           | 16 (19)          |
| Mean (SD)                                  | 0.731 (0.2401)    | 0.825 (0.2174)   |
| Min, max                                   | 0.45, 1.81        | 0.55, 1.35       |
| <b>Country of Patient Residence, n (%)</b> |                   |                  |
| n (missing) <sup>b</sup>                   | 84 (21)           | 16 (19)          |
| US                                         | 75 (71.4)         | 16 (45.7)        |
| Ex-US <sup>c</sup>                         | 9 (8.6)           | 0                |

BSA = body surface area; HRNB = high-risk neuroblastoma; US = United States

<sup>a</sup> Multiple includes 1 patient each: Asian and Black or African American; Asian and White; Black or African American and White; Native Hawaiian or other Pacific Islander and White; and unknown

<sup>b</sup> Data not available for non-transfer patients.

<sup>c</sup> All patients were enrolled at US sites; however, 9 patients were international patients for whom treatment prior to Study 3b participation would have been managed per local standard of care.

Source: Study 3b CSR Table 14.1.3.2, Table 14.1.4.2, and Listing 16.2.4.1.2

### The Applicant's Position:

The demographics for patients are consistent with expected characteristics for the target patient population. More than half of patients were male consistent with published literature in HRNB. Stratum 2 patients were on average older at Baseline as expected given these were patients that would have been in treatment longer for refractory disease or previous relapse(s).

### The FDA's Assessment:

FDA agrees with the Applicant's presentation of demographics in Study 3(b).

Of the 140 patients treated in Study 3(b), 90 patients were included in the experimental treatment arm in the Applicant-proposed primary efficacy population of the ECT. The demographics of these two populations were similar (refer to Section 8.1.4).

Notably, the majority of patients in the ECT investigational arm were enrolled on Stratum 1 (89 patients), and one patient was enrolled on Stratum 2. Both Study 3(b) and ANBL0032 eligibility

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criteria required “histologic verification at the time of original diagnosis or previous relapse of HRNB.” However, ANBL0032 allowed an exception for patients who were initially diagnosed as non-high-risk neuroblastoma, but later converted (and/or relapsed) to HRNB. The one patient enrolled on Study 3(b) Stratum 2 was originally diagnosed as low risk and underwent complete surgical resection. Eighteen months later, the tumor recurred and MYCN was amplified (thus diagnosed with high-risk neuroblastoma at that time). The patient underwent induction and consolidation therapy, followed by immunotherapy on ANBL0032. The patient met all criteria to be included in primary efficacy population.

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

Data:

The key disease characteristics for patients enrolled to Stratum 1 and Stratum 2 are presented in Table 14.

**Table 14: Stratum 1 Disease Characteristics, Intent-to-Treat Set**

| Parameter                             | Stratum 1 (N=105) | Stratum 2 (N=35) |
|---------------------------------------|-------------------|------------------|
| <b>Age at HRNB diagnosis, n (%)</b>   |                   |                  |
| < 18 months                           | 15 (14.3)         | 3 (8.6)          |
| 18 months to < 6 years                | 76 (72.4)         | 29 (82.9)        |
| ≥6 years                              | 14 (13.3)         | 3 (8.6)          |
| <b>Stage at HRNB Diagnosis, n (%)</b> |                   |                  |
| 2                                     | 3 (2.9)           | 0                |
| 3                                     | 7 (6.7)           | 1 (2.9)          |
| 4                                     | 93 (88.6)         | 32 (91.4)        |
| 4s                                    | 2 (1.9)           | 2 (5.7)          |
| <b>Histology, n (%)</b>               |                   |                  |
| Favorable                             | 8 (7.6)           | 3 (14.3)         |
| Unfavorable                           | 82 (78.1)         | 22 (62.9)        |
| Not available                         | 15 (14.3)         | 8 (22.9)         |
| <b>MYCN Amplification, n (%)</b>      |                   |                  |
| Amplified                             | 47 (44.8)         | 10 (28.6)        |
| Non-amplified                         | 56 (53.3)         | 22 (62.9)        |
| Unknown                               | 2 (1.9)           | 3 (8.6)          |

HRNB = high-risk neuroblastoma

Source: Study 3b CSR Table 14.1.4.2 and Table 14.1.6.2

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The Applicant's Position:

Disease characteristics for patients enrolled in Study 3b are also consistent with the target patient population. The majority of patients had Stage 4 disease and unfavorable histology, and approximately half of Stratum 1 patients were MYCN amplified, consistent with expected rates in HRNB patients. A lower proportion of Stratum 2 patients were MYCN amplified; however, rates in this poorer-risk cohort may reflect that fewer MYCN amplified patients are able to reach initial remission when treated for refractory disease or able to achieve a second remission following a relapse.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of baseline disease characteristics in Study 3(b).

The majority of patients in both groups had Stage 4 disease and were between 18 months and 6 years of age at diagnosis. While it is well-established that *MYCN* amplification is correlated with poor prognosis, it is less clear whether these patients are less likely to achieve an initial remission (Kaneko et al, 2002; Bartolucci et al, 2022).

Potentially important treatment-related characteristics not provided in the summary include whether patients had surgery during induction, whether patients had radiation during consolidation (type, dose, location), and the transplant conditioning regimen used. Potentially important disease-related characteristics not provided in the summary include tumor cytogenetics and performance status at the end of immunotherapy. See Section 8.1.4 for further details.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Data:

During DFMO administration, no patient received parallel anti-cancer therapy or other investigational products. Use of concomitant therapy was primarily for typical childhood illnesses. In the event of relapse, the protocol required DFMO therapy to stop and the patient treated according to investigator discretion in consult with patient's family/guardian.

The Applicant's Position:

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Concomitant anti-cancer therapy was not permitted per protocol, and there were no concerns regarding site and patient treatment compliance. DFMO was evaluated in Study 3b as a single agent treatment and the data support interpretability of the EFS outcomes which can be attributed to DFMO alone.

#### The FDA's Assessment:

FDA agrees that the Study 3(b) protocol excluded patients who were currently receiving other anticancer agents. The following medications were not permitted during the trial:

- Any cytotoxic chemotherapy
- Any other investigational treatment
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy, targeted therapies, anti-angiogenic therapies, or monoclonal antibody therapy
- Any radiotherapy, including systemically administered radioisotopes, unless administered with palliative intent

The most common concomitant medications were anti-infectives, followed by vitamins/supplements, topical/nasal/inhaled steroids, and antihistamines. Anti-emetics and opioids were also used as supportive care medications. Oral steroids were used in approximately 10% of patients and typically administered in short courses for an acute indication (e.g., cough, croup, allergic reaction).

#### **Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)**

##### Data:

The primary endpoint of the study was to compare the Stratum 1 time-to-event outcome of EFS at 24 months to a historical control rate of 70% from the COG Study ANBL0032 as reported in [Yu, 2010](#) and to compare Stratum 2 EFS at 24 months to a historical control rate of 10% from [Santana, 2008](#). Patients represented in the historical control had similar treatment histories to those patients in each strata, but were not treated with DFMO. Kaplan-Meier estimates for EFS over time and historical control comparison at 24 months are summarized in [Figure 17](#) (Stratum 1), [Figure 18](#) (Stratum 2), and Table 15.

The results from Kaplan-Meier analyses suggest that the EFS rate at 24 months was higher for DFMO treated patients in Stratum 1 (85%) and Stratum 2 (46%) compared to the historical control (70% and 10% for Stratum 1 and 2, respectively). These statistically significant results, at

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the 5% level, favor DFMO treatment for both the Stratum 1 comparison ( $p = 0.0021$ ) and for the Stratum 2 comparison ( $p < 0.0001$ ).

**Table 15: Kaplan-Meier Estimates for Event Free Survival at 24 Months, Intent-to-Treat Set**

|                                                           | Stratum 1<br>(N=105) | Stratum 2<br>(N=35) |
|-----------------------------------------------------------|----------------------|---------------------|
| Kaplan-Meier Estimates at 24 months vs historical control |                      |                     |
| Historical control KM estimate                            | 0.7                  | 0.1                 |
| KM estimate at 24 months                                  | 0.85                 | 0.46                |
| Standard error <sup>a</sup>                               | 0.250                | 0.235               |
| P-value <sup>b</sup>                                      | 0.0021               | <0.0001             |

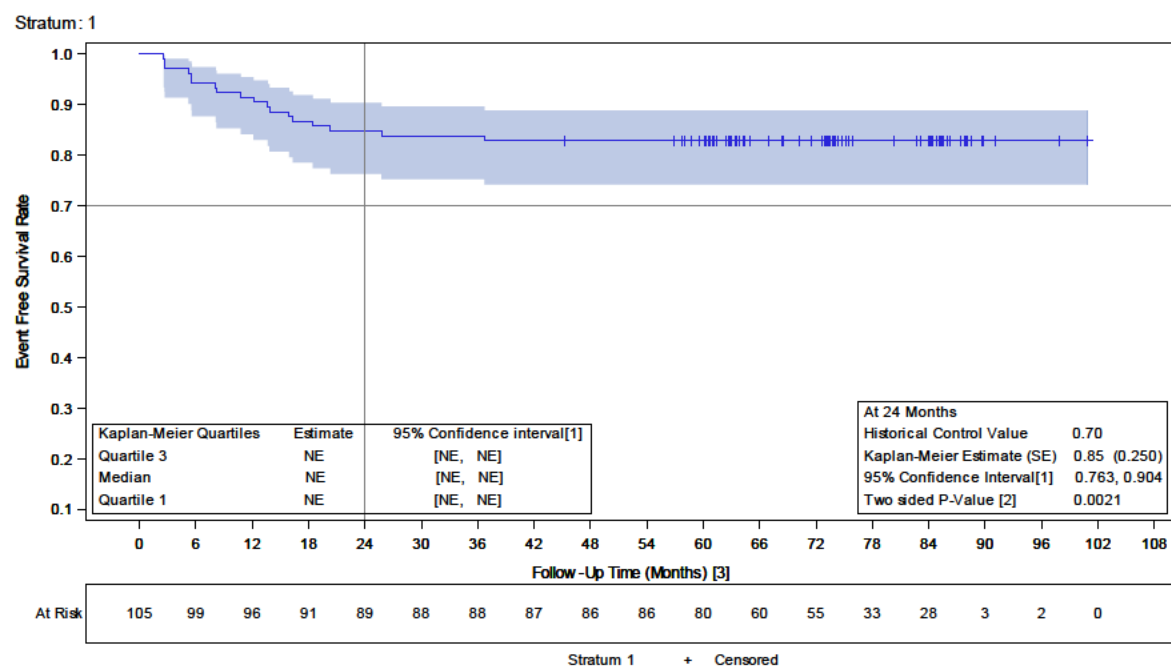
KM = Kaplan-Meier

<sup>a</sup> Standard error is computed using the log-log transformation.

<sup>b</sup> Two-sided p-value associated with z-score following a standard normal distribution derived using the log-log transformed observed and relevant historical KM estimate as (observed value – historical value)/standard error.

Source: Study 3b CSR Table 14.2.1.1.1

**Figure 17: Kaplan-Meier Estimates for EFS over Time and 24 Month Historical Control Comparison for Stratum 1, Intent-to-Treat Set**



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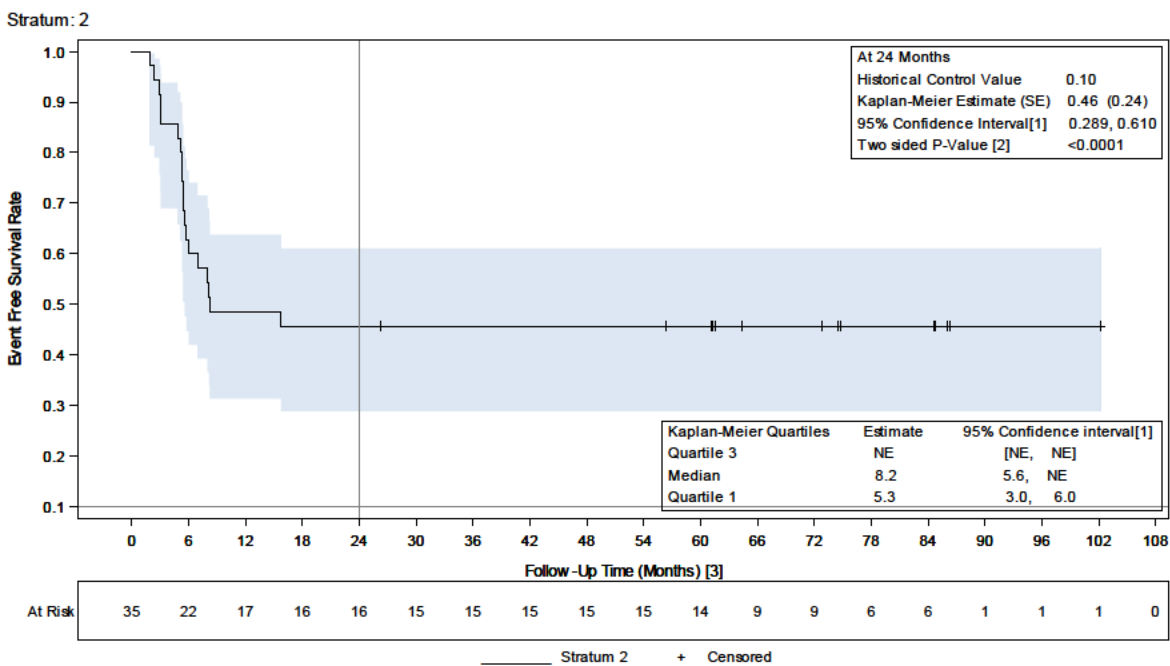
NE = not estimable; SE = standard error

[1] 95% confidence interval for the Kaplan-Meier estimate of the observed values at the relevant timepoint using the log-log transformation.

[2] Standard error was computed using the log-log transformed observed and relevant historical Kaplan-Meier estimate as (observed value – historical value)/standard error.

[3] From date of first DFMO treatment to date of first occurrence of relapse, progressive disease, secondary cancer or death. If none of these events occurred, the patient is censored at the date of last contact.

Source: Study 3b CSR Figure 14.2.1.1.1

**Figure 18: Kaplan-Meier Estimates for EFS over Time and 24 Month Historical Control Comparison for Stratum 2, Intent-to-Treat Set**

NE = not estimable; SE = standard error

[1] 95% confidence interval for the Kaplan-Meier estimate of the observed values at the relevant timepoint using the log-log transformation.

[2] Standard error was computed using the log-log transformed observed and relevant historical Kaplan-Meier estimate as (observed value – historical value)/standard error.

[3] From date of first DFMO treatment to date of first occurrence of relapse, progressive disease, secondary cancer or death. If none of these events occurred, the patient is censored at the date of last contact.

Source: Study 3b CSR Figure 14.2.1.1.1

**The Applicant's Position:**

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The primary endpoint analyses of EFS support a meaningful improvement over published rates for those patients in initial remission following upfront treatment and following relapse/refractory treatment. The use of a published point estimate as the basis for comparison; however, limits the strength of the conclusion that can be drawn as potential differences in the populations cannot be fully evaluated. These limitations, in particular for the target patient population enrolled in Stratum 1, are addressed by the analyses vs. ANBL0032 in Section 8.1.3.

#### The FDA's Assessment:

FDA agrees that the historical control rates for Strata 1 and 2 were pre-specified as described and known prior to ECT initiation. For Stratum 1, the K-M estimate for EFS at 24 months was 0.85 (95% CI: 0.76, 0.90). For Stratum 2, the K-M estimate for EFS at 24 months was 0.46 (95% CI: 0.29, 0.61). However, FDA considers the comparisons of EFS and OS results with benchmark historical control rates to be exploratory only. In general, FDA considers the results of time-to-event endpoints in single arm studies to be uninterpretable, due to the lack of a comparator which would allow for attribution of the treatment effect to the investigational agent of interest.

It is notable that the results of Study 3(b) were published in 2018 (Sholler et al), and thus known prior to the design of the externally controlled trial. Therefore, the design of the ECT could not be prespecified, which FDA considers to be a limitation. However, FDA provided recommendations on the development of the statistical analysis plan which may reduce the potential for bias introduced by the sponsor's knowledge of Study 3(b) and ANBL0032 results.

### **Data Quality and Integrity**

#### The Applicant's Position:

Study 3b has not yet been audited by any government authority. The Sponsor-Investigator, Dr. Sholler, followed internal SOPs for monitoring including weekly email follow-up and monthly coordinator meetings specifically to address any known global data inconsistencies. The Applicant has no concerns with data quality and integrity.

#### The FDA's Assessment:

FDA inspections conducted by OSI during the review period did not identify any concerns regarding data quality or integrity.

**Efficacy Results – Secondary and other relevant endpoints**Data:

Other planned endpoints included EFS analyses to 48-months. The approach for the primary analysis was repeated assuming an EFS historic value at 48 months of 0.6 for Stratum 1 (based on a subsequent publication of ANBL0032 outcomes by [Yu 2014](#)) and 0.1 for Stratum 2 (maintaining the same 24-month estimate from [Santana 2008](#)). Maintaining the same rate for Stratum 2 conservatively assumed that no further events would be observed between 24 and 48 months for the control.

**Table 16: Kaplan-Meier Estimates for Event Free Survival at 48 Months, Intent-to-Treat Set**

|                                                           | <b>Stratum 1<br/>(N=105)</b> | <b>Stratum 2<br/>(N=35)</b> |
|-----------------------------------------------------------|------------------------------|-----------------------------|
| Kaplan-Meier Estimates at 48 months vs historical control |                              |                             |
| Historical control KM estimate                            | 0.6                          | 0.1                         |
| KM estimate at 48 months                                  | 0.83                         | 0.46                        |
| Standard error <sup>a</sup>                               | 0.236                        | 0.235                       |
| P-value <sup>b</sup>                                      | <0.0001                      | <0.0001                     |

KM = Kaplan-Meier

<sup>a</sup> Standard error is computed using the log-log transformation.

<sup>b</sup> Two-sided p-value associated with z-score following a standard normal distribution derived using the log-log transformed observed and relevant historical KM estimate as (observed value – historical value)/standard error.

Source: Study 3b CSR Table 14.2.1.1.1

At 48 months, the difference in EFS rates between Stratum 1 patients and the historical control became more pronounced from the 24 month timepoint and continued to be significant (83% for Stratum 1 and 60% for historical control,  $p < 0.0001$ ).

There were no EFS events after 24 months and hence no change for Stratum 2 in the EFS rate from 24 to 48 months. In each Strata, results continued to favor DFMO treatment at 48 months.

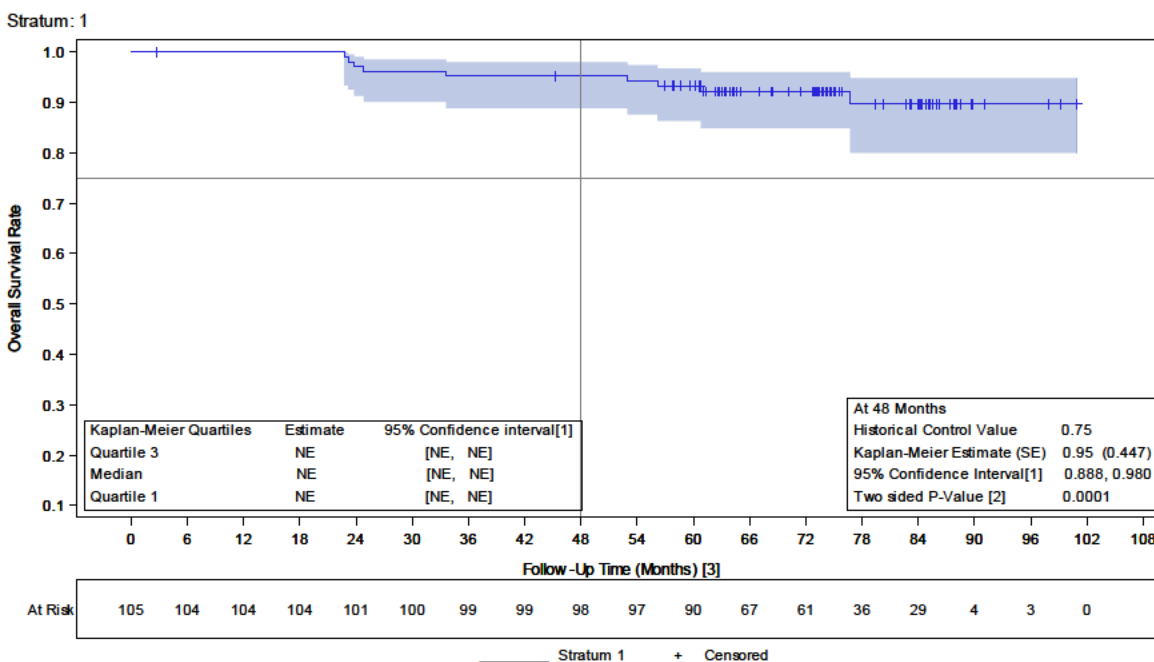
Overall survival was a secondary endpoint for the study, as there was an expected correlation between relapse and mortality. Overall survival analysis was planned for Stratum 1 only; however, a post hoc Kaplan Meier curve of overall survival was also produced for Stratum 2. The Kaplan-Meier estimate for OS over time is presented in Figure 19 and [Figure 20](#) for Stratum 1 and 2, respectively.

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At 24 and 48 months, Stratum 1 DFMO treated patients had a greater likelihood of OS compared to historical control rate of 85% and the results were statistically significant, at the 5% level, for both the ITT set and the treatment evaluable set.

**Figure 19: Kaplan-Meier Estimates for Overall Survival Over Time and 48 Month Historical Comparison for Stratum 1, Intent-to-Treat**



NE = not estimable; SE = standard error

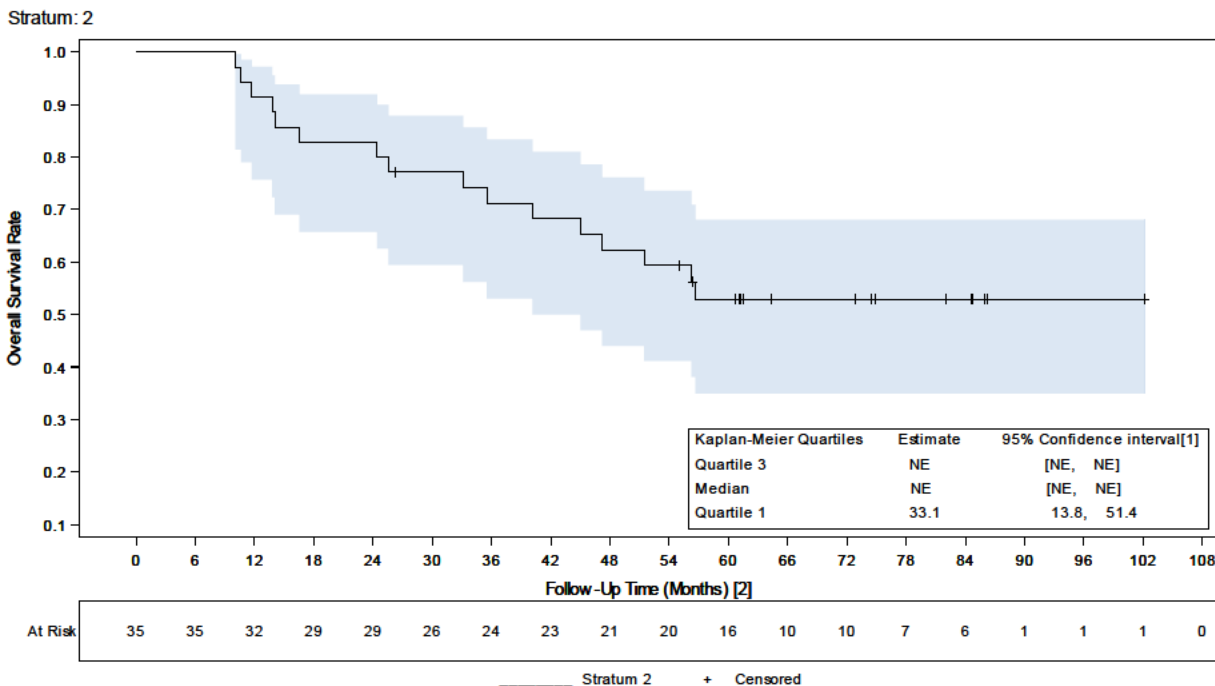
[1] 95% confidence interval for the Kaplan-Meier estimate of the observed values at the relevant timepoint using the log-log transformation.

[2] Standard error was computed using the log-log transformed observed and relevant historical Kaplan-Meier estimate as (observed value – historical value)/standard error.

Source: Study 3b CSR Figure 14.2.4.2.1

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**Figure 20: Posthoc Kaplan-Meier Estimates for Overall Survival Over Time for Stratum 2, Intent-to-Treat**

NE = not estimable

[1] 95% Confidence Interval for the KM estimate of the observed values at the relevant timepoint using the Log-Log transformation.

[2] From date of first DFMO treatment to date of death. If a patient did not die, the patient is censored at the date of last contact.

Source: ISE Figure 14.2.4.2.3

**The Applicant's Position:**

The secondary and exploratory endpoint analyses in Study 3b provide further support for DFMO efficacy in reducing the risk of relapse. EFS results at 48 months continue to outperform historical rates, and overall survival is higher than reported for each HRNB cohort (patients consistent with Stratum 1 or 2) based on the literature. Overall survival in Stratum 1 patients was >90% at 4 years with minimal censoring compared to published rates of 75%. Stratum 2 results were expectedly lower at 53%, with the lower bound of the 95% confidence interval being 35%, by 5 years however, this rate is much higher than scientific literature which characterizes the chances of 5 year survival following a relapse at <10% (Basta 2016); although it should be noted that overall survival rates in a comparable subgroup of such relapsed patients that subsequently

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achieve a second remission is not well characterized. Nonetheless, it is well established that a relapsed HRNB is associated with high mortality. Accordingly reducing the risk of relapse as established by EFS analyses in both strata was expected to also result in reducing the risk of death as established by OS analyses. While it is acknowledged that overall survival rates may also be influenced by post relapse therapy, the results are still considered highly supportive given that maintaining a higher proportion of patients in remission (and therefore not requiring post-relapse therapy with the potential to confound interpretation) is expected to have a correlated outcome that a higher proportion of patients will survive.

**The FDA's Assessment:**

FDA considered the efficacy results presented in this section to be exploratory. FDA did not confirm the results for Study 3(b) Stratum 2 presented in this section. However, the results from Study 3(b) Stratum 2 were considered as a potential source of supportive data; refer to Section 8.1.5.

**Dose/Dose Response****Data:**

A single dose level of 750 +/- 250 mg/m<sup>2</sup> was evaluated in Study 3b. However, BSA dosing categories utilizing multiples of the absolute tablet strength of 250 mg (salt) resulted in nearly a twofold difference in absolute dose/BSA. For example, if a patient's BSA = 0.45m<sup>2</sup> they would receive 1 tablet BID or 500 mg total daily dose, whereas a patient with a slightly higher BSA of 0.5m<sup>2</sup> would fall into the next dose category and receive 2 tablets BID or 1000 mg total daily dose. Additionally, over the course of two years of DFMO treatment, normal childhood growth resulted in patients moving up in BSA dosing categories over time. To evaluate dose response within the range of BSA normalized doses resulting from the recommended dose level, a post hoc analysis was performed to investigate the association between BSA-normalized dose (first dose and last dose) and outcome (relapse vs. ongoing/censored patients with EFS events) in Study 3b (see Section 11.5.8 in Study 3b CSR). The distribution of BSA normalized first and last dose were similar in patients with and without relapse events.

**The Applicant's Position:**

Within the range of BSA normalized doses evaluated in Study 3b, there was no apparent dose effect.

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**The FDA's Assessment:**

FDA agrees with the Applicant's assessment. Refer to Section 6 for details regarding the Clinical Pharmacology review.

**Durability of Response**

**Data:**

Outcomes for Study 3b were based on occurrence of an EFS (i.e., relapse) event or maintained remission. Analyses of the durability of the response were not relevant for the endpoint of interest.

{Eflornithine [DFMO]}

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable

**Persistence of Effect**

Data:

Long term follow up continued for 5 years after the completion of the two year DFMO on-therapy period. In Stratum 1, of those patients remaining in follow up, only 1 patient experienced an EFS events after the final on-therapy study visit (30 day follow up visit after last dose of DFMO). In Stratum 2, of those patients remaining in follow up, no new EFS events were reported after the final on-therapy study visit.

The Applicant's Position:

The low rate of late-occurring events, following completion of the two-year dosing period, supports the persistence of the effect of DFMO therapy.

The FDA's Assessment:

FDA agrees with the Applicant that patients were followed for up to 5 years after completion of DFMO therapy. For patients in remission after completion of up-front therapy, most EFS events occurred within the first 2 years after completion of immunotherapy. In the context of a single arm trial, the evaluation of the persistence of effect is challenging to interpret given the multiple prior therapies patients received.

**Efficacy Results – Secondary or exploratory COA (PRO) endpoints**

Data:

**Table 17: Kaplan-Meier Estimates for Event Free Survival at 24 and 48 Months, Subset for the DFMO PER COG (n=92)**

|                                | <b>24 Month</b> | <b>48 Month</b> |
|--------------------------------|-----------------|-----------------|
| Historical control KM estimate | 0.7             | 0.6             |
| KM estimate at 24 months       | 0.86            | 0.84            |
| Standard error <sup>a</sup>    | 0.278           | 0.259           |

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|                      | <b>24 Month</b> | <b>48 Month</b> |
|----------------------|-----------------|-----------------|
| P-value <sup>b</sup> | 0.0022          | <0.0001         |

KM = Kaplan-Meier

<sup>a</sup>Standard error is computed using the log-log transformation.<sup>b</sup>Two-sided p-value associated with z-score following a standard normal distribution derived using the log-log transformed observed and relevant historical KM estimate as (observed value – historical value)/standard error.

Source: Study 3b CSR Table 14.2.6.1

**The Applicant's Position:**

Stratum 1 evaluated HRNB patients in initial remission completing treatment that minimally consisted of chemotherapy induction, consolidation therapy and immunotherapy. However, some heterogeneity exists within the Stratum 1 group due to differences in upfront treatment for those patients receiving upfront treatment internationally and patients receiving different standard of care in the US (e.g., at MSK). Such patients may have received treatment with other forms of immunotherapy (e.g., 3F8 at MSK or dinutuximab-beta in Europe) and/or may have had other differences in treatment (e.g., ASCT not part of standard of care at MSK) compared to what would have been more standardly employed at US COG sites for upfront therapy at the time of the study (specifically, immunotherapy with dinutuximab/ch14.18 and at least one ASCT). Because Stratum 1 was prospectively planned for comparison to the outcomes in (Yu 2010) from the ANBL0032 study, a subgroup of N=92 patients receiving upfront treatment either by direct participation in ANBL0032 (N=87) or consistent with ANBL0032 (N=5) termed the “DFMO PER COG” subgroup analysis was identified. Analysis of this population permits comparison of outcomes in a more homogenous group of patients, those expected to be most consistent with those patients represented in the historical rate against which the study was designed. The results within this group were consistent with those reported for the full Stratum 1 cohort.

**The FDA's Assessment:**

No COA endpoints were included in Study 3(b). FDA agrees with the efficacy results presented in this section. FDA considered these results to be exploratory.

The Applicant's description of the population included in the ECT is included in Section 8.1.3.

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### **Additional Analyses Conducted on the Individual Trial**

#### Data:

Based on recommendations from the FDA, the DFMO PER COG group of N=92 Study 3b patients that received up-front treatment on or consistent with ANBL0032 prior to enrollment on Study 3b in initial remission, the “DFMO PER COG” group as further described in Section 6.1 of the Study 3b versus ANBL0032 Efficacy Report, were included in a blinded independent central review of imaging (BICR) for outcome determination by independent radiologists (IRs). Outcomes as determined by IRs were evaluated for concordance with Study 3b reported outcomes by the local evaluator (LE). BICR determined outcomes were also used in comparative analyses to patient level data in the external control ANBL0032 database as discussed in Section 8.1.3 below.

All 92 patients planned for evaluation in the BICR met minimum imaging criteria for inclusion in the BICR analysis population. The BICR followed a dual read with adjudication paradigm. All imaging was obtained for patients during both protocol required imaging visits through the 2 year treatment period and, when applicable/available, during the long term follow up period. Readers assessed Baseline imaging for eligibility consistent with Study 3b remission criteria with options of Eligible, Ineligible, Inconclusive and Unevaluable and each set of post-Baseline imaging for a determination of whether an EFS event (neuroblastoma relapse or secondary cancer) had occurred with options of Unequivocal EFS Event, Equivocal EFS Event, No EFS Event or Unevaluable. Unevaluable outcomes were not considered valid and, when reported, would result in the use of the most recent valid outcome in analyses. Only Unequivocal EFS Events were handled as events in analyses.

Fifteen patients had BICR determined Unequivocal EFS Events. A total of 9 patients had a final valid timepoint determination of Equivocal EFS Event and the remaining 68 patients had a final valid timepoint determination of No EFS Event (Study 3b versus ANBL0032 Efficacy Report Table 39).

When compared to the LE determined outcomes for the same 92 patients, there were two discordant post-Baseline outcomes (Study 3b versus ANBL0032 Efficacy Report Table 41). In one instance, the LE reported a relapse event while the IR determined there to be an Equivocal EFS Event at the same timepoint. In the other case, the IR determined an Unequivocal EFS Event at the final imaging timepoint while the LE determined there to be no event. In summary, both LE and BICR called 15 total EFS events, although the groups determined to have events differed by one patient. Additionally, one patient that had an event reported by the IR as well as by the LE was considered to have relapsed at an earlier timepoint based on BICR evaluation.

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Concordance was assessed according to the SAP by the calculation of Cohen’s kappa. The estimated kappa of 0.920 (Full BICR period) and 0.957 (on-treatment BICR period) reflects near perfect agreement between BICR and LE.

#### The Applicant’s Position:

Given the open label nature of Study 3b, there is a potential bias by Investigators to perceive or be predisposed to anticipate a benefit of the investigational treatment which could theoretically influence their interpretation of surveillance assessments against diagnosing a relapse event. As such, FDA required a blinded independent central review of imaging to address potential biases in outcome reporting. The BICR was conducted by independent radiologists based on imaging studies and, when applicable, pathology reports. By contrast, outcome reporting in Study 3b was based on determinations by an oncologist, informed by both imaging radiologist impressions, pathology and other assessments (labs, physical exams, etc.). Having the full clinical context for interpreting imaging is important because new lesions and artifacts which do not represent disease are often observed on imaging. Indeterminate observations or “equivocal” outcomes based on imaging in the BICR reporting, by default, must be interpreted as no event because if a relapse cannot be clearly concluded, then no oncologist would subject a patient to highly toxic relapse therapy. Rather, in such instances further follow up and/or close monitoring would be implemented unless the imaging observations had an alternate explanation when viewed in the context of the full patient work up and history. Despite reliance on purely objective pathology and imaging studies without the ability to interpret findings in the context of full patient work up, the BICR outcomes reported by independent radiologists were highly concordant with Study 3b site reported outcomes. The results confirmed that Study 3b Investigator oncologists appropriately reported relapse events, and because there was not apparent bias in the reporting of events, the EFS data are reliable and interpretable for the assessment of DFMO efficacy.

#### The FDA’s Assessment:

FDA agrees that a blinded independent central review of imaging (BICR) of Study 3(b) was conducted to account for potential bias in the local evaluator reported outcomes (e.g., observer bias). Source imaging was not available to conduct a similar BICR for the control arm data from ANBL0032 of the externally controlled trial. Therefore, BICR data on the study outcome was not available for comparative evaluation within the externally controlled trial.

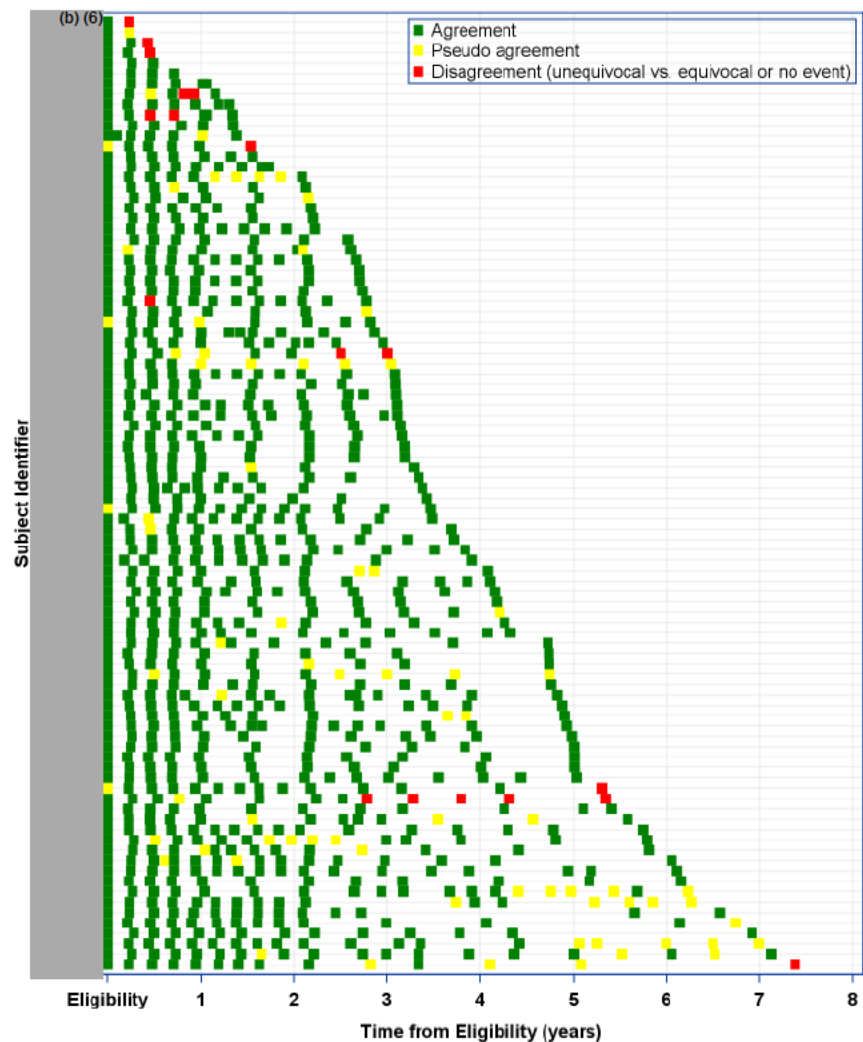
BICR was performed for all tumor imaging assessments on the investigational arm. There was agreement between the independent reviewers (IRs) and local evaluator (LE) in all but two cases in which there were discordant outcomes between the two assessors. One patient was determined to have a relapse event per LE, so no further imaging was done, and the BICR determined only

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an equivocal event based on the lack of confirmatory imaging. The second patient had an unequivocal event per BICR and no event per LE. In addition, two patients were determined to be ineligible at baseline per the BICR readers. The overall agreement between IRs across all timepoints is shown graphically in Figure 21.

In Study 3(b), determinations made by the LE were limited to “unequivocal event” or “no event” when evaluating imaging assessments. However, the BICR evaluators could make a determination of “equivocal EFS event” when in their judgment, sufficient clarity was not available to definitively make a determination of disease recurrence or secondary cancer (Table 18). Twenty-five patients had an equivocal imaging result at any time point. Of these, there were seven instances in which the last event was equivocal per two readers, and four instances when an equivocal event preceded an unequivocal event for the same lesion. The other equivocal events were isolated and only considered equivocal by one reader (the other reader determined no event). Sensitivity analyses were conducted to evaluate the impact of these findings on the overall treatment effect for Study 3(b) and the comparative externally controlled trial described in the following sections.

**Figure 21.** Overall agreement between BICR reviewers across all imaging timepoints



Source: Applicant analysis submitted in NDA 215500, Module 5.3.5.4 Comparison of Study 3b to ANBL0032 External Control Database, page 177.

**Table 18. Rules for Unequivocal Disease Recurrence, No Disease Recurrence, Equivocal Disease Recurrence, or Unevaluable Imaging Assessments per BICR**

| Rules for Unequivocal Disease Recurrence, No Disease | May be called when | May not be called when |
|------------------------------------------------------|--------------------|------------------------|
|                                                      |                    |                        |

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| Recurrence, Equivocal Disease Recurrence, or Unevaluable Outcome |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Unequivocal Disease Recurrence                                   | <ul style="list-style-type: none"> <li>When at least one of the criteria as above are met and support a definitive determination by the IR, of disease recurrence which would refer a patient to relapse treatment.</li> </ul> <p><i>Note: When a lesion meeting at least one of the criteria as above is observed on a post-baseline scan of a newly imaged region for which there is no prior imaging available (e.g., on a head CT performed at Visit 3, without any head CTs available for review at prior timepoints), a determination of Unequivocal Disease Recurrence should be made.</i></p>     | <ul style="list-style-type: none"> <li>A new lesion observed on imaging is accompanied by a pathology report confirming histologically that the mass is benign, is a mature lesion (e.g., ganglioneuroma), or otherwise not consistent with active neuroblastoma or ganglioneuroblastoma,</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>There is insufficient clarity in the imaging studies/data to definitively assess disease recurrence.</li> </ul>                                 |
| No Disease Recurrence                                            | <ul style="list-style-type: none"> <li>When none of the criteria as above are met and the IR feels there is sufficient clarity based on available imaging/data to determine that disease recurrence has not occurred.</li> </ul> <p>NOTE: Bone marrow assessments are not expected to be available at each timepoint, thus the absence of a bone marrow pathology report will not prevent an IR from calling a No Disease Recurrence outcome against the criteria.</p> <p>OR</p> <ul style="list-style-type: none"> <li>When a new lesion consistent with the criteria for Unequivocal Disease</li> </ul> | <ul style="list-style-type: none"> <li>When a bone marrow, soft tissue or bone biopsy pathology result definitely establishes an Unequivocal Disease Recurrence.</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>At the first timepoint at which imaging for a new anatomical region (i.e., an anatomical region that was NOT available for review at any prior timepoint) is included for review by the reader at the current timepoint., unless the new region is definitely</li> </ul> |

|                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              | Recurrence is observed on imaging but is ruled out by biopsy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                           |
| Equivocal Disease Recurrence | <ul style="list-style-type: none"> <li>When the IR determines there to be inadequate clarity in the available imaging/data to definitely call Unequivocal Disease Recurrence or No Disease Recurrence (e.g., a suspicious uptake is observed but there is insufficient clarity that it represents a change from a prior scan consistent with a new lesion or because the observation has possible alternate explanations based on the IRs experience that prevent a definitive confirmation of whether or not it constitutes recurrent disease)</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>When information that would be necessary to make a definitive evaluation is missing from the timepoint (e.g., missing MIBG to assess observations on MRI).</li> </ul> <p>Note: If a lesion is observed on a post-baseline scan of a newly</p> <p>prior imaging available (e.g., on a head CT performed at Visit 3, without any head CTs available for review at prior timepoints) and IR is unable to definitively call Unequivocal Disease</p> | <ul style="list-style-type: none"> <li>When a soft tissue or bone biopsy definitively establishes No Disease Recurrence or Unequivocal Disease Recurrence for a suspicious lesion on imaging</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>When a bone marrow result definitively establishes an Unequivocal Disease Recurrence.</li> </ul> |

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|             |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                               |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|             | <p>Recurrence as described above, a determination of Equivocal Disease Recurrence should be made.</p> <p>OR</p> <ul style="list-style-type: none"> <li>• When the IR suspects that a lesion has been subject to intervention but there are no clinical data available to verify.</li> </ul>                                                                   |                                                                                                                                                                                                                                                                                                                                                               |
| Unevaluable | <ul style="list-style-type: none"> <li>• When one or more images at the timepoint are of such poor quality as to prevent any assessment.</li> <li>• IRs will be instructed to assess available information and, whenever possible, to provide a finding of Unequivocal Disease Recurrence, No Disease Recurrence, or Equivocal Disease Recurrence.</li> </ul> | <ul style="list-style-type: none"> <li>• When a soft tissue or bone biopsy definitively establishes a No Disease Recurrence or Unequivocal Disease Recurrence for a suspicious lesion on imaging</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>• When a bone marrow result definitely establishes an Unequivocal Disease Recurrence.</li> </ul> |

Source: Imaging Charter for (b) (4) submitted to NDA 215500, pages 24-26.

### 8.1.3. Study 3b vs. ANBL0032

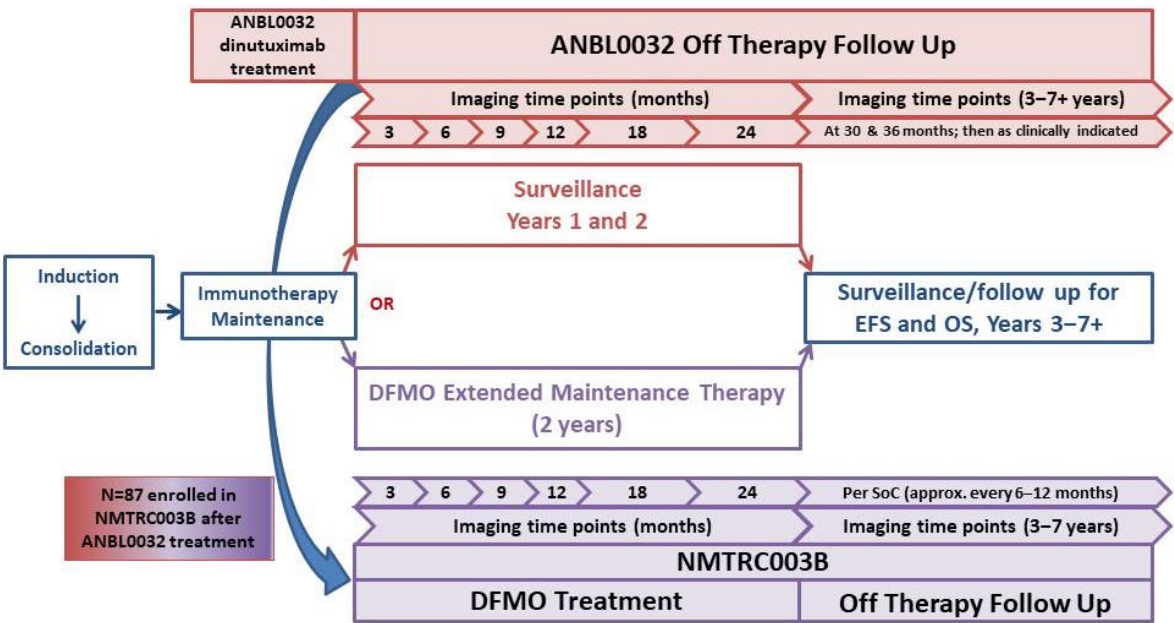
Given the interpretation challenges of the single arm study, outcome comparisons to ANBL0032 provide the primary evidence of efficacy for the application. ANBL0032 was a large phase III randomized open-label trial in HRNB patients. Patients were randomized to an induction regimen of cis-RA (Regimen A), or cis-RA plus sargramostim, dinutuximab and aldesleukin (Regimen B). Following completion of enrollment of the randomized phase of the study, enrollment continued under a single arm, open-label phase of the study, with all patients receiving the investigational treatment combination (Regimen B). Endpoints of the study included EFS and OS and long-term follow-up is still ongoing. Importantly, ANBL0032 supported the registration of dinutuximab for the treatment of HRNB in 2015. Since its approval, dinutuximab is recommended as part of the standard COG HRNB treatment protocol (until just recently, the standard COG HRNB protocol administered dinutuximab concomitantly with sargramostim [GM-CSF] and aldesleukin [IL-2], however, concomitant use of IL-2 is no longer

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recommended [Ladenstein 2018])). Given that the study met regulatory requirements to support product registration, the reliability of this source of real-world evidence (RWE) contributing real-world data (RWD) to serve as an external control is well supported. A comprehensive assessment of ANBL0032 as RWD contributing RWE to support a regulatory decision is presented in Appendix 3 of the 3b vs. ANBL0032 Efficacy Report.

Figure 22 depicts the staggered and overlapping study designs which permit a direct comparison of DFMO-treated and external control patients for EFS and OS outcomes from the common treatment point, the end of immunotherapy, which aligns with the end of ch14.18 therapy in ANBL0032 and the beginning of DFMO treatment in Study 3b. Both studies followed patients at regular intervals for 7-10 years. ANBL0032 enrolled from 2001-2015 and Study 3b enrolled from 2012 through 2016. The overlapping timelines resulted in cross-over between the studies; 87 patients enrolled in Study 3b following the ANBL0032 on-therapy portion (following the end of immunotherapy).

Figure 22: ANBL0032 and Study 3b Placement in HRNB Care Continuum



**Trial Design**

**Trial Location**

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Study 3b was conducted at 22 US centers and ANBL0032 was conducted at 197 centers, with the majority in the US.

### **Choice of control**

ANBL0032 is uniquely suited to be an appropriate external control for Study 3b for the following reasons:

Study 3b Stratum 1 EFS and OS analyses were prospectively planned to be compared to published rates from ANBL0032 (Yu 2010).

In the primary treated analysis population, the DFMO PER COG group, 87 of the 92 patients participated in ANBL0032 prior to Study 3b. This is a result of the largely overlapping enrollment timeframe and the Study 3b requirement that patients receive immunotherapy prior to being eligible for DFMO therapy. During the Study 3b enrollment period (Jun 2012 to Feb 2016), ANBL0032 was the largest immunotherapy study and immunotherapy access was only possible through trial participation until late 2015 (the commercial launch of dinutuximab). As such, ANBL0032 was the main source of patients that could be eligible for Study 3b.

Immunotherapy maintenance as investigated in ANBL0032 represents the most recent advancement in the standard of care for HRNB. Outcomes reported from ANBL0032 reflect survival following contemporary multimodality, multiagent therapy in three phases, induction, consolidation and maintenance, followed by regular surveillance to monitor for relapse without DFMO therapy. Outcome comparisons to patients completing the same contemporary standard of care and then further treated with DFMO therapy permit extension of the results to the current target population of high risk neuroblastoma patients in remission upon completion of multiagent, multimodality therapy.

### **Diagnostic criteria**

Both studies required patients to have a confirmed HRNB diagnosis according to risk staging by the INSS. Patients entering both studies were required to have received prior treatment that is specifically reserved for HRNB patients including high risk induction therapy, high dose chemotherapy with ASCT, and (in ANBL0032, prior to Study 3b) anti-GD2 immunotherapy treatment.

### **Key Inclusion/Exclusion Criteria**

Key inclusion/exclusion criteria for Study 3b are described above in Section 8.1.1. Key inclusion/exclusion criteria for ANBL0032 are described in the 3b. vs. ANBL0032 Efficacy Report.

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Selection rules were developed, considering the inclusion/exclusion criteria of the studies, to identify patients that received comparable upfront treatment either on or consistent with ANBL0032 and achieved disease status at the end of such upfront treatment who either were enrolled on DFMO treatment (Study 3b treated patients) or could have been eligible but did not enroll on DFMO treatment (ANBL0032 control patients). The primary analysis populations were the DFMO PER COG (N=92) and the NO DFMO (N=852) groups ( and ). Propensity score matching was used to ensure balance across 11 covariates, utilizing a 3:1 fixed ratio match within “Complete Case” groups of 516 DFMO PER COG and 91 NO DFMO patients with no missing covariate data. Overall populations of treated and control patients as well as propensity score matched cohorts of patients were compared for EFS and OS outcomes.

**Figure 23: DMO PER COG Analysis Population Selection Consort**

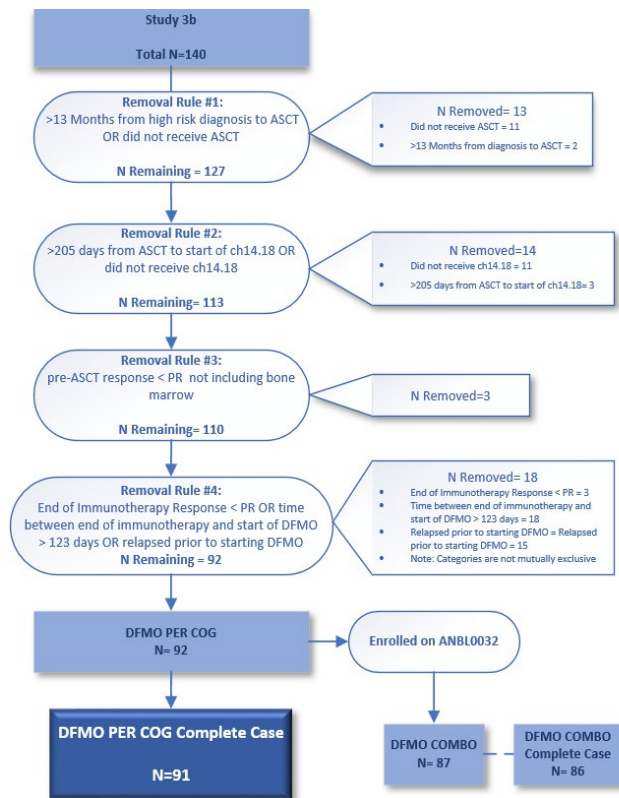
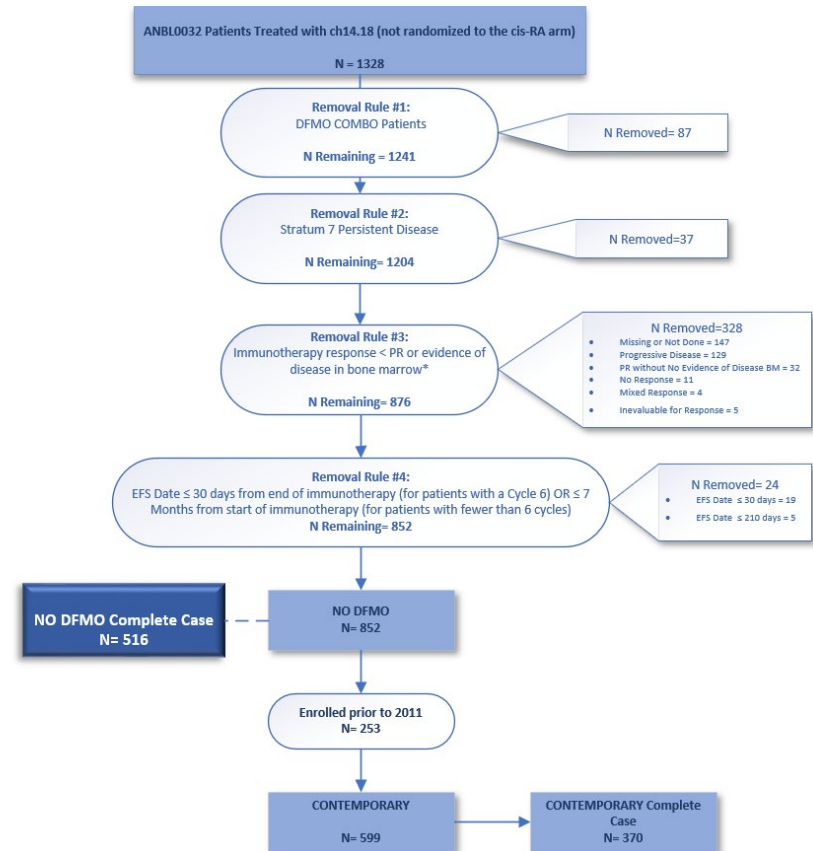


**Figure 24: NO DFMO Analysis Population Selection Consort**



### **Study Treatments**

The external control analyses compare the group of DFMO PER COG patients which received DFMO 750 mg +/-250 mg/m<sup>2</sup> BID for two years following the completion of immunotherapy to the group of NO DFMO patient were followed by standard of care surveillance procedures without DFMO therapy.

### **Assignment to treatment and blinding**

Patients in the DFMO PER COG group were non-randomly assigned to DFMO treatment in Study 3b. Patients in the NO DFMO group were either randomly or non-randomly assigned to ch14.18/dinutuximab immunotherapy treatment in ANBL0032; patients that were initially randomly assigned to the ANBL0032 control arm (Regimen A) and later crossed over to receive ch14.18/dinutuximab were excluded from the dataset against which population selection rules were applied.

### **Administrative structure**

This study was conducted by the Children's Oncology Group (COG) and sponsored by the National Cancer Institute (NCI) under NCI IND 4308 but transferred to United Therapeutics under IND 110494 at a later time. Administrative oversight of the study resided with NCI. Data for use in the 3b vs ANBL0032 analysis were provided to Applicant by COG per an executed Data Transfer Agreement (Study 3bvsANBL0032 Report, Appendix 3 ABNL0032 as Source of RWE).

### **Procedures and Schedule**

The procedures of greatest relevance for the comparison of EFS and OS outcomes between Study 3b and ANBL0032 are related to disease evaluation/long-term follow up assessments from the end of immunotherapy in ANBL0032/start of enrollment on Study 3b. Table 19 summarizes the required imaging and pathology assessments for both studies. Compliance evaluations for patient follow up in both studies are reported in Section 9.4. of the Study 3b vs. ANBL0032 Efficacy Report. Notably, imaging assessments were required at 30 and 36 months from the end of immunotherapy in ANBL0032 vs. follow up by standard of care during this timeframe in Study 3b; however, imaging obtained for the conduct of the BICR supports that the majority of DFMO PER COG patients were followed by imaging studies beyond the protocol required timeframe, including many with visits at approximately 30 and/or 36 months.



**Table 19 Tumor Assessments Requirements and Frequency by Protocol**

| <b>Tumor Assessments</b>                |                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Relative Treatment Step/Timeline</b> | <b>ANBL0032</b>                                                                                                                                                                                                                                                                                                                                                                                              | <b>Study 3b</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Start of Immunotherapy                  | <p>Within 4 weeks prior to study enrollment, the following assessments were required per protocol:</p> <p>MRI or CT scan, MIBG scan in MIBG-avid disease patients or bone scan in MIBG non-avid patients<br/>bone marrow aspiration and biopsy (biopsy may be omitted if negative prior to ASCT)<br/>and optional collection of blood and bone marrow samples for assessment of Minimal Residual Disease</p> | <p>Eligible patients for Study 3b were required to have previously completed induction, consolidation, and immunotherapy. Start of immunotherapy (end of consolidation) tumor assessment response data was required to be collected at enrollment.</p>                                                                                                                                                                                                                                  |
| Immunotherapy Cycle 3                   | <p>The following assessments were optional for Cycle 3:</p> <p>MRI or CT scan, MIBG scan in MIBG-avid disease patients or bone scans in MIBG non-avid patients<br/>bone marrow aspiration and biopsy (biopsy may be omitted if negative prior to ASCT)</p>                                                                                                                                                   | Not applicable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| End of Immunotherapy                    | <p>Within 2 weeks of completion of Cycle 6, the following were required:</p> <p>MRI or CT scan<br/>MIBG scan in MIBG-avid disease patients or bone scans in MIBG non-avid patients<br/>bone marrow aspiration and biopsy (biopsy may be omitted if negative prior to ASCT)<br/>and optional collection of blood and bone marrow samples</p>                                                                  | <p>Eligible patients for Study 3b were required to have previously completed induction, consolidation and immunotherapy. Within 14 days (+ 7 day window) prior to first dose of study drug and after last treatment of malignancy (within 30-120 days), the following assessments were required:</p> <p>MRI or CT scan<br/>MIBG and/or FDG-PET<sup>1</sup><br/>bone marrow aspiration and biopsy<br/>and optional collection of blood and bone marrow samples for assessment of MRD</p> |

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| Tumor Assessments                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                      |
|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Relative Treatment Step/Timeline      | ANBL0032                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Study 3b                                                                                                                                                                                                                                                             |
|                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Patients enrolling within 30 days of end of immunotherapy scans were not required to repeat imaging studies to confirm eligibility.                                                                                                                                  |
| Post Immunotherapy Maintenance Year 1 | <p>MRI or CT scans required 3 months after 2-week post-Cycle 6 evaluation and every 3 months during the 1<sup>st</sup> year off treatment (i.e., post- Cycle 6)</p> <p>Bone marrow aspiration/biopsy and MIBG or bone scan (for MIBG non-avid patients) were required every 3 months only if positive at completion of cis-RA acid therapy and were repeated until at least three consecutive (immunocytologically) negative bone marrows or MIBG scans were documented</p> <p>Except as required above, MIBG and bone marrow collection were optional unless a relapse was determined. MIBG and bone marrow assessments were required at relapse</p> | <p>MRI or CT and MIBG and/or FDG-PET required every 3 months during the first year of treatment (<sup>2</sup>End of DFMO Cycles 3, 6, 9 and 13)</p> <p>Bone marrow biopsy and aspirate is to be performed if the treating physician has concerns for progression</p> |

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| Tumor Assessments                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Relative Treatment Step/Timeline      | ANBL0032                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Study 3b                                                                                                                                                                                                                                                                                                                                                                             |
| Post Immunotherapy Maintenance Year 2 | <p>MRI or CT scans required every 6 months after 1<sup>st</sup> year off treatment to Year 3.</p> <p>Bone marrow aspiration/biopsy and MIBG or bone scan (for MIBG non-avid patients) were required every 3 months only if positive at completion of cis-RA acid therapy and were repeated until at least three consecutive (immunocytologically) negative bone marrows or MIBG scans were documented. MIBG was also required upon determination of relapse at any time during follow up.</p> <p>Except as required above, MIBG and bone marrow collection were optional unless a relapse was determined. MIBG and bone marrow assessments were required at relapse.</p> | <p>MRI or CT and MIBG and/or FDG-PET required every 6 months during the second year of DFMO treatment (End of DFMO Cycles 20 and 27<sup>2</sup>):</p> <p>Optional collection of blood and bone marrow samples for assessment of MRD at the end of DFMO Cycle 27</p> <p>Bone marrow biopsy and aspirate is to be performed if the treating physician has concerns for progression</p> |

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| Tumor Assessments                                       |                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Relative Treatment Step/Timeline                        | ANBL0032                                                                                                                                                                                                                                                                                                       | Study 3b                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Post Immunotherapy Maintenance Years 3 – 7 <sup>3</sup> | MRI or CT scans required every 6 months after 1 <sup>st</sup> year off treatment (corresponding to first year of DFMO) to Year 3 then as clinically indicated. MIBG blood and bone marrow collection were optional unless a relapse was determined. MIBG and bone marrow assessments were required at relapse. | <p>Per standard of care at treating sites.</p> <p>All Study 3b sites are affiliated with BCC. BCC sites follow standard of care imaging after DFMO treatment discontinuation including imaging yearly from 3-5 years and as clinically indicated for symptoms. To further characterize follow-up frequency, a description of surveillance guidelines by individual Study 3b site is included as Appendix 2 of the SAP.</p> <p>Follow-up information was obtained by continuing follow-up at the participating Study 3b sites or, for patients that transferred care back to their local hospital following study completion, by parent contact who confirmed status (continued remission vs. relapse) and survival. Long-term follow-up assessment information was collected at least every 12 months in the 3<sup>rd</sup> year and beyond.</p> |

Source: ANBL0032 Protocol Amendments through 19A (Appendix 4)

ASCT = autologous stem cell transplant; BCC = Beat Childhood Cancer; cis-RA = 13-cis-retinoic acid; CT = computed tomography; FDG-PET = fluorodeoxyglucose – positron emission tomography; MIBG = meta-iodobenzylguanidine; MRD = minimal residual disease

<sup>1</sup> PET was required at study entry for patients with remaining MIBG-avid tumors to confirm they were inactive for Study 3b enrollment. PET could also have been used performed in place of MIBG for patients with MIBG non-avid tumors.

<sup>2</sup> For Study 3/3b: Scans were done within +/-14 days of the start of next cycle. Off therapy/end of cycle 27 scans were done within 30 days (+7) after stopping study drug. Scans may have been done more often per institutional standards. For patients in first remission who required evaluations for previous front-line treatments that were different than the timing of the above schedule, the patients previously scheduled evaluations could have been accepted instead of repeating the above studies.

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<sup>3</sup> Per ANBL0032 protocol, long-term follow-up continued for up to 10 years from enrollment with annual site outreach to patients to assess disease/health status.

**The FDA's Assessment:**

FDA agrees with the Applicant's description of the externally controlled trial design, with additions as described below.

The ECT is comprised of a single-arm trial, Study 3(b), compared to an external control arm derived from the National Cancer Institute (NCI)/Children's Oncology Group (COG)-sponsored clinical trial, Study ANBL0032.

Study 3(b) is described in detail in Sections 8.1.1 and 8.1.2.

Study ANBL0032 was a large, multi-center, randomized, open-label trial of isotretinoin (cis-RA) (Regimen A) vs. cis-RA plus immunotherapy (dinutuximab + sargramostim [GM-CSF] + aldesleukin [IL-2]) (Regimen B) in patients with newly diagnosed HRNB who had previously received induction and consolidation therapy, achieving at least a partial response prior to autologous stem cell transplant treatment. Patients were enrolled between November 2004 and July 2015 at 197 sites including 172 in the United States, as well as sites in Australia, New Zealand, and Canada. The major efficacy outcome measure was investigator-assessed EFS, defined as the time from randomization to the first occurrence of relapse, progressive disease, secondary malignancy, or death.

In January 2009, the Data Safety Monitoring Committee performed a review of an interim analysis that demonstrated statistically significantly improved outcomes (both EFS and OS) among patients randomized to immunotherapy plus cis-RA (Regimen B) as compared to those randomized to standard cis-RA alone (Regimen A). As published by Yu et al in 2010, immunotherapy was superior to standard therapy with regard to rates of EFS ( $66 \pm 5\%$  vs.  $46 \pm 5\%$  at 2 years,  $P=0.01$ ) and OS ( $86 \pm 4\%$  vs.  $75 \pm 5\%$  at 2 years,  $P=0.02$ ). As a result, randomization was halted. The study was amended, and on April 20, 2009, it was reopened to accrual, with all patients assigned to receive immunotherapy plus cis-RA (Regimen B).

Publication of these findings resulted in adoption of immunotherapy into the standard of care and supported the approval of dinutuximab in the United States in 2015. While the study supported

approval of dinutuximab, use in another context such as an external control is not directly translational.

To provide the primary evidence of efficacy in this application, the Applicant conducted a comparative analysis of a subset of patients from Study 3(b) with an external control derived from Study ANBL0032, which the Applicant obtained from Children's Oncology Group. The selection algorithms for Study 3(b) and the ANBL0032 external control populations are provided as flow-charts in Figure 23 and Figure 24, respectively. Because a time-to-event endpoint cannot be interpreted in a single arm study, Study ANBL0032 was used as an external comparator. This external control arm not considered real-world data as it was sourced from a previously conducted clinical trial.

Of 140 patients who enrolled on Study 3(b) and received eflornithine at the proposed dose, 87 were treated on ANBL0032 prior to enrolling on Study 3(b) and were included in the investigational treatment arm (referred as DFMO COMBO patients in Figure 23) for the comparative analysis against the external control arm. An additional 5 patients were not enrolled on ANBL0032, but were treated as per the protocol, and were also included in the investigational arm. Therefore, a total of 92 patients (referred as DFMO PER COG patients) from the investigational arm contributed to the comparative analyses of outcomes.

Of 1,440 patients who enrolled on ANBL0032 between 2004 and 2015, 1,328 patients received up-front treatment including immunotherapy. Subsequently, 1,241 patients were observed with serial imaging and received no further treatment.

The Applicant proposed to use clinically important baseline covariates to build a propensity score model for the comparison of Study 3(b) patients to the external control group. Propensity score and exact matching were used to ensure balance across 11 key clinical covariates.

Of 852 patients who met the selection rules for inclusion in the analysis, 336 patients were removed due to missing covariate data, leaving 516 patients with data for all 11 clinical covariates.

To evaluate the potential for selection bias due to this exclusion, FDA evaluated the 516 patients who met the selection rules vs. the 336 excluded due to missing data. In general, patients excluded due to missing data were similar with respect to clinical and demographic characteristics to those in the complete case NO DFMO group that were ultimately used to select

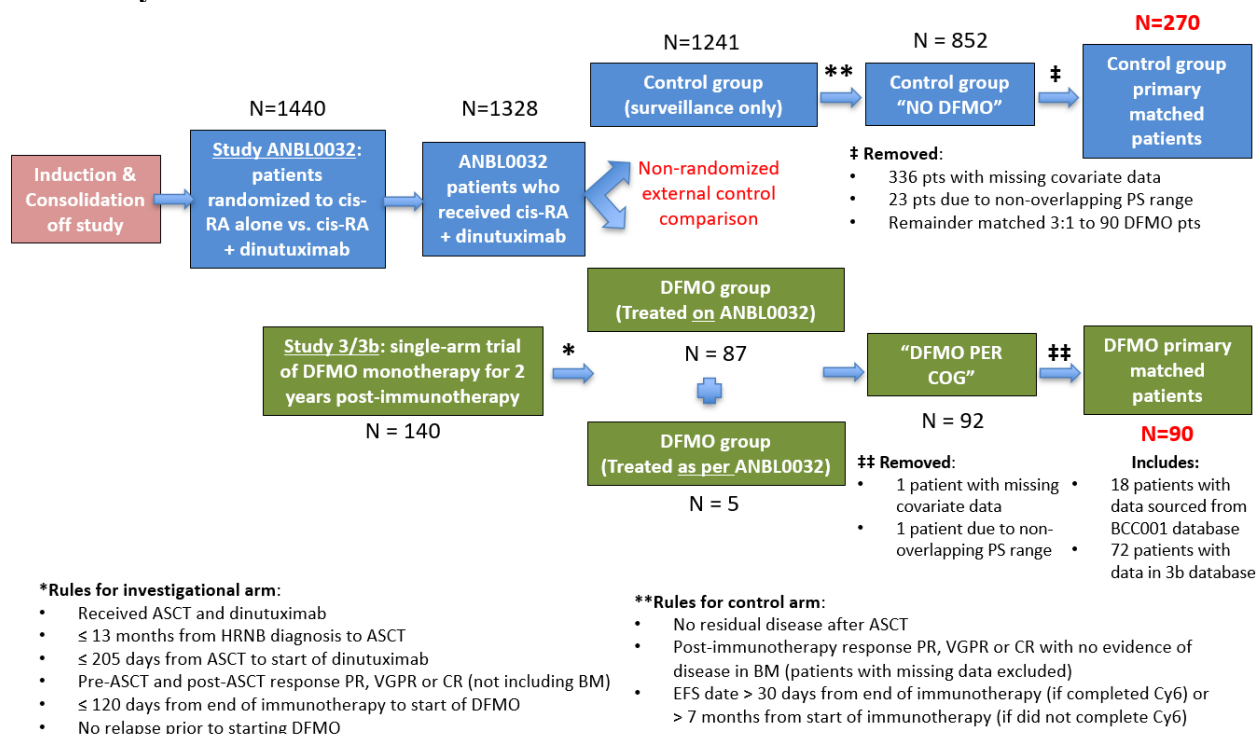
{Eflornithine [DFMO]}

the DFMO-matched patients. There were no major concerns that systematic missingness led to bias in the control patient sample.

Ultimately patients were matched utilizing a 1:3 ratio within the groups of 91 patients treated with DFMO and 516 control patients who were not missing any key covariate data.

This resulted in a primary analysis comparing 90 patients treated with DFMO to 270 patients observed without further treatment after immunotherapy (Figure 25).

**Figure 25. FDA Analysis of Patient Selection Process for Final Matched Populations in Externally Controlled Trial**



HRNB = high-risk neuroblastoma; PS = propensity score; CR = complete response; VGPR = very good partial response; PR = partial response; ASCT = autologous stem cell transplantation; BM = bone marrow; EFS = event-free survival

Source: FDA Analysis

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In addition to the Tumor Assessment Requirements summarized in Table 19, a comparison of the eligibility criteria for the two studies is provided in Table 20.

**Table 20. Key Eligibility Criteria for Comparative Analysis Populations**

|                       | <b>Study 3(b)</b><br>“A Phase II Preventative Trial of DFMO as a Single Agent in Patients with HRNB in Remission”                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>ANBL0032</b><br>“Phase III Randomized Study of Chimeric Antibody 14.18 in HRNB Following Myeloablative Therapy and Autologous Stem Cell Rescue”                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Age</b>            | 0 to 21 years at the time of diagnosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | ≤ 30.99 years of age at the time of diagnosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Diagnosis</b>      | Histologic verification at the time of original diagnosis or previous relapse of HRNB                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HRNB at time of diagnosis (exception: patients who are initially diagnosed as non high-risk neuroblastoma, but later converted (and/or relapsed) to high risk neuroblastoma are also eligible)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Disease Status</b> | <p>HRNB in remission (“no evidence of disease or having no active disease and who would not have otherwise received any further therapy per standard of care”)</p> <p>– <b>Stratum 1:</b> Patients who are in remission at the end of up-front therapy (defined as chemotherapy [5-7 cycles], surgery as indicated, consolidation therapy as indicated, radiation therapy as indicated, anti-GD2 antibody therapy with retinoic acid up to 6 cycles)</p> <p>– <b>Stratum 2:</b> Patients who are in remission after any previous relapse or refractory therapy</p> | <ul style="list-style-type: none"> <li>• Prior to enrollment a determination of mandatory disease staging was to be performed (tumor imaging studies including CT or MRI, MIBG scan, bone marrow aspiration &amp; biopsy)</li> <li>• At pre-ASCT evaluation patients must have met INRC for CR, VGPR, or PR for primary site, soft tissue metastases and bone metastases. Patients who meet those criteria must also meet the protocol specified criteria for bone marrow response as outlined below: <ul style="list-style-type: none"> <li>– ≤ 10% tumor (of total nucleated cellular content) seen on any specimen from a bilateral bone marrow aspirate/biopsy.</li> <li>– Patients who had no tumor seen on the prior bone marrow, and then have ≤10% tumor on any of the bilateral marrow</li> </ul> </li> </ul> |

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|                           |                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           |                                                                                                                                                                                                                                                                                             | aspirate/biopsy specimens done at pre-ASCT and/or pre-enrollment evaluation will also be eligible (note that per INRC this would have been defined as “overall” response of PD).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Prior Therapy</b>      | <p>&gt; 30 days from completion of cytotoxic and antibody therapy and &lt; 120 days from previous therapy</p> <p>No other ongoing anticancer agents permitted</p>                                                                                                                           | <ul style="list-style-type: none"> <li>• Must have completed therapy including intensive induction followed by ASCT and radiotherapy. (Radiotherapy may be waived for patients who have small adrenal masses completely resected up-front or who never had identifiable primary tumor)</li> <li>• No more than 12 months from the first induction chemotherapy after diagnosis to the date of ASCT except for patients initially diagnosed as non HRNB but later converted or relapsed to high-risk. For tandem ASCT patients, this will be the date of the FIRST stem cell infusion.</li> <li>• The date protocol therapy is projected to start must have been no later than 10 days after the date of study enrollment. Patients were enrolled between Day 56 and Day 85 after PBSC infusion (day from 2nd stem cell infusion for tandem transplant). Patients were enrolled no later than Day 100 after PBSC infusion. Enrollment occurred after completion of radiotherapy, and after completion of tumor assessment post-ASCT and radiotherapy.</li> </ul> |
| <b>Performance status</b> | <ul style="list-style-type: none"> <li>• Lansky score <math>\geq 60\%</math></li> <li>• Adequate organ function (ANC <math>&gt; 500</math>, PLT <math>&gt; 50</math>, AST/ALT <math>&lt; 10 \times</math> ULN, bilirubin <math>&lt; 2.0</math> mg/dL, creatinine normal for age)</li> </ul> | <ul style="list-style-type: none"> <li>• Lansky or Karnofsky Performance Scale score of <math>\geq 50\%</math> and patients must have had a life expectancy of <math>\geq 2</math> months.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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|  |  |                                                                                                                                                               |
|--|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  | <ul style="list-style-type: none"> <li>• Adequate organ function (APC &gt;1000, ALT &lt;5x ULN, bilirubin &lt;1.5x ULN, creatinine normal for age)</li> </ul> |
|--|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------|

Source: Adapted from Applicant analysis submitted in NDA 215500, Module 5.3.5.4 Comparison of Study 3b to ANBL0032 External Control Database, page 53

For both arms, tumor assessments were required at baseline, 3, 6, 9, 12, 18, and 24 months after completion of immunotherapy and then per institutional standard. Study ANBL0032 had two additional required tumor assessments at 30 and 36 months after completion of immunotherapy. No anti-cancer therapies were permitted during study therapy for patients on the investigational arm and there are no approved therapies in the maintenance setting after up-front therapy.

In summary, the efficacy population for the comparative analysis of Study 3(b) and ANBL0032 included patients from both studies who were less than 21 years of age with histologic verification of HRNB and who demonstrated at least a partial response based on imaging, with no evidence of disease in the bone marrow at the end of immunotherapy, and did not experience a relapse event prior to starting eflornithine therapy (for Study 3(b)), or for at least 30 days from the end of immunotherapy (for ANBL0032). Eligible patients on Study 3(b) received immunotherapy while enrolled on ANBL0032 or were treated according to the ANBL0032 protocol off study; notably, 94% of patients in the primary matched population from Study 3(b) received immunotherapy on ANBL0032 within the preceding 1 to 4 months (the remaining 6% were treated as per ANBL0032 off study).

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## Study Endpoints

### The Applicant's Description:

EFS and OS event definitions were identical for Study 3b and ANBL0032. Although each individual study used a different index date, all sources of data contain the end of immunotherapy date allowing harmonization of the index date for the comparative analyses. All available follow-up data were used in the analyses.

The primary endpoint is EFS and the key secondary endpoint is OS. Both endpoints are time-to-event endpoints, with details around the definitions of each endpoint shown in Table 21.

**Table 21: EFS and OS Definitions for Primary and Secondary Analyses**

| Endpoint | Definition                                                                                                                                                                                                                                                                                                                                                                            |
|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| EFS      | EFS was defined as the period from the last day of immunotherapy until the first occurrence of relapse, progressive disease, secondary cancer, or death for any cause. If none of these events occurred, the patient was censored using the last day of contact. Last day of immunotherapy was defined as last date of immunotherapy (completion of Cycle 6 or last cycle completed). |
| OS       | OS was defined as the period from the last day immunotherapy until death for any cause. If death did not occur, the patient was censored using the last day of contact. Last day of immunotherapy was defined as last date of immunotherapy (completion of Cycle 6 or last cycle completed).                                                                                          |

Source: Table 14 in Section 8.2.1 of the SAP

EFS = event free survival; OS = overall survival

The primary analysis 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 model used the DFMO PER COG – Complete Case and the MATCHED population using the primary propensity model described in Section 8.2.1.1.1 of the SAP as selected from the NO DFMO – Complete Case control analysis population. Estimated hazard ratio, two-sided 95% confidence interval, and two-sided p-value testing against a value of 1 for the treatment effect comparing DFMO to the control are reported.

### The FDA's Assessment:

FDA agrees that the definitions of EFS and OS were the same in Study 3(b) and ANBL0032. For the ECT, the pre-defined primary endpoint was EFS per International Neuroblastoma Response Criteria (INRC) as assessed by investigator. If no event occurred, the patient was censored using

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the last day of contact.

The index date for the ECT was defined as the end of immunotherapy; this was a study visit date at the end of all completed cycles of immunotherapy in ANBL0032, which for most patients is the visit date following completion of 6 cycles of immunotherapy. For patients in the investigational arm (DFMO), if the last date of cis-RA administration was later than the last visit date in the immunotherapy phase of treatment, the date of cis-RA administration was used.

The INRC criteria were established in 1993 and summarized in Figure 26 (Barr et al, 2020). The INRC criteria were updated in 2017 (Park et al, 2017), but this was after completion of study enrollment for both ANBL0032 and Study 3(b).

## Figure 26. International Neuroblastoma Response Criteria (INRC) Determination of Overall Response

1993 International Neuroblastoma Research Criteria (INRC). Adapted from Brodeur *et al*<sup>2</sup>

| Response                          | Primary Tumor                                                    | Metastatic Sites                                                                                                                   |
|-----------------------------------|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Complete Response (CR)            | No Tumor                                                         | No tumor.<br>Normal catecholamines                                                                                                 |
| Very Good Partial Response (VGPR) | Decreased by 90-99%                                              | No tumor.<br>Normal catecholamines                                                                                                 |
| Partial Response (PR)             | Decreased by > 50%                                               | All measurable sites decreased by >50%.<br>Bone and bone marrow sites decreased by >50%. No more than one BM site can be positive. |
| Mixed Response (MXR)              | At least one lesion decreased by >50%. No increase more than 25% | No new lesions.<br>At least one lesion decreased by >50%.<br>No increase more than 25%                                             |
| No Response (NR)                  | Decreased by less than 50% but no increase more than 25%         | No new lesions.<br>No lesion decreased by greater than 50% but no increase more than 25%                                           |
| Progressive Disease (PD)          | Lesions increase by more than 25%.                               | Any new lesion.<br>Lesions increase by more than 25%.<br>Previous negative bone marrow now positive.                               |

Source: Barr EK, Laurie K, Wroblewski K, Applebaum MA, Cohn SL. Association between end-induction response according to the revised International Neuroblastoma Response Criteria (INRC) and outcome in high-risk neuroblastoma patients. *Pediatr Blood Cancer*. 2020 Oct;67(10):e28390. doi: 10.1002/pbc.28390.

## Statistical Analysis Plan and Amendments

### The Applicant's Description:

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Preliminary comparisons of Study 3b and ANBL0032 data with a cut-off of December 30, 2017 were performed by the Investigator-Sponsor to support a request for Breakthrough Therapy Designation. The formal SAP was developed by the Applicant with input from FDA. The SAP was finalized prior to the Applicant's receipt of the final cut of outcome data from the external control database which included 18 months of additional follow up data (data cut-off June 30, 2019) compared the dataset used in support of the BTDR. There were no amendments to the SAP; however, an addendum to the SAP was developed to outline the analysis plans for results of the BICR, including the planned comparative analyses to the NO DFMO external control analysis population where IR outcomes were to be used instead of LE reported outcomes for the DFMO PER COG treated patients. The SAP addendum for the BICR was finalized prior to receipt of any data transfers from the BICR.

#### The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical analysis plan. The SAP was submitted in Module 5.3.5.4 as Appendix 1, with the addendum related to the BICR assessment as Appendix 2.

The Applicant proposed to use clinically important baseline covariates to build the propensity score model for the comparison of Study 3(b) to the external control arm from Study ANBL0032. Propensity score and exact matching were used to ensure balance across 11 key clinical covariates, utilizing a 3:1 ratio match within the groups of 516 complete-case control patients and 91 patients treated with DFMO who were not missing any key covariate data. The 10 covariates in the propensity score included: age at high-risk diagnosis, sex, race, stage at diagnosis, pre-ASCT response, transplant type (single vs. tandem), time from transplant to start of immunotherapy, response at end of immunotherapy, time from start of immunotherapy to end of immunotherapy, and time from diagnosis to end of immunotherapy. The Applicant used an exact match for *MYCN* status, as it was considered the most important predictor of relapse and survival outcomes.

In the Applicant's proposed primary analysis, propensity-score matched treated and control patients were compared for EFS and OS outcomes using an unadjusted Cox proportional hazards model. Unadjusted analyses of the unmatched complete-case populations (NO DFMO Complete Case and DFMO per COG) were also conducted. The Applicant also conducted several sensitivity analyses of the primary analysis including those considering variations to the primary analysis method (alternate matching algorithm and matching ratios, covariate modifications in

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propensity score model, pooled analysis of repeated matched samples using various random seeds), those considering alternative primary analysis methods (inverse probability of treatment weighting, propensity score stratified analysis), those considering the sensitivity of results to the selection of the analysis population (matched analyses using alternate analyses populations, imputation of missing values, variations of patient selection rules), and those considering various sources of bias (modifications to index date).

FDA communicated to the Applicant via meeting comments in October 2021 that given the complexity of this study design and the uncertainty introduced by the retrospective use of data to design this ECT, FDA would rely upon an 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. FDA also indicated that the efficacy analyses based on blinded independent review of imaging assessments in Study 3(b) would be required to support filing of the planned application. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs. The finding of substantial evidence of effectiveness is necessary but not sufficient for FDA approval.

As described in Section 8.1.2, to account for potential bias in the local evaluator reported outcomes, a blinded independent central review (BICR) was conducted for patients in the investigational arm. Source imaging was not available to conduct a similar BICR for the control arm. As all images were available for the investigational arm patients, the same 90 treated patients and 270 control patients selected by the primary PSM analysis for Study 3(b) vs. ANBL0032 were compared, only using BICR reported outcomes rather than local evaluator reported outcomes for the treated patients. Refer to Section 8.1.4 for additional details.

## **Protocol Amendments**

### The Applicant's Description:

Study 3b amendments are described in Section 8.1.1 above. No amendment impacted the selection rules, covariates, or interpretability of the ANBL0032 external control comparisons.

ANBL0032 enrolled from 2001 to 2015, with multiple amendments from version 1 through 19A. The Applicant completed a comprehensive assessment of all protocol amendments, and full text versions are contained in the NDA. Amendments were primarily reviewed with an emphasis on

the potential to impact selection rules used to identify analysis populations for comparison and the potential impact to covariates used in the calculation of propensity scores for matched analyses. Generally, eligibility criteria changes were the only changes with the potential for any impact. Over the course of the study, inclusion/exclusion modifications were made that permitted more patients to enroll on ANBL0032. Allowable maximum duration between induction and ASCT was expanded from 8 months to 12 months, and allowable maximum duration between (last) ASCT and start of immunotherapy was expanded from 77 days up to 200 days. The protocol was amended to introduce additional strata based on the larger concurrent induction/consolidation studies that patients were completing prior to being eligible for ANBL0032 (which required prior completion of high risk induction and ASCT). The protocol was amended to permit enrollment of patients that received either single or tandem ASCT (defined in separate strata as added over time). Stratum 7, a stratum designated for enrollment of patients that would receive non-randomized treatment with dinutuximab, was modified to enroll only patients with biopsy verified active disease; the change permitted patients with minimal residual disease in the bone marrow at the pre-ASCT or pre-enrollment (start of immunotherapy) to be enrolled in other strata. Finally, the protocol was amended to clarify that patients that progressed or relapsed to high risk neuroblastoma were eligible as well as those with an initial HRNB diagnosis. Overall, the criteria for enrollment were made less stringent, permitting more patients to receive ch14.18 under later versions of the protocol. The amendments resulted in the potential for greater variability in certain characteristics in the enrolled patients, particularly in the non-randomized enrollment period compared to the more stringent criteria in place during the randomized portion of the study. Despite the potential for greater variability in the enrolled patients in these different periods of enrollment, the overall EFS outcomes between the randomized and non-randomized patients are consistent with reported 4-year and 5-year event rates of approximately 60% from the beginning of immunotherapy (Yu 2014, Yu 2021, Desai 2022).

The broadest versions of the eligibility criteria were used to define the selection rules for the DFMO PER COG group to ensure the full range of patient characteristics meeting eligibility for ANBL0032 would have also been included in the treated analysis population. Additionally, covariates were included in the propensity score model to ensure balance between treated and control groups on treatment variables including those affected by protocol amendments. Stratum 7 patients were excluded from the control analysis population. The additional control group selection rules required that patients have no evidence of disease in the bone marrow at the end of immunotherapy. Patients with new minimal bone marrow involvement at the pre-ASCT or pre-enrollment (start of immunotherapy) involvement that would have been placed in the original

version of Stratum 7 would have also been eligible for Study 3b, provided the bone marrow was negative for disease prior to Study 3b enrollment (at or within 120 days of completion of immunotherapy). Importantly, 87 of the 92 patients in the DFMO PER COG group came directly from ANBL0032; and the Contemporary population analysis (Figure 11, panel C, Figure 13) address the potential influence of treatment era/active protocol amendments in place during the time Study 3b could have enrolled patients from ANBL0032.

Overall, the Applicant assesses no material impact on the interpretability of the comparisons as a result of ANBL0032 protocol amendments.

**The FDA's Assessment:**

In general, FDA agrees that protocol amendments were unlikely to have impacted the comparison of Studies 3(b) and ANBL0032. Both studies had completed enrollment at the time of the design of the externally controlled trial.

**8.1.4. Study 3b vs. ANBL0032 Results**

**Compliance with Good Clinical Practices**

**The Applicant's Position:**

Study 3b compliance with GCP is described above in Section 8.1.1.

ANBL0032 was a study sponsored by the National Cancer Institute (NCI). Although the study was transferred to United Therapeutics, NCI /CTEP held the majority of clinical trial records and was subsequently inspected by the FDA as part of the Biomonitoring program for BLA 125516. Although NCI did not fully comply with 21 CFR 312, data submitted in to BLA 125516 were determined to be reliable for use in support of US registration of dinutuximab.

**The FDA's Assessment:**

FDA agrees.

**Financial Disclosure**

**The Applicant's Position:**

Study 3b financial disclosure requirements are described above in Section 8.1.1.



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For ANBL0032, issues regarding the collection of financial disclosure information is detailed in the Clinical Inspection Summary for BLA 125516. The OSI identified instances where financial disclosure forms were not in place until 3 years after Part 54 went into effect. Although procedural violations were present, the reliability of the data for use in support of the BLA was maintained.

The FDA's Assessment:

FDA agrees.

**Patient Disposition**

The Applicant's Position:

Table 22 shows overall study status for the NO DFMO and DFMO PER COG and complete case populations. ANBL0032 did not capture completion of study as a reason for exiting the study therefore, NO DFMO patients are considered to have completed ANBL0032 if they have an EFS date reported at least 10 years from the start of immunotherapy. NO DFMO patients followed < 10 years are considered ongoing if they have not discontinued from the study and had their last contact within 15 months prior to the data cut-off. DFMO PER COG patients are considered to have completed Study 3b if they reported "completed study" as the reason for going off study. To further aid in interpretation of time to event analyses, details on reason for censoring in patients without EFS events are included. Data on reasons for discontinuing the study were received in a separate transfer from COG following finalization of the SAP, thus these data are provided in the application datasets requested by FDA although they were not utilized in the any planned sensitivity analyses of Study 3b vs. ANBL0032. Although not presented in the table, patients Alive with No Event with a study status of Discontinued, comprising approximately 10% of NO DFMO patients and 2% of DFMO PER COG patients, are those that were lost to follow up, except in a few cases in the control group.

**Table 22: Study Status with Event and Censoring Reasons for Event Free Survival**

|                     | <b>NO DFMO<br/>(N=852)<br/>n (%)</b> | <b>NO DFMO -<br/>Complete Case<br/>(N=516)<br/>n (%)</b> | <b>DFMO PER<br/>COG<br/>(N=92)<br/>n (%)</b> | <b>DFMO PER COG<br/>-Complete Case<br/>(N=91)<br/>n (%)</b> |
|---------------------|--------------------------------------|----------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------|
| <b>Completed</b>    | 52 (6.1)                             | 27 (5.2)                                                 | 34 (37.0)                                    | 34 (37.4)                                                   |
| Alive with No Event | 44 (5.2)                             | 23 (4.5)                                                 | 30 (32.6)                                    | 30 (33.0)                                                   |
| EFS Event =         |                                      |                                                          |                                              |                                                             |
| Relapse             | 7 (0.8)                              | 4 (0.8)                                                  | 4 (4.3)                                      | 4 (4.4)                                                     |

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|                     | <b>NO DFMO<br/>(N=852)<br/>n (%)</b> | <b>NO DFMO -<br/>Complete Case<br/>(N=516)<br/>n (%)</b> | <b>DFMO PER<br/>COG<br/>(N=92)<br/>n (%)</b> | <b>DFMO PER COG<br/>-Complete Case<br/>(N=91)<br/>n (%)</b> |
|---------------------|--------------------------------------|----------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------|
| Second Malignancy   | 1 (0.1)                              | 0                                                        | 0                                            | 0                                                           |
| <b>Discontinued</b> | 277 (32.5)                           | 157 (30.4)                                               | 11 (12.0)                                    | 11 (12.1)                                                   |
| Alive with No Event | 89 (10.4)                            | 53 (10.3)                                                | 2 (2.2)                                      | 2 (2.2)                                                     |
| EFS Event =         |                                      |                                                          |                                              |                                                             |
| Death               | 10 (1.2)                             | 7 (1.4)                                                  | 0                                            | 0                                                           |
| Relapse             | 177 (20.8)                           | 97 (18.8)                                                | 9 (9.8)                                      | 9 (9.9)                                                     |
| Second Malignancy   | 1 (0.1)                              | 0                                                        | 0                                            | 0                                                           |
| <b>Ongoing</b>      | 523 (61.4)                           | 332 (64.3)                                               | 47 (51.1)                                    | 46 (50.5)                                                   |
| Alive with No Event | 467 (54.8)                           | 290 (56.2)                                               | 45 (48.9)                                    | 44 (48.4)                                                   |
| EFS Event =         |                                      |                                                          |                                              |                                                             |
| Relapse             | 50 (5.9)                             | 37 (7.2)                                                 | 2 (2.2)                                      | 2 (2.2)                                                     |
| Second Malignancy   | 6 (0.7)                              | 5 (1.0)                                                  | 0                                            | 0                                                           |

Censor=1 for Alive with No Event; Censor = 0 for Relapse, Second Malignancy or Death

**Applicant's Position:**

Approximately one third of patients in the DFMO PER COG population have completed Study 3b compared to <10% of patients completing ANBL0032 in the NO DFMO population; however this is a function of 1) the defined follow up for ANBL0032 is longer by 3 years and 2) the data-cut off differences between the two studies results in follow up information being shorter by 2 years (data-cut offs of June 30, 2019 vs. June 30, 2021 for NO DFMO and DFMO PER COG groups, respectively). As a result of the long (7 and 10 year) follow up periods for the studies, most patients that did not experience an EFS event are censored strictly because they are ongoing in follow up.

**The FDA's Assessment:**

FDA agrees with the Applicant's description of study status for the subgroups of patients presented in Table 22. In addition, patient disposition for the primary efficacy populations per the Applicant's proposed primary analysis is provided in Table 23.

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**Table 23: FDA Analysis of Patient Disposition for the Primary Populations in the Externally Controlled Trial**

|                                       | <b>DFMO<br/>(N=90)<br/>N (%)</b> | <b>Control<br/>(N=270)<br/>N (%)</b> |
|---------------------------------------|----------------------------------|--------------------------------------|
| Discontinued Treatment                | <b>18 (20)</b>                   | <b>2 (1)</b>                         |
| Adverse Event                         | 1 (1)<br>(Grade 3 fatigue)       | 0                                    |
| Relapse                               | 12 (13)                          | 0                                    |
| Other                                 | 5 (6)                            | 2 (1)                                |
| Completed Study                       | <b>34 (38)</b>                   | <b>18 (7)</b>                        |
| Discontinued Study                    | <b>10 (11)</b>                   | <b>87 (32)</b>                       |
| Lost to Follow-Up                     | 3 (3)                            | 26 (10)                              |
| Death                                 | 7 (8)                            | 57 (21)                              |
| Withdrawal of consent                 | 0                                | 2 (1)                                |
| Enrolled on another therapeutic trial | 0                                | 2 (1)                                |
| Ongoing on study                      | <b>46 (51)</b>                   | <b>165 (61)</b>                      |

Source: FDA analysis of datasets submitted in NDA 215500

**Protocol Violations/Deviations**The Applicant's Position:

Study 3b protocol deviations are described above in Section 8.1.1. ANBL0032 protocol deviations were not reported in the ANBL0032 data transfer.

**Table of Demographic Characteristics**

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The Applicant's Position:

Demographics data for the overall, complete case, and primary matched NO DFMO and DFMO PER COG populations are presented below. Demographic characteristics are similar in overall treated and control groups, although there is some missing data, primarily in the control group. Balance is further improved in the complete case and matched cohorts, for whom there are no missing data.

**Table 24: Demographics DFMO PER COG and NO DFMO Population**

|                                           | NO DFMO          |                                                     |                                            | DFMO PER COG    |                                                    |                                           |
|-------------------------------------------|------------------|-----------------------------------------------------|--------------------------------------------|-----------------|----------------------------------------------------|-------------------------------------------|
|                                           | (N=852)<br>n (%) | Complete<br>Case <sup>[1]</sup><br>(N=516)<br>n (%) | Matched <sup>[2]</sup><br>(N=270)<br>n (%) | (N=92)<br>n (%) | Complete<br>Case <sup>[1]</sup><br>(N=91)<br>n (%) | Matched <sup>[2]</sup><br>(N=90)<br>n (%) |
| <b>Sex</b>                                |                  |                                                     |                                            |                 |                                                    |                                           |
| Female                                    | 298 (35.0)       | 225 (43.6)                                          | 113 (41.9)                                 | 37 (40.2)       | 37 (40.7)                                          | 36 (40.0)                                 |
| Male                                      | 390 (45.8)       | 291 (56.4)                                          | 157 (58.1)                                 | 55 (59.8)       | 54 (59.3)                                          | 54 (60.0)                                 |
| Unknown                                   | 164 (19.2)       | 0                                                   | 0                                          | 0               | 0                                                  | 0                                         |
| <b>Race</b>                               |                  |                                                     |                                            |                 |                                                    |                                           |
| American Indian or Alaska Native          | 2 (0.2)          | 1 (0.2)                                             | 1 (0.4)                                    | 0               | 0                                                  | 0                                         |
| Asian                                     | 28 (3.3)         | 24 (4.7)                                            | 15 (5.6)                                   | 1 (1.1)         | 1 (1.1)                                            | 1 (1.1)                                   |
| Black or African American                 | 92 (10.8)        | 81 (15.7)                                           | 17 (6.3)                                   | 7 (7.6)         | 6 (6.6)                                            | 6 (6.7)                                   |
| Multiple                                  | 0                | 0                                                   | 0                                          | 3 (3.3)         | 3 (3.3)                                            | 3 (3.3)                                   |
| Native Hawaiian or Other Pacific Islander | 1 (0.1)          | 1 (0.2)                                             | 1 (0.4)                                    | 0               | 0                                                  | 0                                         |
| White                                     | 493 (57.9)       | 409 (79.3)                                          | 236 (87.4)                                 | 81 (88.0)       | 81 (89.0)                                          | 80 (88.9)                                 |
| Unknown                                   | 236 (27.7)       | 0                                                   | 0                                          | 0               | 0                                                  | 0                                         |

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[1] Complete case means without missing values of the 11 covariates: amplification of MYCN, sex, race, pre-ASCT response, single/tandem transplant, stage at high-risk diagnosis, overall response at end of immunotherapy, age at high-risk diagnosis (days), time from ASCT to start of immunotherapy (days), duration of immunotherapy (days), time from diagnosis to end of immunotherapy (days).

[2] Matched patients are the Propensity Score Matched Samples (3:1) from the primary analysis specified in Section 8.2.1 of the SAP.

Source: Study 3b vs ANBL0032 Tables 14.1.3.1 and 14.1.3.2

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**Disease Characteristics**

The Applicant's Position:

Similar to the demographic characteristics, disease characteristics are comparable between overall treated and control groups, though again there is some missing data. Good balance across all disease characteristics is observed in the matched cohorts of treated and control patients.

**Table 25: Disease and Prior Treatment Characteristics DFMO PER COG and NO DFMO Population**

|                                           | NO DFMO            |                                                     |                                            | DFMO PER COG      |                                                    |                                           |
|-------------------------------------------|--------------------|-----------------------------------------------------|--------------------------------------------|-------------------|----------------------------------------------------|-------------------------------------------|
|                                           | (N=852)<br>n (%)   | Complete<br>Case <sup>[1]</sup><br>(N=516)<br>n (%) | Matched <sup>[2]</sup><br>(N=270)<br>n (%) | (N=92)<br>n (%)   | Complete<br>Case <sup>[1]</sup><br>(N=91)<br>n (%) | Matched <sup>[2]</sup><br>(N=90)<br>n (%) |
| <b>Age at High-risk Diagnosis (Years)</b> |                    |                                                     |                                            |                   |                                                    |                                           |
| 0 - < 18 months                           | 93 (10.9)          | 79 (15.3)                                           | 46 (17.0)                                  | 12 (13.0)         | 12 (13.2)                                          | 12 (13.3)                                 |
| >= 18 months - < 6 years                  | 497 (58.3)         | 366 (70.9)                                          | 190 (70.4)                                 | 68 (73.9)         | 68 (74.7)                                          | 67 (74.4)                                 |
| >= 6 years                                | 98 (11.5)          | 71 (13.8)                                           | 34 (12.6)                                  | 12 (13.0)         | 11 (12.1)                                          | 11 (12.2)                                 |
| Unknown                                   | 164 (19.2)         | 0                                                   | 0                                          | 0                 | 0                                                  | 0                                         |
| n, Mean (SD)                              | 688, 3.7<br>(2.49) | 516, 3.6<br>(2.56)                                  | 270, 3.6<br>(2.59)                         | 92, 3.8<br>(2.86) | 91, 3.7<br>(2.86)                                  | 90, 3.7 (2.87)                            |
| <b>Stage at Diagnosis</b>                 |                    |                                                     |                                            |                   |                                                    |                                           |
| Stage 4                                   | 565 (66.3)         | 414 (80.2)                                          | 233 (86.3)                                 | 80 (87.0)         | 79 (86.8)                                          | 78 (86.7)                                 |
| Other                                     | 123 (14.4)         | 102 (19.8)                                          | 37 (13.7)                                  | 12 (13.0)         | 12 (13.2)                                          | 12 (13.3)                                 |
| Unknown                                   | 164 (19.2)         | 0                                                   | 0                                          | 0                 | 0                                                  | 0                                         |
| <b>MYCN</b>                               |                    |                                                     |                                            |                   |                                                    |                                           |
| Amplified                                 | 250 (29.3)         | 220 (42.6)                                          | 120 (44.4)                                 | 40 (43.5)         | 40 (44.0)                                          | 40 (44.4)                                 |

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|                                                                                       | NO DFMO          |                                                     |                                            | DFMO PER COG    |                                                    |                                           |
|---------------------------------------------------------------------------------------|------------------|-----------------------------------------------------|--------------------------------------------|-----------------|----------------------------------------------------|-------------------------------------------|
|                                                                                       | (N=852)<br>n (%) | Complete<br>Case <sup>[1]</sup><br>(N=516)<br>n (%) | Matched <sup>[2]</sup><br>(N=270)<br>n (%) | (N=92)<br>n (%) | Complete<br>Case <sup>[1]</sup><br>(N=91)<br>n (%) | Matched <sup>[2]</sup><br>(N=90)<br>n (%) |
| Not amplified                                                                         | 345 (40.5)       | 296 (57.4)                                          | 150 (55.6)                                 | 51 (55.4)       | 51 (56.0)                                          | 50 (55.6)                                 |
| Unknown                                                                               | 257 (30.2)       | 0                                                   | 0                                          | 1 (1.1)         | 0                                                  | 0                                         |
| <b>Histology</b>                                                                      |                  |                                                     |                                            |                 |                                                    |                                           |
| Favorable                                                                             | 32 (3.8)         | 29 (5.6)                                            | 13 (4.8)                                   | 7 (7.6)         | 6 (6.6)                                            | 6 (6.7)                                   |
| Unfavorable                                                                           | 550 (64.6)       | 435 (84.3)                                          | 229 (84.8)                                 | 76 (82.6)       | 76 (83.5)                                          | 75 (83.3)                                 |
| Unknown                                                                               | 270 (31.7)       | 52 (10.1)                                           | 28 (10.4)                                  | 9 (9.8)         | 9 (9.9)                                            | 9 (10.0)                                  |
| <b>Pre-ASCT Response (primary tumor, soft tissue metastases, and bone metastases)</b> |                  |                                                     |                                            |                 |                                                    |                                           |
| CR                                                                                    | 253 (29.7)       | 154 (29.8)                                          | 113 (41.9)                                 | 38 (41.3)       | 38 (41.8)                                          | 38 (42.2)                                 |
| VGPR                                                                                  | 311 (36.5)       | 192 (37.2)                                          | 82 (30.4)                                  | 32 (34.8)       | 32 (35.2)                                          | 31 (34.4)                                 |
| PR                                                                                    | 288 (33.8)       | 170 (32.9)                                          | 75 (27.8)                                  | 22 (23.9)       | 21 (23.1)                                          | 21 (23.3)                                 |
| <b>Transplant</b>                                                                     |                  |                                                     |                                            |                 |                                                    |                                           |
| Single                                                                                | 748 (87.8)       | 434 (84.1)                                          | 245 (90.7)                                 | 84 (91.3)       | 83 (91.2)                                          | 82 (91.1)                                 |
| Tandem                                                                                | 104 (12.2)       | 82 (15.9)                                           | 25 (9.3)                                   | 8 (8.7)         | 8 (8.8)                                            | 8 (8.9)                                   |
| <b>Time from Transplant to Start of Immunotherapy (Days)</b>                          |                  |                                                     |                                            |                 |                                                    |                                           |
| < 100 days                                                                            | 552 (64.8)       | 337 (65.3)                                          | 193 (71.5)                                 | 67 (72.8)       | 66 (72.5)                                          | 65 (72.2)                                 |
| 100 to < 150 days                                                                     | 246 (28.9)       | 155 (30.0)                                          | 69 (25.6)                                  | 23 (25.0)       | 23 (25.3)                                          | 23 (25.6)                                 |
| 150 to 205 days                                                                       | 37 (4.3)         | 24 (4.7)                                            | 8 (3.0)                                    | 2 (2.2)         | 2 (2.2)                                            | 2 (2.2)                                   |
| Unknown                                                                               | 17 (2.0)         | 0                                                   | 0                                          | 0               | 0                                                  | 0                                         |

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|                                                                            | NO DFMO               |                                                     |                                            | DFMO PER COG         |                                                    |                                           |
|----------------------------------------------------------------------------|-----------------------|-----------------------------------------------------|--------------------------------------------|----------------------|----------------------------------------------------|-------------------------------------------|
|                                                                            | (N=852)<br>n (%)      | Complete<br>Case <sup>[1]</sup><br>(N=516)<br>n (%) | Matched <sup>[2]</sup><br>(N=270)<br>n (%) | (N=92)<br>n (%)      | Complete<br>Case <sup>[1]</sup><br>(N=91)<br>n (%) | Matched <sup>[2]</sup><br>(N=90)<br>n (%) |
| n, Mean (SD)                                                               | 835, 96.9<br>(22.76)  | 516, 97.2<br>(24.00)                                | 270, 92.9<br>(20.99)                       | 92, 91.7<br>(21.39)  | 91, 91.7<br>(21.51)                                | 90, 91.8<br>(21.62)                       |
| <b>Response at End of Immunotherapy</b>                                    |                       |                                                     |                                            |                      |                                                    |                                           |
| CR                                                                         | 631 (74.1)            | 377 (73.1)                                          | 236 (87.4)                                 | 79 (85.9)            | 78 (85.7)                                          | 77 (85.6)                                 |
| VGPR                                                                       | 166 (19.5)            | 110 (21.3)                                          | 21 (7.8)                                   | 9 (9.8)              | 9 (9.9)                                            | 9 (10.0)                                  |
| PR                                                                         | 55 (6.5)              | 29 (5.6)                                            | 13 (4.8)                                   | 4 (4.3)              | 4 (4.4)                                            | 4 (4.4)                                   |
| <b>Time from Start of Immunotherapy to<br/>End of Immunotherapy (Days)</b> |                       |                                                     |                                            |                      |                                                    |                                           |
| < 168 days                                                                 | 88 (10.3)             | 46 (8.9)                                            | 20 (7.4)                                   | 16 (17.4)            | 15 (16.5)                                          | 15 (16.7)                                 |
| 168 – 200 days                                                             | 654 (76.8)            | 401 (77.7)                                          | 211 (78.1)                                 | 63 (68.5)            | 63 (69.2)                                          | 63 (70.0)                                 |
| > 200 – 240 days                                                           | 102 (12.0)            | 67 (13.0)                                           | 37 (13.7)                                  | 9 (9.8)              | 9 (9.9)                                            | 9 (10.0)                                  |
| > 240 days                                                                 | 8 (0.9)               | 2 (0.4)                                             | 2 (0.7)                                    | 4 (4.3)              | 4 (4.4)                                            | 3 (3.3)                                   |
| n, Mean (SD)                                                               | 852, 185.6<br>(18.93) | 516, 185.9<br>(18.69)                               | 270, 187.0<br>(17.87)                      | 92, 187.4<br>(28.98) | 91, 187.6<br>(29.04)                               | 90, 186.2<br>(25.80)                      |
| <b>Number of Immunotherapy Cycles</b>                                      |                       |                                                     |                                            |                      |                                                    |                                           |
| <= 3                                                                       | 7 (0.8)               | 5 (1.0)                                             | 1 (0.4)                                    | 1 (1.1)              | 1 (1.1)                                            | 1 (1.1)                                   |
| 4                                                                          | 1 (0.1)               | 1 (0.2)                                             | 0                                          | 2 (2.2)              | 2 (2.2)                                            | 2 (2.2)                                   |
| 5                                                                          | 4 (0.5)               | 2 (0.4)                                             | 0                                          | 0                    | 0                                                  | 0                                         |
| 6                                                                          | 840 (98.6)            | 508 (98.4)                                          | 269 (99.6)                                 | 89 (96.7)            | 88 (96.7)                                          | 87 (96.7)                                 |
| <b>Time from Diagnosis to Transplant<br/>(Days)</b>                        |                       |                                                     |                                            |                      |                                                    |                                           |
| < 150 days                                                                 | 34 (4.0)              | 17 (3.3)                                            | 9 (3.3)                                    | 6 (6.5)              | 6 (6.6)                                            | 6 (6.7)                                   |



|                                                           | NO DFMO                |                                                     |                                            | DFMO PER COG         |                                                    |                                           |
|-----------------------------------------------------------|------------------------|-----------------------------------------------------|--------------------------------------------|----------------------|----------------------------------------------------|-------------------------------------------|
|                                                           | (N=852)<br>n (%)       | Complete<br>Case <sup>[1]</sup><br>(N=516)<br>n (%) | Matched <sup>[2]</sup><br>(N=270)<br>n (%) | (N=92)<br>n (%)      | Complete<br>Case <sup>[1]</sup><br>(N=91)<br>n (%) | Matched <sup>[2]</sup><br>(N=90)<br>n (%) |
| 150 to < 200 days                                         | 528 (62.0)             | 337 (65.3)                                          | 180 (66.7)                                 | 61 (66.3)            | 60 (65.9)                                          | 60 (66.7)                                 |
| 200 to 250 days                                           | 198 (23.2)             | 124 (24.0)                                          | 63 (23.3)                                  | 19 (20.7)            | 19 (20.9)                                          | 18 (20.0)                                 |
| > 250 days                                                | 69 (8.1)               | 38 (7.4)                                            | 18 (6.7)                                   | 6 (6.5)              | 6 (6.6)                                            | 6 (6.7)                                   |
| Unknown                                                   | 23 (2.7)               | 0                                                   | 0                                          | 0                    | 0                                                  | 0                                         |
| n, Mean (SD)                                              | 829, 208.2<br>(127.80) | 516, 213.4<br>(152.66)                              | 270, 202.7<br>(119.35)                     | 92, 199.2<br>(84.11) | 91, 199.5<br>(84.51)                               | 90, 199.1<br>(84.89)                      |
| <b>Time from Diagnosis to End of Immunotherapy (Days)</b> |                        |                                                     |                                            |                      |                                                    |                                           |
| < 400 days                                                | 16 (1.9)               | 9 (1.7)                                             | 6 (2.2)                                    | 3 (3.3)              | 3 (3.3)                                            | 3 (3.3)                                   |
| 400 to < 450 days                                         | 260 (30.5)             | 151 (29.3)                                          | 91 (33.7)                                  | 33 (35.9)            | 32 (35.2)                                          | 32 (35.6)                                 |
| 450 to < 500 days                                         | 353 (41.4)             | 220 (42.6)                                          | 106 (39.3)                                 | 32 (34.8)            | 32 (35.2)                                          | 32 (35.6)                                 |
| 500 to 550 days                                           | 148 (17.4)             | 90 (17.4)                                           | 49 (18.1)                                  | 13 (14.1)            | 13 (14.3)                                          | 13 (14.4)                                 |
| > 550 days                                                | 69 (8.1)               | 46 (8.9)                                            | 18 (6.7)                                   | 11 (12.0)            | 11 (12.1)                                          | 10 (11.1)                                 |
| Unknown                                                   | 6 (0.7)                | 0                                                   | 0                                          | 0                    | 0                                                  | 0                                         |
| n, Mean (SD)                                              | 846, 489.0<br>(131.36) | 516, 495.8<br>(157.13)                              | 270, 481.3<br>(130.05)                     | 92, 481.3<br>(90.33) | 91, 481.9<br>(90.60)                               | 90, 480.2<br>(89.58)                      |

[1] Complete case means without missing values of the 11 covariates: amplification of MYCN, sex, race, pre-ASCT response, single/tandem transplant, stage at high-risk diagnosis, overall response at end of immunotherapy, age at high-risk diagnosis (days), time from ASCT to start of immunotherapy (days), duration of immunotherapy (days), time from diagnosis to end of immunotherapy (days).

[2] Matched patients are the Propensity Score Matched Samples (3:1) from the primary analysis specified in Section 8.2.1 of the SAP.

Source: Study 3b vs ANBL0032 Tables 14.1.3.1 and 14.1.3.2

While there was very little demographic and disease data missing for the DFMO PER COG group almost 40% of the patients were omitted from the PSM analyses due to missing covariate data. The large control population allowed sufficient patients with complete data to provide

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balanced populations with a 3:1 ratio (3 NO DFMO: 1 DFMO PER COG). The missing data were considered as missing at random and NO DFMO patients with missing covariate data had a comparable relapse rate to the complete case patients.

#### **The FDA's Assessment:**

FDA agrees with the Applicant that the available demographic and disease characteristics were generally similar across treatment arms in the Applicant's proposed primary analysis population. However, there may be some important characteristics that were unmeasured, and therefore that the comparability of populations for these characteristics was not quantifiable. In the Applicant's proposed primary analysis population, 85 of 90 patients treated with DFMO in the investigational arm had completed immunotherapy on Study ANBL0032 within the prior 120 days with no other intervening anti-cancer therapy.

Table 26 describes both matched and unmatched clinical and demographic characteristics by arm, and Figure 27 and Figure 28 display population characteristics before and after matching. Among the matched characteristics, patients were matched exactly on *MYCN* amplification due to its prognostic importance, and the remaining 10 characteristics were included in the propensity score model.

HRNB is slightly more common in males, which is reflected in these data. The median age of diagnosis was approximately 3 years in both arms, as expected per the published literature. Black or African American and Asian patients are slightly under-represented compared to the general population, particularly given there are some data to suggest that Black and Native American patients with neuroblastoma have a higher prevalence of high-risk disease (Henderson et al, 2010).

**Table 26: FDA Analysis of Matched and Unmatched Demographic and Disease Characteristics for the Applicant's Proposed Primary Analysis Populations in the Externally Controlled Trial**

| <b>MATCHED CHARACTERISTICS</b>                  | <b>DFMO<br/>(N=90)</b> | <b>External Control<br/>(N=270)</b> |
|-------------------------------------------------|------------------------|-------------------------------------|
| <b>Age at diagnosis (years), median (range)</b> | 2.9 (0.1 – 15.8)       | 3.1 (0.2 – 20.1)                    |

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|                                                                    |                           |                 |                 |
|--------------------------------------------------------------------|---------------------------|-----------------|-----------------|
| <b>Sex, %</b>                                                      | Male                      | 60              | 58              |
|                                                                    | Female                    | 40              | 42              |
| <b>Race, %</b>                                                     | White                     | 89              | 87              |
|                                                                    | Black or African American | 7               | 6               |
|                                                                    | Asian                     | 1               | 5               |
|                                                                    | Other                     | 3               | 1               |
| <b>MYCN status (exact match), %</b>                                | Amplified                 | 44              | 44              |
|                                                                    | Not amplified             | 56              | 56              |
| <b>Stage at diagnosis, %</b>                                       | 4                         | 87              | 86              |
|                                                                    | 4S                        | 1               | 1               |
|                                                                    | Other (1, 2, 3)           | 12              | 13              |
| <b>Pre-ASCT response, %</b>                                        | CR                        | 42              | 42              |
|                                                                    | VGPR                      | 34              | 30              |
|                                                                    | PR                        | 23              | 28              |
| <b>Single vs. Tandem ASCT, %</b>                                   | Single                    | 91              | 91              |
|                                                                    | Tandem                    | 9               | 9               |
| <b>End of immunotherapy overall response, %</b>                    | CR                        | 86              | 87              |
|                                                                    | VGPR                      | 10              | 8               |
|                                                                    | PR                        | 4               | 5               |
| <b>Days from ASCT to immunotherapy, median (range)</b>             |                           | 88 (60, 186)    | 89 (58, 201)    |
| <b>Duration of immunotherapy in days, median (range)</b>           |                           | 185 (108, 328)  | 185 (34, 259)   |
| <b>Days from diagnosis to end of immunotherapy, median (range)</b> |                           | 460 (391, 1068) | 466 (309, 2414) |

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| UNMATCHED CHARACTERISTICS                                  |                     | DFMO<br>(N=90) | External Control<br>(N=270) |
|------------------------------------------------------------|---------------------|----------------|-----------------------------|
| <b>Demographics<sup>a</sup></b>                            |                     |                |                             |
| Ethnicity, %                                               | Hispanic/Latino     | 9              | 6                           |
|                                                            | Not Hispanic/Latino | 19             | 93                          |
|                                                            | Missing             | 72             | 1                           |
| Geographic site of enrollment on ANBL0032 <sup>b</sup> , % | United States       | 99             | 86                          |
|                                                            | Canada              | 1              | 9                           |
|                                                            | Australia           | 0              | 5                           |
|                                                            | New Zealand         | 0              | <1                          |
| <b>Tumor Characteristics</b>                               |                     |                |                             |
| Histology, %                                               | Favorable           | 7              | 5                           |
|                                                            | Unfavorable         | 83             | 85                          |
|                                                            | Missing             | 10             | 10                          |
| Primary Tumor Location <sup>c</sup> , %                    | Adrenal             | 56             | 28                          |
|                                                            | Abdomen             | 13             | 13                          |
|                                                            | Retroperitoneum     | 14             | 9                           |
|                                                            | Other               | 16             | 6                           |
|                                                            | Missing             | 4              | 51                          |
| Tumor Cytogenetics, %                                      | 1p deletion         | 17             | -                           |
|                                                            | 11q deletion        | 9              | -                           |
|                                                            | 17q gain            | 3              | -                           |

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|                                                      |                        |                             |                                                            |
|------------------------------------------------------|------------------------|-----------------------------|------------------------------------------------------------|
|                                                      | ALK mutation           | 3                           | -                                                          |
|                                                      | Missing                | 68                          | 100                                                        |
| <b>Treatment-Related Characteristics</b>             |                        |                             |                                                            |
| Days from Diagnosis to ASCT, median (range)          |                        | 179.5 (137-804)             | 188 (139-2023)                                             |
| Surgery during induction <sup>d</sup> , %            | Yes                    | 93                          | 71                                                         |
|                                                      | Missing                | 2                           | 29                                                         |
| Radiation during consolidation <sup>e</sup> , %      | Yes                    | 83                          | 90                                                         |
|                                                      | Missing                | 17                          | 10                                                         |
| Transplant regimen, %                                | Bu/Mel                 | 36                          | 11                                                         |
|                                                      | CEM                    | 53                          | 22                                                         |
|                                                      | TC and CEM             | 7                           | 3                                                          |
|                                                      | Other/Missing          | 4                           | 64                                                         |
| Cycles of immunotherapy, %                           | < 6 cycles             | 3                           | < 1                                                        |
|                                                      | 6 cycles               | 97                          | 99                                                         |
| End of immunotherapy bone marrow response, %         | No evidence of disease | 100                         | 74                                                         |
|                                                      | Missing                | 0                           | 1% no change;<br><1% improved;<br>25% missing <sup>f</sup> |
| Lansky performance status at end of immunotherapy, % | 100                    | 59                          | -                                                          |
|                                                      | 80-90                  | 18                          | -                                                          |
|                                                      | Missing                | 23                          | 100                                                        |
| End of immunotherapy date, range                     |                        | 03/22/2012 to<br>01/25/2016 | 06/03/2005 to<br>01/28/2016                                |

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{Eflornithine [DFMO]}

<sup>a</sup> Social determinants of health (e.g., socioeconomic status) were considered but data were unavailable;

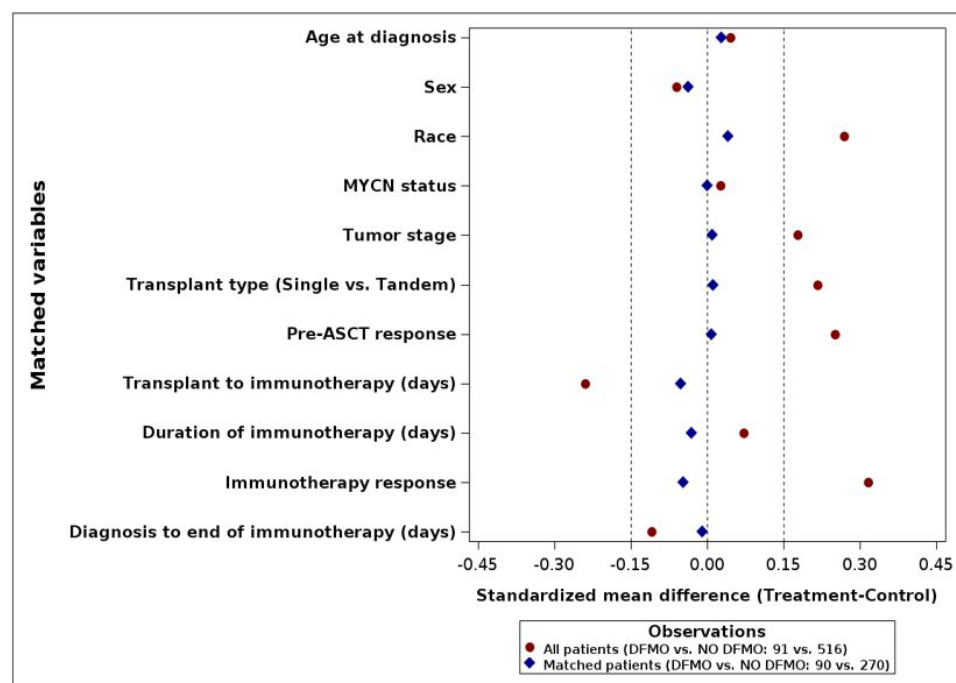
<sup>b</sup> All Study 3(b) sites were in the United States; <sup>c</sup> Patients may have multiple primary tumor locations;

<sup>d</sup> Extent of surgery not specified; <sup>e</sup> Information regarding dose and type of radiation limited; <sup>f</sup> Optional field on ANBL0032 case report form and all patients with missing bone marrow response had an overall response documented of CR or VGPR

ASCT = autologous stem cell transplantation; Bu/Mel = busulfan/melphalan; CEM = carboplatin/etoposide/melphalan; CR = complete response; PR = partial response; TC = cyclophosphamide/thiotepa; VGPR = very good partial response

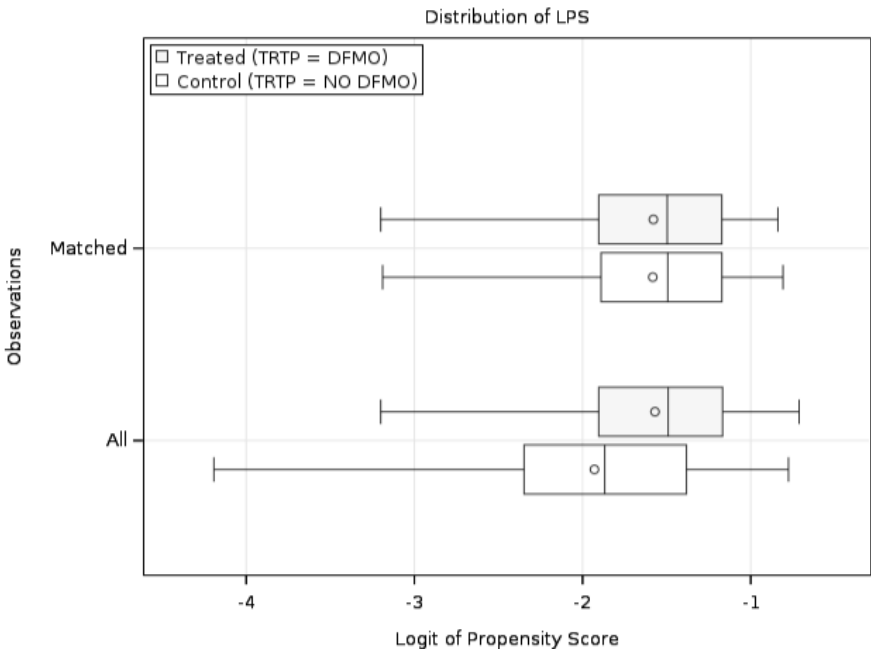
Source: FDA analysis based on datasets submitted in NDA 215500

**Figure 27. Plot of Standardized Difference Before and After Matching**



Source: FDA Analysis of Applicant submitted data 3bvanbl0032 ADTTE

Figure 28. Box plot of Logit Propensity Scores Before and After Matching



Source: FDA Analysis of Applicant submitted data 3bvanbl0032 ADTTE

***FDA assessment of comparability of external control arm and investigational arm***

Whether the external control arm was adequately comparable to the investigational arm was a key review issue in order to assess the interpretability of results from the ECT. FDA’s assessment of the major strengths and limitations of the comparability of populations is outlined in Table 27. In the Applicant’s proposed primary analysis population, 85 of 90 patients treated with eflornithine on the investigational arm had completed immunotherapy on Study ANBL0032 within the prior 120 days with no other intervening anti-cancer therapy, and 5 patients had been treated according to ANBL0032 protocol off study. As shown in Table 26, matched demographic and clinical characteristics were similar across arms. Notably, the Applicant used an exact match for MYCN status, given its important prognostic significance. Patients were required to be in remission at the end of immunotherapy, and although all patients were assessed as having at least a partial response, approximately 10% of patients in the control arm did not have available imaging assessments to corroborate the response data. While 25% of patients had missing bone marrow response evaluations at the end of immunotherapy, all of those patients had an overall response documented as CR or VGPR. The 1993 INRC response criteria do not require bone

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marrow evaluation as part of that determination.

Unmatched or unmeasured patient characteristics can raise the concern for potential measured and unmeasured confounding. Certain patient characteristics, such as geography, were not included in the propensity score. Since ANBL0032 enrolled patients at sites outside the US (including 14% of patients in the matched external control arm), sensitivity analyses which assessed the impact of country of enrollment were performed. Other potentially significant non-matched patient characteristics include demographic information (ethnicity and social determinants of health), disease characteristics (tumor histology, primary tumor location, tumor cytogenetics), pre-immunotherapy treatment characteristics (surgery during induction, radiation during consolidation, and transplant regimen), and post-immunotherapy treatment characteristics (performance status at end of immunotherapy and end of immunotherapy date). These variables were not included in the propensity score because they were either not collected, unmeasurable, or had substantial missingness across one or both study arms.

Given that patients who enrolled Study 3(b) elected to enroll on an additional clinical trial, whereas patients on the control arm did not, it is possible that the groups differed in ways that may be associated with differences in outcome, such as social determinants of health (SDOH), performance status, or other related unmeasured factors. Since literature suggests that exposure to household poverty has an impact on patient outcomes (i.e., EFS and OS) (Bona, 2021) FDA considered analyses to assess the potential impact of imbalances in SDOH between the investigational and external control arm on the treatment effect.

Data regarding cytogenetics were limited in ANBL0032. All the chromosomal alterations/genetic mutations recorded in patients in the DFMO arm (i.e., 1p deletion, 11q deletion, 17q gain, ALK mutations) are associated with worse prognosis; however, these data were not available for patients on the control arm. Sensitivity analyses performed by FDA assessed the potential impact of these unmeasured confounding factors on the estimated treatment effect in the ECT.

FDA considers the populations of matched patients in the external control arm and the investigational arm to be adequately comparable to permit an inferential analysis while acknowledging the need to evaluate the impact of unmeasured confounders using statistical analyses, where feasible.



**Table 27: Assessment of Strengths and Limitations of Comparability of ECT Populations**

| <b>Strengths</b>                                                                      | <b>Limitations</b>                                                             |
|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Similar eligibility and tumor assessment criteria per protocol                        | Unknown factors in decision to enroll vs. not enroll on Study 3(b)             |
| Patients matched on 11 pre-specified clinical characteristics                         | Unmeasured variables may result in confounding                                 |
| Patients did not receive additional treatment after up-front therapy, except for DFMO | Non-contemporaneous treatment era                                              |
| Use of comparable index dates (end of immunotherapy)                                  | Imaging pre-specified for 2 years post-immunotherapy and limited after 5 years |
| Study 3(b) sites were also ANBL0032 sites                                             | 14% of patients in control arm treated on ANBL0032 outside U.S.                |

***End of Immunotherapy Response Assessments***

The ANBL0032 dataset was limited with regard to imaging and tumor assessments. The exact dates of tumor assessments were not recorded in the case report forms. A 6- to 12-month time window was recorded during which investigators could record “no disease present” or “disease present”, or “failed during period”. All patients on the control arm had an end of immunotherapy overall response status of complete response (CR), very good partial response (VGPR), partial response (PR), however the datasets did not include imaging results to corroborate these assessments.

Most patients on the control arm had “no disease present” recorded for their first imaging assessment, consistent with being in remission. However, 36 patients on the control arm (13%) had “Disease present” or “Failed during period” during their first imaging time period as per the ADOPTF dataset (Table 28). The Applicant was able to obtain source data to confirm the end of immunotherapy overall response status in 8 patients (details provided in Table 28). Two patients had incorrect EFS events determined upon further investigation of source data (Patient ID (b) (6) relapsed earlier than recorded in the dataset; Patient ID (b) (6) never relapsed whereas the dataset recorded relapse). No additional data was obtained for the remaining 26 patients.

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**Table 28. Patients on Control Arm with Disease Present During First Imaging Time Period**

| Patient ID                                                                       | End of immunotherapy date | EFS event date | First imaging time period (FUPSDT to FUEDT) includes disease status of “Disease present” or “Failed during period” | Follow-up Data submitted by Applicant on 3/8/2023 in response to FDA Information Request                                                                                                                                                                     |
|----------------------------------------------------------------------------------|---------------------------|----------------|--------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Patients with final EFS determination of “Alive with No Event”</b>            |                           |                |                                                                                                                    |                                                                                                                                                                                                                                                              |
| (b) (6)                                                                          | (b) (6)                   | (b) (6)        | (b) (6)                                                                                                            | None                                                                                                                                                                                                                                                         |
| (b) (6)                                                                          | (b) (6)                   | (b) (6)        | (b) (6)                                                                                                            | None                                                                                                                                                                                                                                                         |
| (b) (6)                                                                          | (b) (6)                   | (b) (6)        | (b) (6)                                                                                                            | Patient in remission at end of immunotherapy (PR due to residual disease in liver), with CT, MIBG, BM (b) (6); due to residual disease, additional cycles of cis-RA were administered between (b) (6) with no further treatment, and patient did not relapse |
| (b) (6)                                                                          | (b) (6)                   | (b) (6)        | (b) (6)                                                                                                            | Patient in remission at end of immunotherapy (PR due to residual disease in liver), with CT, CT, MIBG, BM, HVA/VMA (b) (6); no additional anti-cancer treatment administered, and patient did not relapse                                                    |
| (b) (6)                                                                          | (b) (6)                   | (b) (6)        | (b) (6)                                                                                                            | None                                                                                                                                                                                                                                                         |
| (b) (6)                                                                          | (b) (6)                   | (b) (6)        | (b) (6)                                                                                                            | None                                                                                                                                                                                                                                                         |
| (b) (6)                                                                          | (b) (6)                   | (b) (6)        | (b) (6)                                                                                                            | None                                                                                                                                                                                                                                                         |
| <b>Patients with final EFS determination of “Relapse/Progression” or “Death”</b> |                           |                |                                                                                                                    |                                                                                                                                                                                                                                                              |
| (b) (6)                                                                          | (b) (6)                   | (b) (6)        | (b) (6)                                                                                                            | None                                                                                                                                                                                                                                                         |

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|         |         |         |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------|---------|---------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (b) (6) | (b) (6) | (b) (6) | (b) (6) | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|         |         |         |         | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|         |         |         |         | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|         |         |         |         | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|         |         |         |         | <p>Patient in remission at end of immunotherapy (CR), with BMA and CT (b) (6); Scheduled BMA on (b) (6) identified “low level involvement by neuroblastoma (&lt;1%); patient admitted on (b) (6) to receive chemotherapy (cyclophosphamide, vincristine, and irinotecan) prior to his travel to (b) (6) to receive 3F8 therapy; progress note on (b) (6) stated that the patient returned from (b) (6) where he received 3F8 infusion; progress note on (b) (6) documented the patient had undergone resection, transplant, local radiation to the tumor bed and had “completed 5 cycles”; Scheduled (~6 month) assessments included CT C/A/P (b) (6) with impressions supporting no disease; however the patient chart notes that the patient received doses of 3F8 on (b) (6) and (b) (6). Subsequent period of (b) (6) to (b) (6) returns to “disease present” and Anticancer therapy =Yes, consistent with ANBL0032 reported EFS Event on (b) (6) Additional detail on (b) (6) reported relapse was not provided.</p> |
| (b) (6) | (b) (6) | (b) (6) | (b) (6) | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|         |         |         |         | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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|         |         |         |         |                                                                                                                                                                                                                                                                    |
|---------|---------|---------|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (b) (6) | (b) (6) | (b) (6) | (b) (6) | Patient in remission at end of immunotherapy (CR), with MRI, CT, MIBG, BM (b) (6); imaging identified new intracranial lesion (left temporal) on CT (b) (6) s/p resection on (b) (6) which confirmed relapse                                                       |
|         |         |         |         | None                                                                                                                                                                                                                                                               |
|         |         |         |         | None                                                                                                                                                                                                                                                               |
|         |         |         |         | None                                                                                                                                                                                                                                                               |
|         |         |         |         | None                                                                                                                                                                                                                                                               |
|         |         |         |         | Patient in remission at end of immunotherapy (CR), with MRI, BM, MIBG, CT C/A/P (b) (6); Symptoms of headaches and emesis prompted early MRI which showed 2 lesions (right cerebellar and left parietal) s/p resection on (b) (6) which confirmed relapse          |
| (b) (6) | (b) (6) |         |         | Patient in remission at end of immunotherapy (CR), with MRI, BM, MIBG, CT C/A/P (b) (6); Unscheduled imaging visit (reason and specific modalities not described) from (b) (6) identified new lesion in the brain s/p resection on (b) (6) which confirmed relapse |
| (b) (6) | (b) (6) |         |         | None                                                                                                                                                                                                                                                               |
| (b) (6) | (b) (6) |         |         | Patient in remission at end of immunotherapy (CR), with CT, MIBG, BM (b) (6); patient never experienced relapse (whereas dataset states patient had relapse/progression event on (b) (6)); per study site he was                                                   |

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|         |         |         |         |                                                                                                                                                                                                                                                                                       |
|---------|---------|---------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         |         |         |         | still in complete remission at the last follow up on (b) (6)                                                                                                                                                                                                                          |
| (b) (6) | (b) (6) | (b) (6) | (b) (6) | None                                                                                                                                                                                                                                                                                  |
|         |         |         |         | None                                                                                                                                                                                                                                                                                  |
|         |         |         |         | None                                                                                                                                                                                                                                                                                  |
|         |         |         |         | None                                                                                                                                                                                                                                                                                  |
|         |         |         |         | Patient in remission at end of immunotherapy (CR), with MIBG, CT, BM (b) (6) scheduled disease evaluation with MIBG (b) (6) and BM (b) (6) concerning for relapse, CT stable (b) (6)                                                                                                  |
| (b) (6) | (b) (6) |         |         | None                                                                                                                                                                                                                                                                                  |
|         |         |         |         | None                                                                                                                                                                                                                                                                                  |
|         |         |         |         | None                                                                                                                                                                                                                                                                                  |
|         |         |         |         | None                                                                                                                                                                                                                                                                                  |
|         |         |         |         | None                                                                                                                                                                                                                                                                                  |
|         |         |         |         | Patient in remission at end of immunotherapy (CR), with MRI, BMA, MIBG, HVA/VMA (b) (6); relapse during 1 <sup>st</sup> imaging period with new lesion on abdominal MRI on (b) (6) (other assessments negative), prompted surgical resection on (b) (6) which confirmed tumor relapse |
| (b) (6) | (b) (6) |         |         | Patient in remission at end of immunotherapy (CR), with CT, MIBG, BM (b) (6) relapse identified at scheduled 3 month disease evaluation                                                                                                                                               |

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|  |  |  |  |                                                  |
|--|--|--|--|--------------------------------------------------|
|  |  |  |  | with single intracranial lesion (MIBG<br>(b) (6) |
|--|--|--|--|--------------------------------------------------|

Source: FDA Analysis of ANBL0032 ADOPTF dataset and Clinical Information Amendments submitted by Applicant during review period.

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

#### Data:

Upfront treatment was comparable between DFMO PER COG and NO DFMO groups through the end of immunotherapy, and >96% of patients completed dinutuximab immunotherapy in both groups.

For Study 3b, DFMO treatment compliance is discussed in Section 8.1.1. Concomitant investigational and anticancer therapy was prohibited and would have only been used following determination of disease recurrence, an EFS event which would have resulted in discontinuation of DFMO therapy.

In ANBL0032, patients were to be censored at the point they entered another COG study with therapeutic intent. Limited information on administration of anticancer therapy was provided in a supplemental transfer of the ANBL0032 database for the off-therapy long term follow up. In NO DFMO patients with EFS Events, anticancer treatment was reported for nearly all patients in the long term follow up period (following the end of immunotherapy). Reporting patterns generally suggested anticancer therapy was administered in timeframes that were aligned with or later than timing of EFS events. In NO DFMO patients without EFS events, ~11% of patients report anticancer therapy at any reporting period beyond the end of immunotherapy.

#### The Applicant's Position:

The target patient population are those patients that are in remission at the completion of multiagent, multimodality treatment. The use of anticancer therapy following the completion of immunotherapy would be expected only in instances when an EFS event occurred, and relapse (or secondary cancer) therapy was required. Study 3b prohibited the use of additional anticancer therapies unless a patient was discontinued from treatment due to relapse. As expected, the vast majority of anticancer therapy reporting in ANBL0032 is consistent with the administration of post-relapse therapy. Anticancer therapy is reported in a small proportion of patients that did not experience EFS events and additional information is not available to explain such reports. This may reflect potential inconsistencies in EFS reporting which would favor the control group and/or data entry errors. However, assuming that such reporting indicates that there was a group

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of patients receiving the benefit of additional treatment that are not contributing events to the NO DFMO group, this would theoretically work against the treated arm. The results of the comparative analyses consistently favor the DFMO PER COG group, nonetheless.

The FDA's Assessment:

FDA agrees with the Applicant that concomitant investigational and anticancer therapy was not allowed until the time of relapse in both studies.

In the control arm, FDA identified two patients who received anti-cancer therapy during the observational period. However, receipt of additional anti-cancer therapy would have biased the observed treatment effect toward the null.

- (b) (6): Patient completed immunotherapy on (b) (6) and had an EFS evaluation of “Alive with No Event” on (b) (6). However, the patient received 24 cycles of DMFO in (b) (6) and (b) (6) via Study NMTRC006 (Expanded Access Protocol).
- (b) (6): Patient completed immunotherapy on (b) (6) and had an EFS evaluation of Relapse on (b) (6). However, the patient received chemotherapy and immunotherapy (3F8 (b) (6)) between (b) (6).

In Study 3(b), one patient received topotecan for 4 days ((b) (6)), but this patient was not included in the Applicant's proposed primary efficacy population (N=90).

Data on other concomitant medications were not available for patients on the control arm. In the investigational arm, data regarding concomitant medications were available for the 72 patients consented on NMTRC003B (not available in 18 patients with data sourced from BCC001). In the 72 patients, 81% received anti-infectives; 39% received vitamins/supplements; 35% received topical, nasal or inhaled steroids; 32% received antihistamines; 28% received anti-emetics; 19% received opioids; 11% received oral steroids (for indications including cough, croup, allergic reaction, adrenal insufficiency, lung infection); and 10% received levothyroxine. Other concomitant medications were administered in <10% of patients. It is possible that more patients may have received these medications as investigators may not have recorded all concomitant medications.

While patients did not receive additional treatment-directed therapies during the observational period, the use of concomitant medications described above reflects typical supportive care for patients who have received intensive multi-modality therapies. It is likely that those supportive

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care treatments evolve over time, and changes in supportive care during induction, consolidation and immunotherapy may impact dose intensity and ultimately treatment outcomes; however, given the nature of the concomitant medications administered in the post-immunotherapy setting, it is unlikely that differences in concomitant medications during this time period would substantially affect results overall, or result in a difference in outcomes between arms.

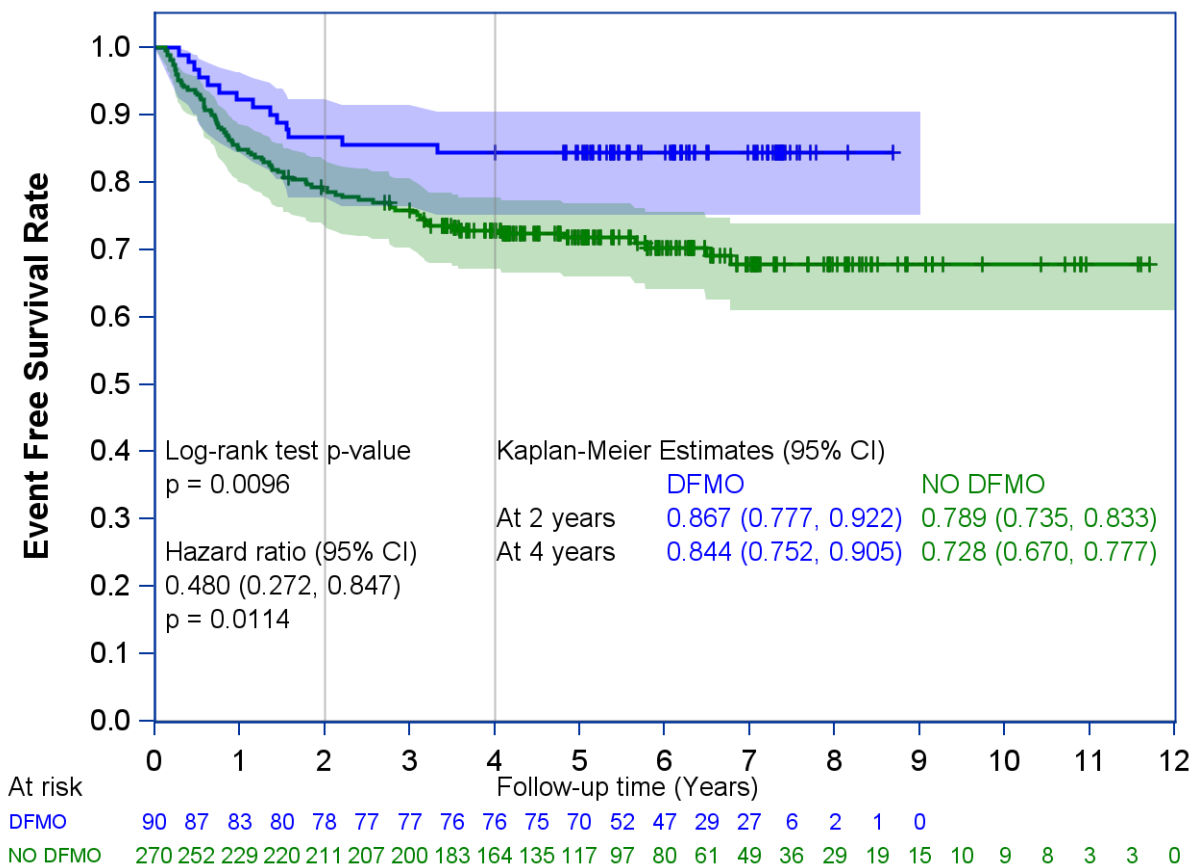
### **Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)**

#### Data:

Figure 29 displays the Kaplan-Meier curves with 2-year and 4-year KM Estimates along with the 95% confidence interval for the SAP-defined primary PSM comparison. The 4-year EFS rates are 0.84 and 0.73 for the DFMO treated and matched control population, respectively. The EFS comparison results in a hazard ratio of 0.48 and p-value of 0.0114.



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**Figure 29: Kaplan-Meier Curve of EFS Using PS Matched Samples from DFMO PER COG and NO DFMO Populations**

Source: Study 3b vs. ANBL0032 Efficacy Report Figure 14.2.1.a

Extensive sensitivity analyses were performed based on FDA input during SAP development. Notable sensitivity analyses include those that applied more conservative selection rules designed to favor the control group, analyses that restricted the control population to those in the same era as the treated patients, and analyses to address missing data.

The NO DFMO selection rules include patients that have an end of immunotherapy response of PR or better, provided they have no disease in the bone marrow. This is consistent with the eligibility criteria for Study 3b; however, PR patients have higher event rates within the NO DFMO group as compared to their VGPR and CR counterparts, thus this conservative analysis removes patients with PR end of immunotherapy response in an effort to restrict the control

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group to better-risk patients while maintaining PR patients in the treated group. Additionally, VGPR and CR are combined into a single category in the revised INRC (Park 2017). Thus, VGPR and CR patients are those that would almost invariably be considered to be in remission at the conclusion of immunotherapy, whereas there could be some debate about PR patients in the absence of additional assessments that confirm inactivity of residual tumor on imaging. A sensitivity analysis restricting the control patients eligible for matching to only those with VGPR or better response at the end of immunotherapy was performed, with results consistent with those reported for the primary EFS analysis (Figure 30, panel B).

Additionally, the NO DFMO selection rules included patients with an EFS date (event or censored) that was >30 days from the end of immunotherapy. Study 3b required enrollment of patients within 120 days of completion of immunotherapy; however, the median observed time was 31 days. This served as the basis for the selection rule; however, the most conservative modification on this rule would be to exclude any control patients with an EFS date <120 days, thus ensuring removal of any early relapsed patients that could have theoretically relapsed before they could have been evaluated for Study 3b eligibility. A sensitivity analysis restricting the control patients eligible for matching to only those with EFS dates >123 days was performed. The end of immunotherapy date in ANBL0032 is generally reported as the date of the end of treatment visit when end of immunotherapy scans would have been conducted. Notably, ANBL0032 required imaging at 3 months from the end of immunotherapy visit, thus the 123-day EFS date selection rule applied from the end of the ANBL0032 reported date of end of immunotherapy is expected to remove any control patients that were determined to have relapsed based on 3-month imaging with a further 1 month window to account for possible scheduling or reporting delays. The results of this modified analysis are consistent with the primary matched EFS analysis (Figure 30, panel A).

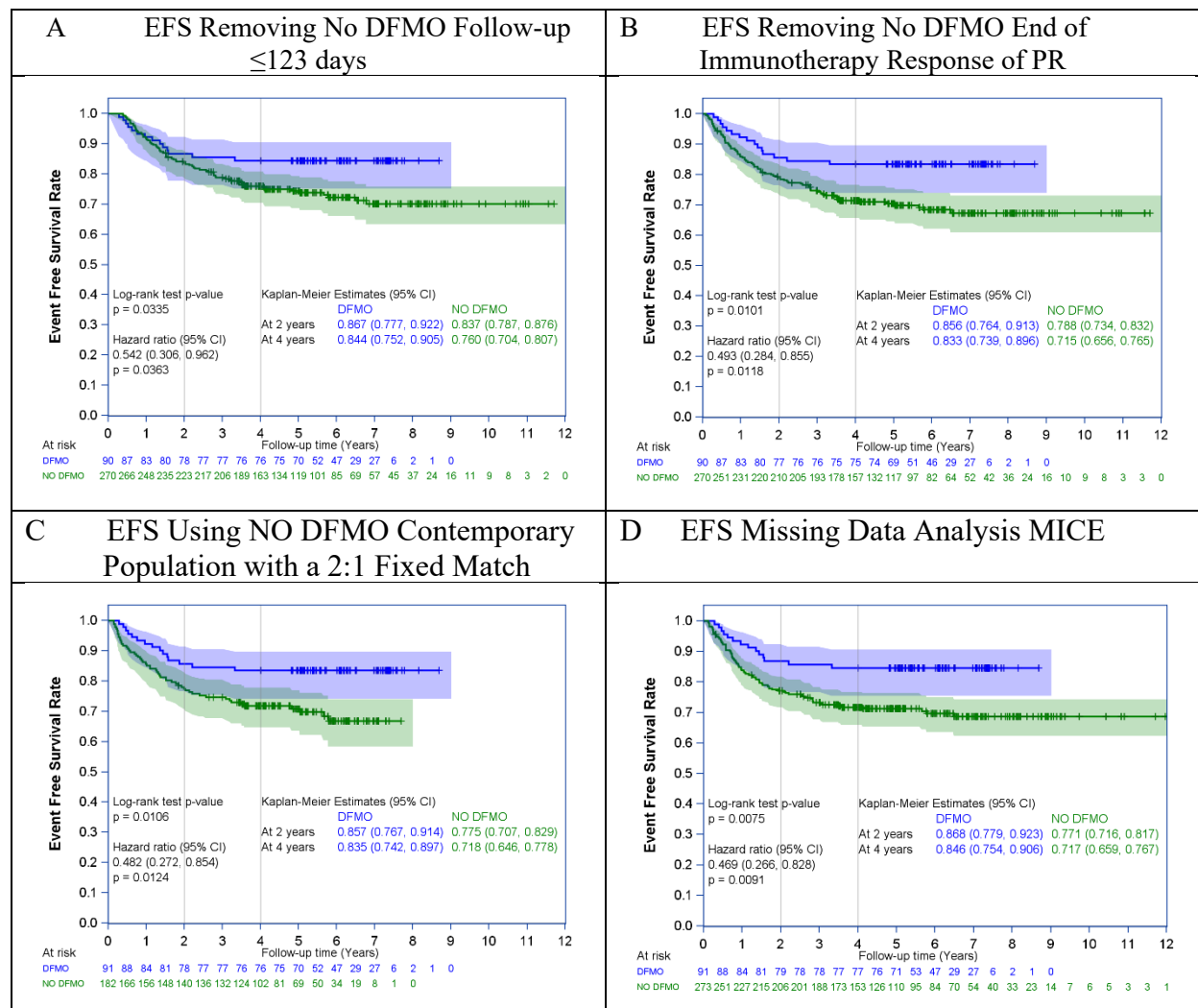
Another important analysis considered the enrollment timeframe for Study 3b. The NO DFMO selection rules ignored year of enrollment in ANBL0032. To address any potential effect of era of treatment a contemporary population was created for the NO DFMO group, limiting the control patients to only those that would have completed immunotherapy in the approximate enrollment timeframe of Study 3b (initiated in 2012). Patients enrolling in ANBL0032 in 2011 or later, thus completing an approximate 6-month course of immunotherapy (+ up to 120 days per Study 3b eligibility criteria) in approximately 2012 or later are included in the NO DFMO Contemporary population. A sensitivity analysis subsetting the control patients to the contemporary timeframe was performed. Given the reduction in available patients with complete case data in the NO DFMO (n=516) to the NO DFMO contemporary population (n=370) requiring approximately 270 patients resulted in insufficient balance after the match. As a result a 2:1 fixed ratio was used in the analysis and the results are consistent with the primary

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matched EFS analysis (Figure 30, panel C).

A sensitivity analysis was performed to explore how the choice of using complete data and excluding patients with missing covariate information influences the propensity score matched analysis. Multiple-imputation-by-chained-equations (MICE) algorithm as described in van Buuren is a commonly used approach for imputation ([van Buuren 2011](#)). MICE was used to impute any missing value for any covariate used in the propensity score model separately for the NO DFMO and DFMO PER COG patients. This approach assumed the data were missing at random. Once the data were imputed, the propensity score matched analysis as performed for the primary endpoint was repeated and the results are consistent with the primary matched EFS analysis (Figure 30, panel D).

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**Figure 30: Key PSM Sensitivity Analyses from DFMO PER COG and NO DFMO Populations**

Source: Study 3b versus ANBL0032 Efficacy Report Figure 14.2.10.1.2.7.a (Panel A), Figure 14.2.10.4.a (Panel B), Figure 14.2.16.2.a (Panel C) Figure 14.2.9.a (Panel D)

A number of other sensitivity analyses were performed that evaluated changes to the matching ratio, alternate matching approaches, modification of covariates used in calculation of the PS score, and analyses in secondary analysis populations, among others. The results across this wide array of sensitivity analyses were generally consistent with the primary EFS result, both in

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terms of magnitude of effect (HR values generally ranged 0.4 to 0.6) and in terms of statistical significance (3b vs. ANBL0032 Efficacy Report Sections beginning at 8.6.3).

#### The Applicant's Position:

DFMO treatment provided meaningful clinical reduction in relapse events for HRNB patients completing immunotherapy with HR ranging from 0.4 to 0.6 across many analyses. Sensitivity analyses of specific interest were designed to further address potential sources of residual bias based on the primary endpoint methodology. The results are consistent despite modifications that conservatively favor the control group, limit the compared patients to those with treatment in the same era, and with imputation of missing data.

#### The FDA's Assessment:

FDA's independent analyses confirm that the observed EFS hazard ratio using the Applicant's proposed primary analysis was 0.48 (95% CI 0.27, 0.85). The efficacy results per the Applicant's proposed primary analysis for EFS are summarized in Table 29 and Figure 31.

**Table 29. FDA Analysis of Primary Endpoint EFS – Propensity Score Matched (3:1)**

|                                                | <b>DFMO</b><br>(N=90) <sup>1</sup> | <b>NO DFMO</b><br>(N=270) <sup>2</sup> |
|------------------------------------------------|------------------------------------|----------------------------------------|
| <b>Event-free Survival (EFS)<sup>3,4</sup></b> |                                    |                                        |
| EFS events, n (%) <sup>5</sup>                 | 14 (16)                            | 79 (29)                                |
| Censored, n (%)                                | 76 (84)                            | 191 (71)                               |
| Hazard Ratio (95% CI)                          | 0.48 (0.27, 0.85)                  |                                        |

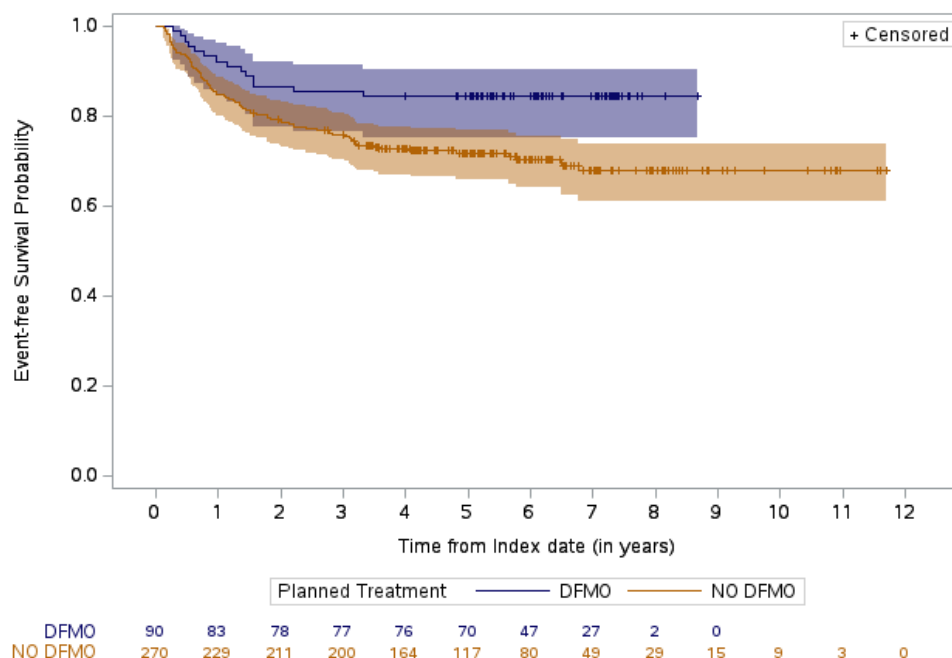
<sup>1</sup>Derived from 91 patients with no missing data out of 92 total eligible patients; <sup>2</sup>Derived from 516 patients with no missing data out of 852 total eligible patients; <sup>3</sup>Final analysis; DCO: Study NMRTC003b, June 2021; Study ANBL0032, June 2019; <sup>4</sup>Descriptive p-value from unstratified log-rank test = 0.0096; <sup>5</sup>2 events were deaths (both in the NO DFMO arm);

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

**Figure 31. Kaplan-Meier Plots of EFS by Treatment Group - Propensity Score Matched (3:1) Sample from NO DFMO**

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Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

The Applicant's proposed primary analysis did not stratify the treatment effect model by the matched groups (3 external control arm patients and 1 DFMO arm patient). To explore whether the process of matching introduced any bias in the selection of matched controls for the experimental arm, FDA conducted a propensity score matched analysis of EFS and OS with stratification by matched groups. The results, provided in Table 30, were consistent with the unstratified analyses.

**Table 30. Stratified Analysis of EFS and OS Using Applicant Proposed Propensity Score Matched (3:1) Primary Analysis Population**

|                           | DFMO (n=90) | NO DFMO (n=270) |
|---------------------------|-------------|-----------------|
| Event free survival (EFS) |             |                 |
| Events, n (%)             | 14 (16)     | 79 (29)         |
| Censored, n (%)           | 76 (84)     | 191 (71)        |

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|                       |                   |          |
|-----------------------|-------------------|----------|
| HR (95% CI)           | 0.49 (0.28, 0.88) |          |
| Overall Survival (OS) |                   |          |
| Deaths, n (%)         | 7 (8)             | 57 (21)  |
| Censored, n (%)       | 83 (92)           | 213 (79) |
| HR (95% CI)           | 0.36 (0.16, 0.79) |          |

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

Several sensitivity analyses were performed to assess the robustness of the estimation of treatment effect on both the primary endpoint, EFS, and the secondary endpoint, OS. These sensitivity analyses were performed to assess the impact of factors including differential follow-up, immortal time, variations in treatment administration time around index date, potential bias due to investigator assessments of EFS, and temporal changes in analysis population in the control arm on the estimation of treatment effect. The review team considered the Applicant's proposed primary analysis results for EFS and OS in the context of these sensitivity and supportive analyses to characterize the treatment effect of this ECT, as described in the subsections below. Prior to NDA submission, FDA advised the Applicant that additional analyses would be conducted as deemed necessary during the review of statistical data.

All analyses of the externally controlled data used the complete case population for matched or weighted analyses as described, unless otherwise noted.

### **Analyses to assess the impact of differential follow-up/availability of imaging data**

In Study 3(b) and Study ANBL0032, tumor assessments were required at the end of immunotherapy (ANBL0032)/baseline (Study 3(b)), at 3, 6, 9, 12, 18, and 24 months after completion of immunotherapy, and then per institutional standard. Study ANBL0032 also required imaging at 30 and 36 months after completion of immunotherapy. Subsequent imaging was performed per institutional standard.

For patients with relapse events, all patients had imaging through the time of the relapse event.

For patients who did not experience an EFS event, the imaging datasets for Study 3(b) and/or ANBL0032 include imaging through 2 years for >99% of patients in both arms and through 3

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years in >95% of patients in both arms (Table 31). At 5 years, 83% of patients in the investigational arm and 85% of patients on the control arm had imaging recorded in the study database. At 7 years, 33% of patients in the investigational arm and 58% of patients on the control arm had imaging recorded in the study database.

**Table 31. FDA Analysis of Imaging Data Collected in ANBL0032 and/or Study 3(b) Datasets During Follow-Up Period**

| Number of years after end of immunotherapy | DFMO arm,<br>Patients with EFS determination<br>“alive with no event” (N=76)<br>N (%) | Control arm,<br>Patients with EFS determination<br>“alive with no event” (N=191)<br>N (%) |
|--------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| 2 years                                    | 76 (100)                                                                              | 190 (99)                                                                                  |
| 3 years                                    | 76 (100)                                                                              | 181 (95)                                                                                  |
| 4 years                                    | 67 (88)                                                                               | 173 (91)                                                                                  |
| 5 years                                    | 63 (83)                                                                               | 163 (85)                                                                                  |
| 7 years                                    | 25 (33)                                                                               | 111 (58)                                                                                  |

Source: FDA analysis of datasets submitted in NDA 215500 (ANBL0032 ADOPTF, NMTRC003 outcomes, NMTRC003 ADTTE)

Overall, imaging data in each arm to support EFS event determination was available for at least 95% of patients through 3 years, and >80% of patients at 5 years after the end of immunotherapy. Sensitivity analyses were performed restricting the follow-up times at 2-, 3-, and 5-year to minimize the impact of differential follow-up times and differential imaging assessment frequencies or imaging availabilities in long-term follow-up of the studies. The efficacy results for these analyses are presented in Table 32. The Kaplan-Meier plots of EFS and OS based on the first 5 years of follow-up data are provided in Figure 32.

**Table 32. Analysis of EFS and OS using Administratively Censored Data – Propensity Score Matched (3:1)**

|                  | Event-free Survival |                        |                      | Overall Survival |                        |                      |
|------------------|---------------------|------------------------|----------------------|------------------|------------------------|----------------------|
|                  | DFMO<br>Events/N    | NO<br>DFMO<br>Events/N | HR<br>(95% CI)       | DFMO<br>Events/N | NO<br>DFMO<br>Events/N | HR<br>(95% CI)       |
| Primary Analysis | 14/90               | 79/270                 | 0.48<br>(0.27, 0.85) | 7/90             | 57/270                 | 0.32<br>(0.15, 0.70) |
| Follow-up        |                     |                        |                      |                  |                        |                      |

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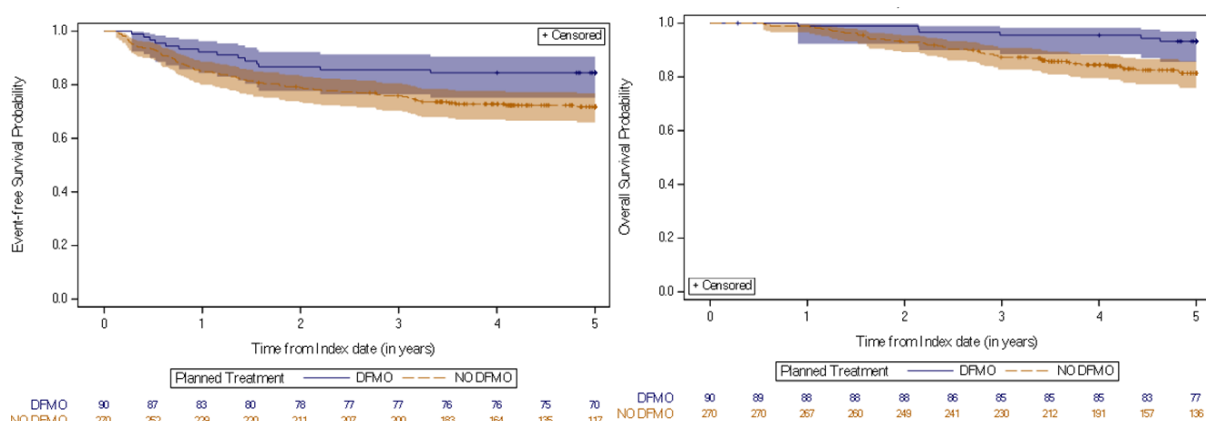


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|                                 |       |        |                      |      |        |                      |
|---------------------------------|-------|--------|----------------------|------|--------|----------------------|
| 2-year administrative censoring | 12/90 | 57/270 | 0.60<br>(0.32, 1.11) | 1/90 | 19/270 | 0.16<br>(0.02, 1.16) |
| 3-year administrative censoring | 13/90 | 65/270 | 0.56<br>(0.31, 1.02) | 4/90 | 34/270 | 0.34<br>(0.12, 0.95) |
| 5-year administrative censoring | 14/90 | 75/270 | 0.51<br>(0.29, 0.91) | 6/90 | 47/270 | 0.34<br>(0.14, 0.79) |

HR, hazard ratio; CI, confidence interval

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

**Figure 32. Kaplan-Meier Plots of EFS and OS (First 5 Years of Follow-up) by Treatment Group - Propensity Score Matched (3:1)**

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

In general, the estimation of treatment effects on EFS and OS when the data are administratively censored to account for potentially different follow-up times and frequencies seems to be consistent with the effect observed in the Applicant's proposed primary analyses of these endpoints.

### Analyses to assess impact of treatment administration and index date variations

Because patients on Study ANBL0032 had no comparable date coinciding with DFMO administration date on Study 3(b), the end of immunotherapy date was selected as the index date for both study arms. The end of immunotherapy date in Study 3(b) was reported as the last date

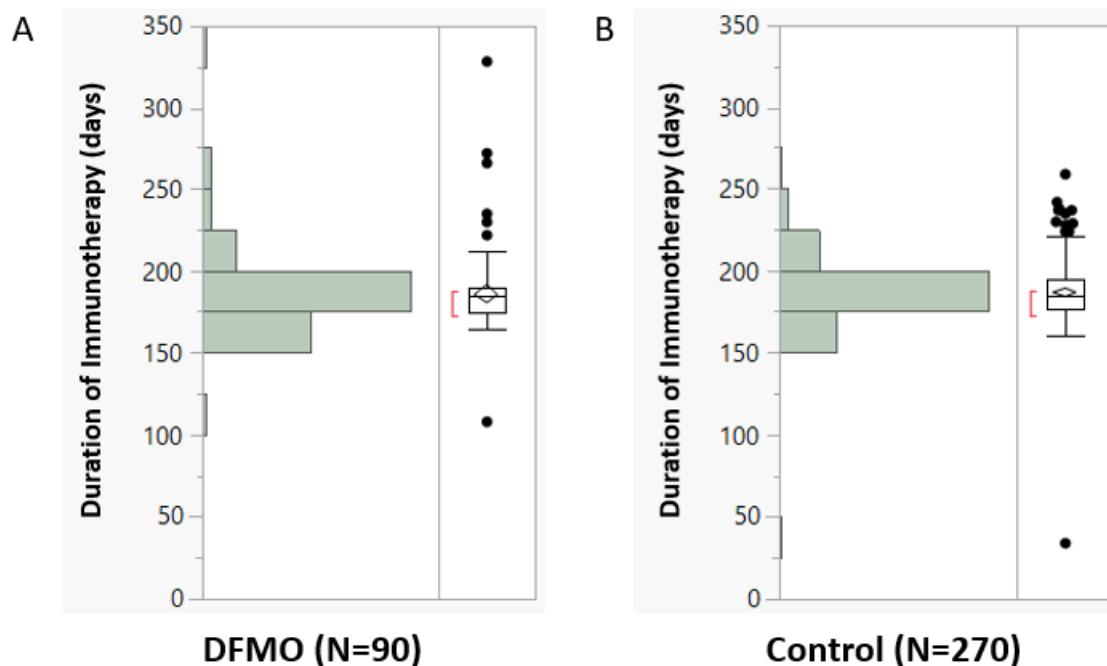
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of pharmacotherapy (e.g., last dose of cis-RA). The end of immunotherapy date reported in Study ANBL0032 was defined by the end of the last reporting period (cycle 6 in most patients), which allows for two weeks for scheduling of the imaging assessments required for disease evaluation.

Study 3(b) was designed to minimize variability by defining eligible patients as having completed immunotherapy > 30 days and < 120 days from the start of DFMO. In the primary analysis, for patients enrolled on Study ANBL0032 who went on to enroll in Study 3(b) (N = 85 of 90), the end of immunotherapy date was defined as the later of the two dates recorded in Study 3(b) (last dose of cis-RA) or Study ANBL0032 (end of treatment visit).

The median duration of immunotherapy was 185 days in both arms with a range of (108, 328) for the DFMO arm and (34, 259) for the external control. There was some variability as shown in the histograms in Figure 33, however the outliers were patients who received <6 cycles of immunotherapy or received additional cycles of cis-RA. To assess the impacts of variations in treatment administration times around the index date, FDA conducted a number of sensitivity analyses including changes in index date, analysis excluding patients who received experimental treatment before index date or received cis-RA after index date, and analyses that added more exclusion rules in addition to the ones described here. The sensitivity analyses results are presented in Table 33.

{Eflornithine [DFMO]}

**Figure 33. Histogram of duration of immunotherapy in days for DFMO (A) and Control (B) arms**

Source: FDA analysis using Applicant submitted datasets in NDA 215500

**Table 33. Sensitivity Analysis of EFS and OS to Assess the Treatment and Index Date Related Variations – Propensity Score Matched (3:1)**

|                                                               | Event-free Survival |                            |                      | Overall Survival |                     |                      |
|---------------------------------------------------------------|---------------------|----------------------------|----------------------|------------------|---------------------|----------------------|
|                                                               | DFMO<br>Events/N    | NO<br>DFMO<br>Events/<br>N | HR<br>(95% CI)       | DFMO<br>Events/N | NO DFMO<br>Events/N | HR<br>(95% CI)       |
| Primary Analysis                                              | 14/90               | 79/270                     | 0.48<br>(0.27, 0.85) | 7/90             | 57/270              | 0.32<br>(0.15, 0.70) |
| Index date is last<br>administration of<br>antibody treatment | 14/90               | 79/270                     | 0.48<br>(0.27, 0.85) | 7/90             | 57/270              | 0.32<br>(0.15, 0.70) |

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|                                                                                                                          |       |        |                      |      |        |                      |
|--------------------------------------------------------------------------------------------------------------------------|-------|--------|----------------------|------|--------|----------------------|
| Excluding DFMO patients receiving treatment prior to index                                                               | 13/86 | 74/258 | 0.48<br>(0.27, 0.87) | 7/86 | 50/258 | 0.38<br>(0.17, 0.85) |
| Excluding DFMO patients receiving cis-RA after index                                                                     | 13/85 | 69/255 | 0.52<br>(0.29, 0.94) | 6/85 | 43/255 | 0.38<br>(0.16, 0.89) |
| Exclusions above + excluding patients who: were on Stratum 2, received < 6 cycles of immunotherapy, received DFMO on EC* | 10/78 | 42/156 | 0.43<br>(0.21, 0.85) | 4/78 | 28/156 | 0.26<br>(0.09, 0.73) |

HR, hazard ratio; CI, confidence interval; EC, external control; \* 2:1 match

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

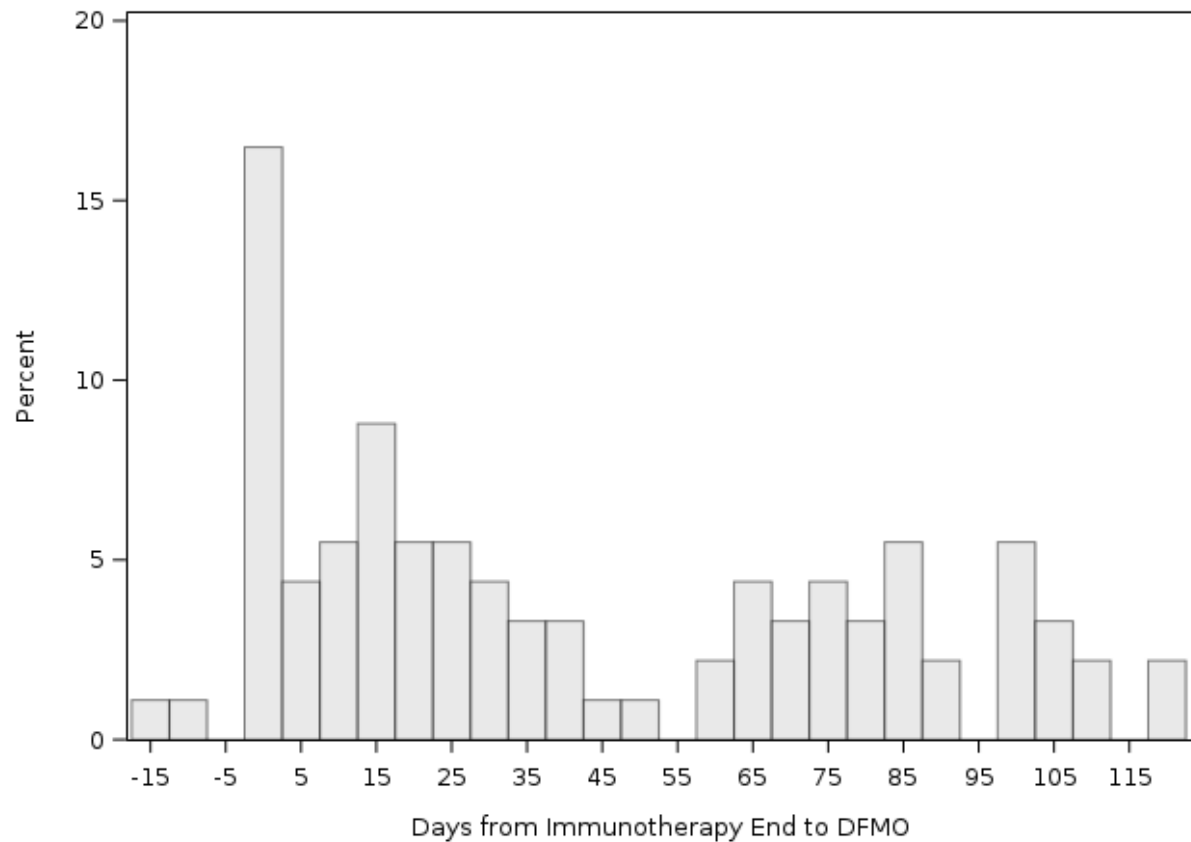
In general, the estimation of treatment effects on EFS and OS, when evaluating the impact of the choice of index date or variations in order of treatments received, seems to be consistent with the effect observed in the Applicant's proposed primary analyses of these endpoints.

### Analyses to assess impact of immortal time bias

When index date is not determined by randomization or a fixed event with little opportunity for inconsistency across arms (such as date of diagnosis), there may be concerns regarding immortal time and its associated bias. In the case of this ECT, for patients enrolled in Study 3(b), the period from end of immunotherapy until the start of DFMO is considered immortal time. If patients had an event during this window, they would not have qualified for enrollment on Study 3(b). To account for this concern when developing the protocol and SAP for the ECT, eligibility criteria were applied such that patients on the control arm would not be included if they had an EFS event within the median observed immortal time for the DFMO arm, which was calculated to be 31 days (see Figure 34 for a histogram of the time from the end of immunotherapy to DFMO initiation on the investigational arm). The intent of this exclusion criterion was to limit the impact of immortal time bias; however, since the immortal time period during which a patient on the DFMO arm would be required to be event-free and alive could be longer for half of the patients on the investigational arm, an additional sensitivity analysis was conducted to explore this potential bias. The analysis, presented in Table 34, presents a conservative approach to immortal time which excluded patients from Study ANBL0032 who had an EFS time within the maximum possible immortal time period (123 days from index date).

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**Figure 34. Histogram of time from index date (end of immunotherapy) to DFMO initiation for patients on the investigational arm**

Source: FDA Analysis using Applicant submitted datasets in NDA 215500 (3bvanbl0032 ADTTE)

**Table 34. Sensitivity Analysis of EFS and OS to Assess the Impact of Immortal Time – Propensity Score Matched (3:1)**

|  | Event-free Survival |                        |                | Overall Survival |                            |                |
|--|---------------------|------------------------|----------------|------------------|----------------------------|----------------|
|  | DFMO<br>Events/N    | NO<br>DFMO<br>Events/N | HR<br>(95% CI) | DFMO<br>Events/N | NO<br>DFMO<br>Events/<br>N | HR<br>(95% CI) |

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|                                                  |       |        |                      |      |        |                      |
|--------------------------------------------------|-------|--------|----------------------|------|--------|----------------------|
| Primary Analysis                                 | 14/90 | 79/270 | 0.48<br>(0.27, 0.85) | 7/90 | 57/270 | 0.32<br>(0.15, 0.70) |
| Excluding controls<br>with EFS time <123<br>days | 14/90 | 72/270 | 0.54<br>(0.31, 0.96) | 7/90 | 45/270 | 0.43<br>(0.19, 0.96) |

HR, hazard ratio; CI, confidence interval

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

Overall, the index date selection appeared to be appropriate, supported by a sensitivity analysis using another relevant date (e.g., last antibody therapy drug administration date) as index date (results presented in Table 33 in the above section). Additionally, the estimation of treatment effects on EFS and OS using the conservative sensitivity analysis, intending to minimize the impact of immortal time, appeared to be consistent with the estimation of treatment effect observed in the Applicant's proposed primary analyses.

### Analyses to assess impact of treatment era

Study ANBL0032 enrolled patients from 2004 to 2015, whereas Study 3(b) enrolled patients from 2012 to 2016. Due to potential differences in supportive care by treatment era, analyses were performed including only patients on the control arm who were enrolled on Study ANBL0032 in 2011 or later, which would include only those patients completing an approximate 6-month course of immunotherapy (+ up to 120 days per Study 3(b) eligibility criteria) in approximately 2012 or later. FDA performed an analysis of contemporaneous populations across treatment arms by including only patients in Study ANBL0032 with index dates after March 22, 2012 (end of immunotherapy for first patient enrolled on Study 3(b)). Analyses of demographic and clinical characteristics of external control patients enrolled before and after March 22, 2012 do not indicate any substantial differences in these two populations. The estimation of treatment effects on EFS and OS endpoints in the two contemporaneous populations (Table 35), as defined by the Applicant and by the FDA per index date, appeared to be consistent with the Applicant's proposed primary analyses results. The Kaplan-Meier plots of EFS and OS in the contemporaneous population per index date are provided in Figure 35.

**Table 35. Sensitivity Analysis of EFS and OS to Assess the Impact of Treatment Era – Propensity Score Matched (3:1)**

|  | Event-free Survival |                        |                | Overall Survival |            |                |
|--|---------------------|------------------------|----------------|------------------|------------|----------------|
|  | DFMO<br>Events/N    | NO<br>DFMO<br>Events/N | HR<br>(95% CI) | DFMO<br>Events/N | NO<br>DFMO | HR<br>(95% CI) |

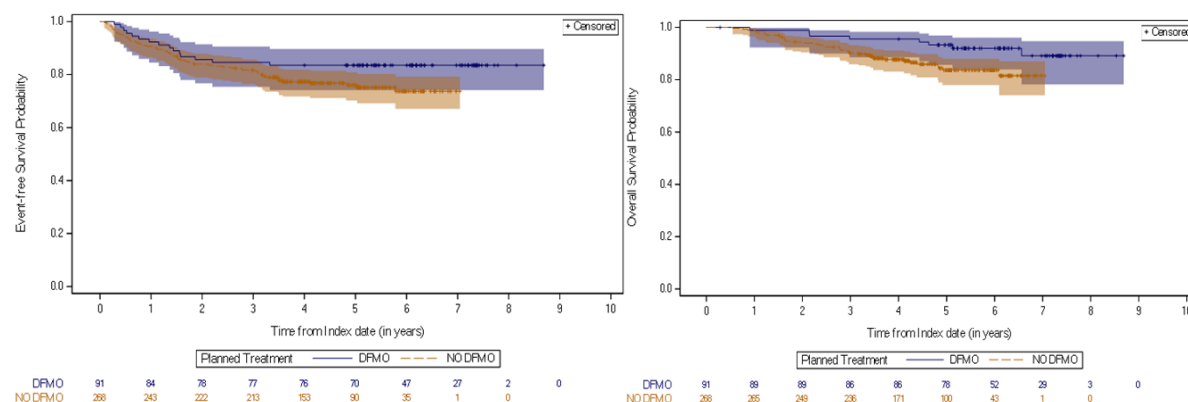
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|                                                                   |       |        |                      |      | Events/<br>N |                      |
|-------------------------------------------------------------------|-------|--------|----------------------|------|--------------|----------------------|
| Primary Analysis                                                  | 14/90 | 79/270 | 0.48<br>(0.27, 0.85) | 7/90 | 57/270       | 0.32<br>(0.15, 0.70) |
| Excluding controls<br>enrolled on<br>ANBL0032 prior to<br>2011    | 15/91 | 71/273 | 0.57<br>(0.33, 1.00) | 8/91 | 46/273       | 0.39<br>(0.18, 0.84) |
| Excluding controls<br>with index dates prior<br>to March 22, 2012 | 15/91 | 64/268 | 0.63<br>(0.36, 1.11) | 8/91 | 39/268       | 0.45<br>(0.21, 0.98) |

HR, hazard ratio; CI, confidence interval

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

**Figure 35. Kaplan-Meier Plots of EFS (left) and OS (right) in the Contemporaneous Population Per Index Date- Propensity Score Matched (3:1)**

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

**Analyses to assess impact of potential bias due to geographic region or site**

In a Clinical Information Amendment submitted by the Applicant via email on April 12, 2023, the Applicant provided additional sensitivity analyses of EFS in patients enrolled on ANBL0032 at sites that did vs. did not contribute patients to the DFMO arm. The EFS outcomes were

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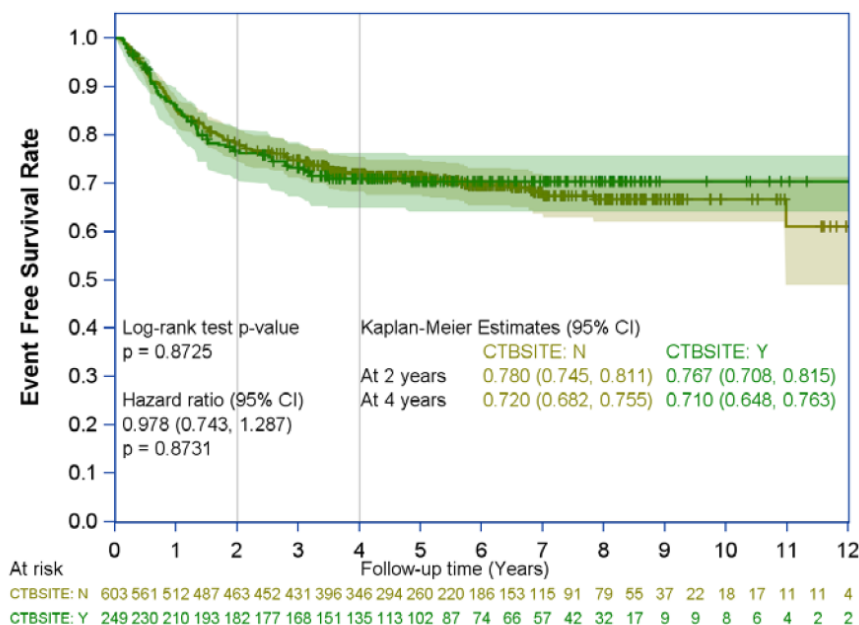
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comparable between the two groups (Figure 36, Figure 37).

In addition, the Applicant provided summary information regarding site of enrollment, including the following:

- 231 of 270 patients (86%) in the matched control arm were enrolled on ANBL0032 in the United States
- 767 of 852 patients (90%) in the overall NO DFMO group were enrolled on ANBL0032 at sites located in North America (US and Canada), while the remaining 85 patients (10%) were treated at sites located in Australia and New Zealand.

**Figure 36. Applicant Analysis of Event Free Survival in Overall NO DFMO Analysis Population (N=852) Patient Subsets at ANBL0032 Sites that Contributed vs. Did Not Contribute to DFMO PER COG group**



Note: CTBSITE represents patients at sites that contributed (Y) or did not contribute (N) patients to the DFMO PER COG (n=92) group.

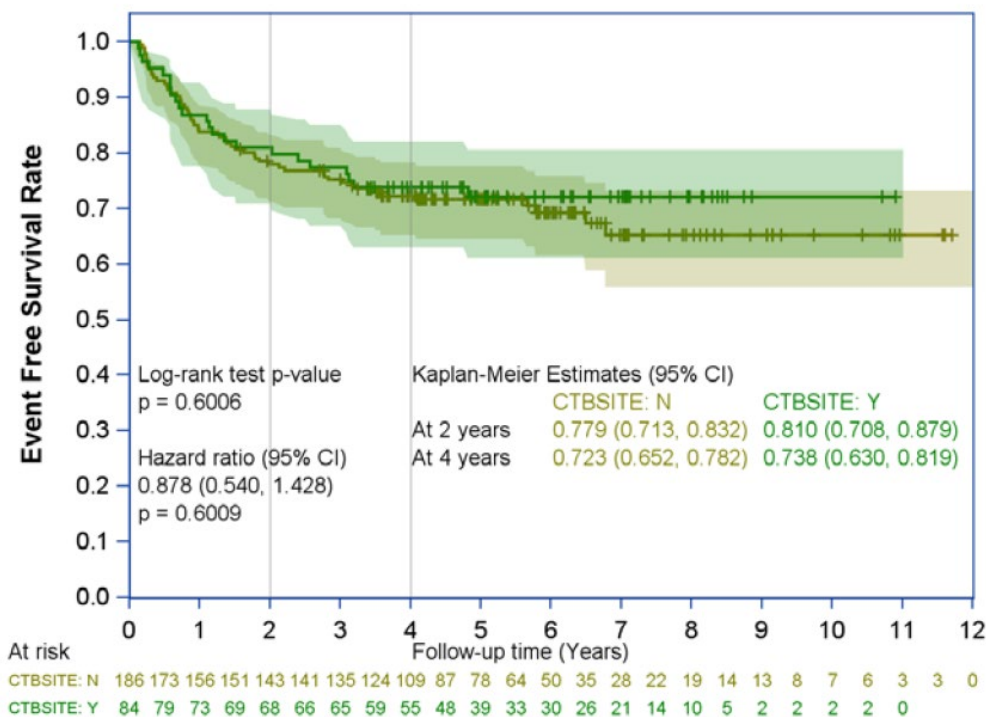
Source: Applicant provided Clinical Information Amendment submitted by email on April 12, 2023

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**Figure 37. Applicant Analysis of Event Free Survival in Primary Matched NO DFMO Analysis Population (N=270) Patient Subsets at ANBL0032 Sites that Contributed vs. Did Not Contribute to DFMO PER COG group**



Source: Applicant provided Clinical Information Amendment submitted by email on April 12, 2023

These results indicate that the site of enrollment is unlikely to be a source of bias in the analysis of EFS in this externally controlled trial.

To further assess the impact of geography, FDA performed sensitivity analyses of EFS and OS (Table 36) using the same approach as the Applicant's proposed primary analysis, however, matching was done after excluding non-US patients from the control arm and an exact matching of patients was done for census region in addition to MYCN status. The efficacy results appear to be consistent with the Applicant's proposed primary analysis result. FDA also conducted a sensitivity analysis of EFS and OS using patients in both arms who received immunotherapy at common clinical study sites. Efficacy results from these analyses, EFS HR: 0.60 (95% CI: 0.23,

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1.54) and OS HR: 0.15 (95% CI: 0.02, 1.28), were supportive of the results from the Applicant's proposed primary analysis. Notably, restricting patients to the same site of immunotherapy receipt resulted in a smaller group of treated (N=78) and control patients (N=148), which may impact the ability to balance potential confounding factors using matching. The matching ratio was accordingly reduced to 1:1. Additionally, there were 64 total deaths in the primary analysis, and this sensitivity analysis includes only 14 deaths due to the smaller matched population. Given the smaller sample size, the results from both of these EFS and OS sensitivity analyses should be interpreted with caution, especially for the OS analysis given the limited events and the resulting increased variability. However, both analyses result in hazard ratios that are consistent in magnitude and direction of treatment effect, providing support for the observed results of the primary analysis.

**Table 36. Sensitivity Analysis of EFS and OS to Assess the Impact of Geographic Region – Propensity Score Matched (3:1)**

|                                             | Event-free Survival |                            |                      | Overall Survival     |                        |                      |
|---------------------------------------------|---------------------|----------------------------|----------------------|----------------------|------------------------|----------------------|
|                                             | DFMO<br>Events/N    | NO<br>DFMO<br>Events/<br>N | HR<br>(95% CI)       | DFMO<br>Events/<br>N | NO<br>DFMO<br>Events/N | HR<br>(95% CI)       |
| Primary Analysis                            | 14/90               | 79/270                     | 0.48<br>(0.27, 0.85) | 7/90                 | 57/270                 | 0.32<br>(0.15, 0.70) |
| Restricting control patients only from USA* | 12/88               | 75/264                     | 0.43<br>(0.23, 0.79) | 5/88                 | 48/264                 | 0.29<br>(0.11, 0.72) |

HR, hazard ratio; CI, confidence interval

\*Patients were exactly matched on Census region and MYCN status

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE & ADSL

### **Analyses to assess impact of potential bias due to investigator assessments of EFS: analysis based on blinded independent central review (BICR) of imaging**

As discussed in Section 8.1.2, in order to account for potential bias in the local evaluator assessed outcomes, a blinded independent central review was conducted for patients in the investigational arm. Source imaging was not available to conduct a similar BICR assessment for external control arm patients. However, as BICR assessment is generally more conservative than

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investigator assessment, we would anticipate that an analysis that includes BICR assessment for the experimental arm and local evaluator assessment for the control arm would be biased towards the null. In the analysis considering BICR assessment for the DFMO arm only, the hazard ratio for EFS was 0.49 (95% CI: 0.27, 0.89). Two patients on the DFMO arm were considered ineligible by the FDA and were excluded from this analysis.

Twenty-five patients had an equivocal imaging result at any time point. Of these, there were seven instances in which the last event was equivocal per two BICR readers (Table 37), and four instances when an equivocal event preceded an unequivocal event for the same lesion per at least one BICR reader (Table 38). The other equivocal events were isolated and only considered equivocal by one reader (the other reader determined no event). In addition, according to FDA's review, two patients had a baseline assessment of "ineligible" per BICR (b) (6) and (b) (6). Refer to Section 8.1.2 for further discussion of the BICR results including equivocal events.

**Table 37. Patients with last event determined equivocal per two BICR readers (N=7)**

| Patient ID | Details regarding imaging as assessed by BICR                                                                                                                                                                                                                                                                                                                     |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (b) (6)    | No event on imaging until (b) (6) when both BICR readers called equivocal event for indeterminate L3 vertebral body marrow signal abnormality                                                                                                                                                                                                                     |
| (b) (6)    | No event on imaging until (b) (6) when both BICR readers called equivocal event for a new enhancing right liver lesion greater than 12 mm on MR and ultrasound was not definitive for an FNH or metastasis; MIBG negative                                                                                                                                         |
| (b) (6)    | No event on imaging until (b) (6) when both BICR readers called equivocal event new enhancing foci in peripheral liver on CT; no metabolic imaging; follow-up imaging needed                                                                                                                                                                                      |
| (b) (6)    | No event on imaging until (b) (6) when both BICR readers called equivocal event for liver lesion, then subsequent imaging with new S2 vertebral lesion. The patient continued to have "equivocal EFS event" through (b) (6)                                                                                                                                       |
| (b) (6)    | One BICR reader called an equivocal event on (b) (6) for new 5 mm left perifissural lung nodule; then no event until both BICR readers called equivocal event on (b) (6) for equivocal abnormal signal in L4 left posterior, similar foci with diffusion restriction in pelvis; "might be old remnants / non vital localizations; we need MIBG or FDG to be sure" |
| (b) (6)    | No event on imaging until (b) (6) when both BICR readers called equivocal event for new enhancing lesion in the left iliac bone; no MIBG or PET to correlate                                                                                                                                                                                                      |

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|         |                                                                                                                                                                 |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (b) (6) | No event on imaging until (b) (6) when both BICR readers called equivocal event for enlarging liver lesions from TP6 to TP7, equivocal for benign vs. malignant |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|

Source: FDA Analysis of BICR datasets submitted in NDA 215500

**Table 38. Patients with equivocal events preceding an unequivocal event for the same lesion per at least one BICR reader (N=4)**

| Patient ID | Details regarding imaging as assessed by BICR                                                                                                                                                                                                                                                                                                       |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (b) (6)    | EFS event of relapse determined by BICR and LE on (b) (6) however, one BICR reader identified an unequivocal event on (b) (6) with a developing right maxillary soft tissue mass near a dentigerous cyst which was positive on MIBG; this is the same lesion later identified on (b) (6) as unequivocal by two BICR readers and the local evaluator |
| (b) (6)    | EFS event of relapse determined by BICR on (b) (6); EFS event of “alive with no event” determined by LE on (b) (6); however, on (b) (6), two BICR readers determined an equivocal event for new hyperenhancing liver lesions (this is the same location as lesions later identified as unequivocal by two BICR readers)                             |
| (b) (6)    | EFS event of relapse determined by BICR on (b) (6); EFS event of relapse determined by LE on (b) (6); however, one BICR reader identified an unequivocal event on (b) (6) with a new >10 mm lesion in sphenoid bone/skull base (this is the same lesion later identified as unequivocal)                                                            |
| (b) (6)    | EFS event of equivocal relapse determined by BICR on (b) (6); EFS event of “alive with no event” determined by LE on (b) (6) however, on (b) (6), one BICR reader identified an unequivocal event with new liver lesions.                                                                                                                           |

Source: FDA Analysis of BICR datasets submitted in NDA 215500

To determine the impact of these discrepancies in assessment, FDA performed a sensitivity analysis considering the 11 equivocal events, described above, as an event and excluding the two patients who were considered as BICR ineligible (Table 39). Notably, some patients who were considered to have an event in this sensitivity analysis were alive with no event as per last follow up, and the results are likely to be conservative. An attenuation of estimation of treatment effect on EFS was observed in this analysis; however, observed results appeared to be directionally consistent with the results from the primary analysis.

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**Table 39. Sensitivity Analysis of EFS and OS to Assess Potential Bias Due to Investigator assessments of EFS – Propensity Score Matched (3:1)**

|                                                                                                                         | Event-free Survival |                        |                      | Overall Survival |                        |                      |
|-------------------------------------------------------------------------------------------------------------------------|---------------------|------------------------|----------------------|------------------|------------------------|----------------------|
|                                                                                                                         | DFMO<br>Events/N    | NO<br>DFMO<br>Events/N | HR<br>(95% CI)       | DFMO<br>Events/N | NO<br>DFMO<br>Events/N | HR<br>(95% CI)       |
| Primary Analysis                                                                                                        | 14/90               | 79/270                 | 0.48<br>(0.27, 0.85) | 7/90             | 57/270                 | 0.32<br>(0.15, 0.70) |
| Changing EFS time to equivocal event time per BICR regardless of INV event (11 patients from Table 37 and Table 38)*    | 22/88               | 79/264                 | 0.75<br>(0.46, 1.20) | 13/88            | 79/264                 | 0.30<br>(0.13, 0.71) |
| Changing EFS time to equivocal event time per BICR for patients with later unequivocal events (4 patients in Table 38)* | 15/88               | 79/264                 | 0.52<br>(0.30, 0.90) | 6/88             | 53/264                 | 0.30<br>(0.13, 0.71) |

HR, hazard ratio; CI, confidence interval; BICR, blinded independent central review; \*2 BICR ineligible patients were excluded

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

### Analyses to assess potential residual confounding

Although many important demographic and clinical covariates were measured and accounted for in the propensity score model to control for confounding, bias due to residual confounding of these measured covariates may still be a concern. The potential for residual confounding was assessed by closely examining the balance in the treatment populations after propensity score matching, examining the results of the efficacy analyses in subgroups defined by observed covariate, and exploring the relationship between each observed covariate and the censoring mechanism for EFS, as described in the following paragraphs.

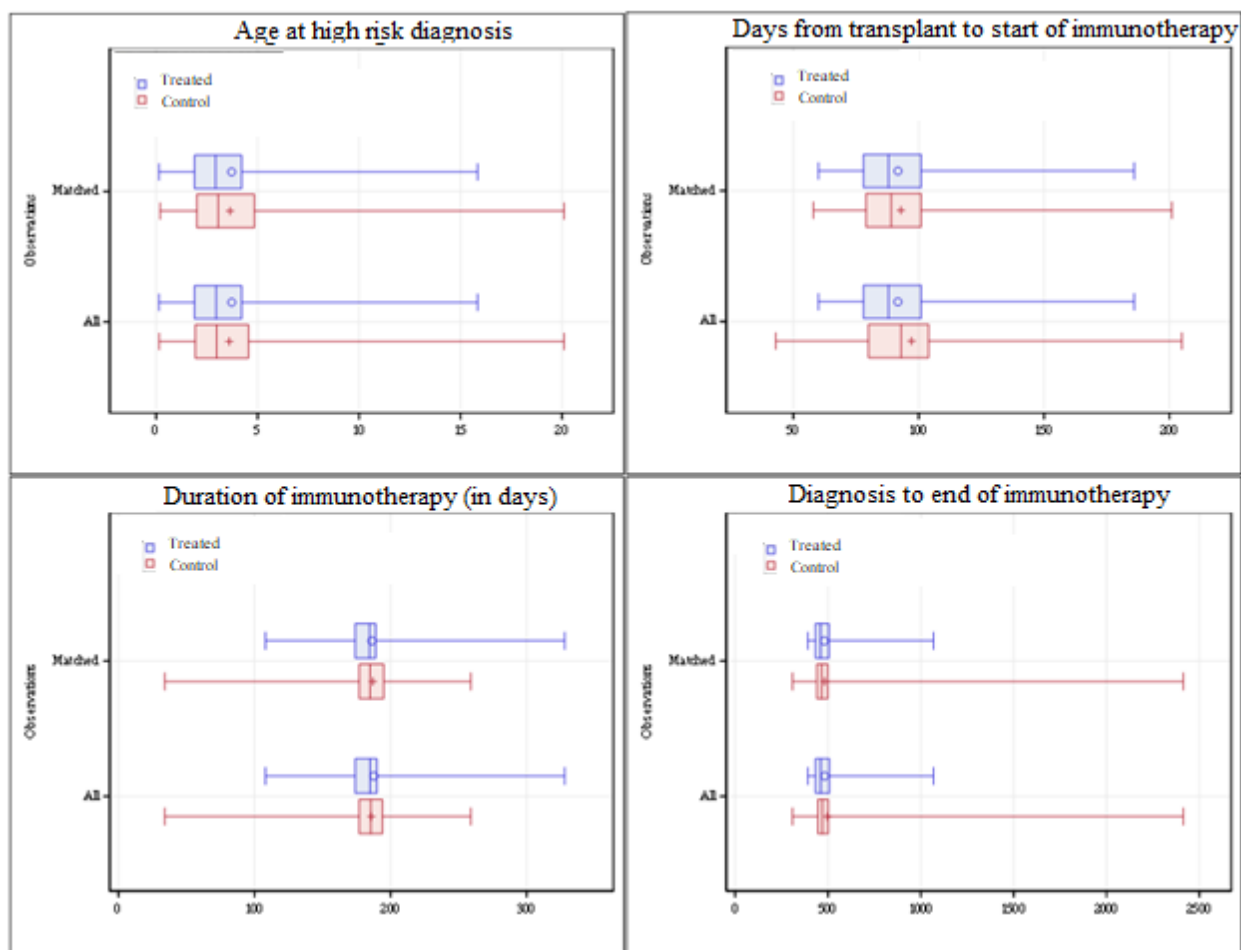
As shown in Table 26 and Figure 27, the distributions of measured clinical covariates included in the propensity score model were well balanced between arms after propensity score matching. Individual plots depicting the balance before and after matching are provided in Figure 38. There were also similar distributions after matching for other clinical covariates what were collected

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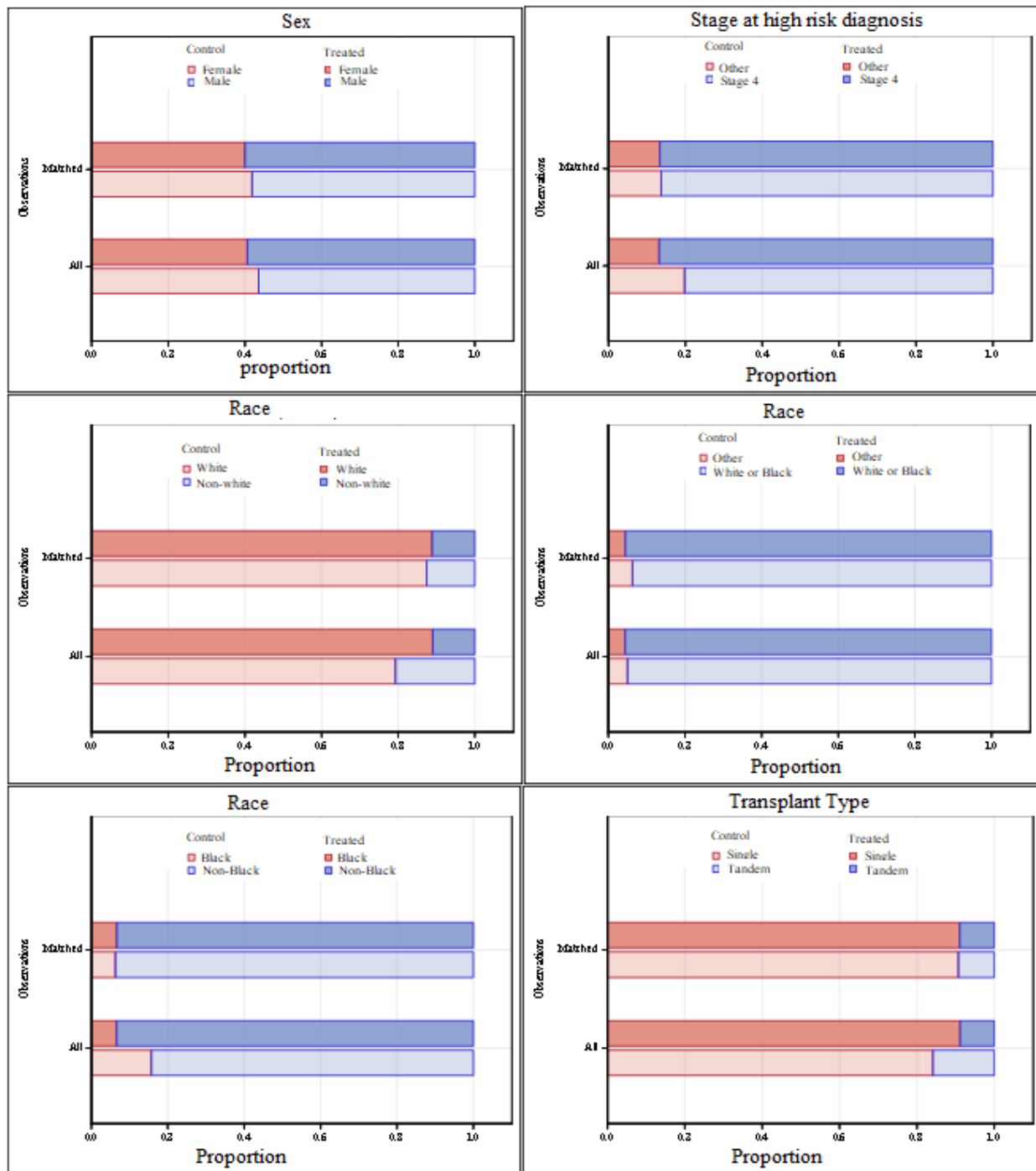
with minimal missing data, but not included in the propensity score model, indicating that the propensity score matching does achieve some balance in the primary analysis population across measured covariates.

**Figure 38. Plots for Individual Covariates in the Propensity Score Model**



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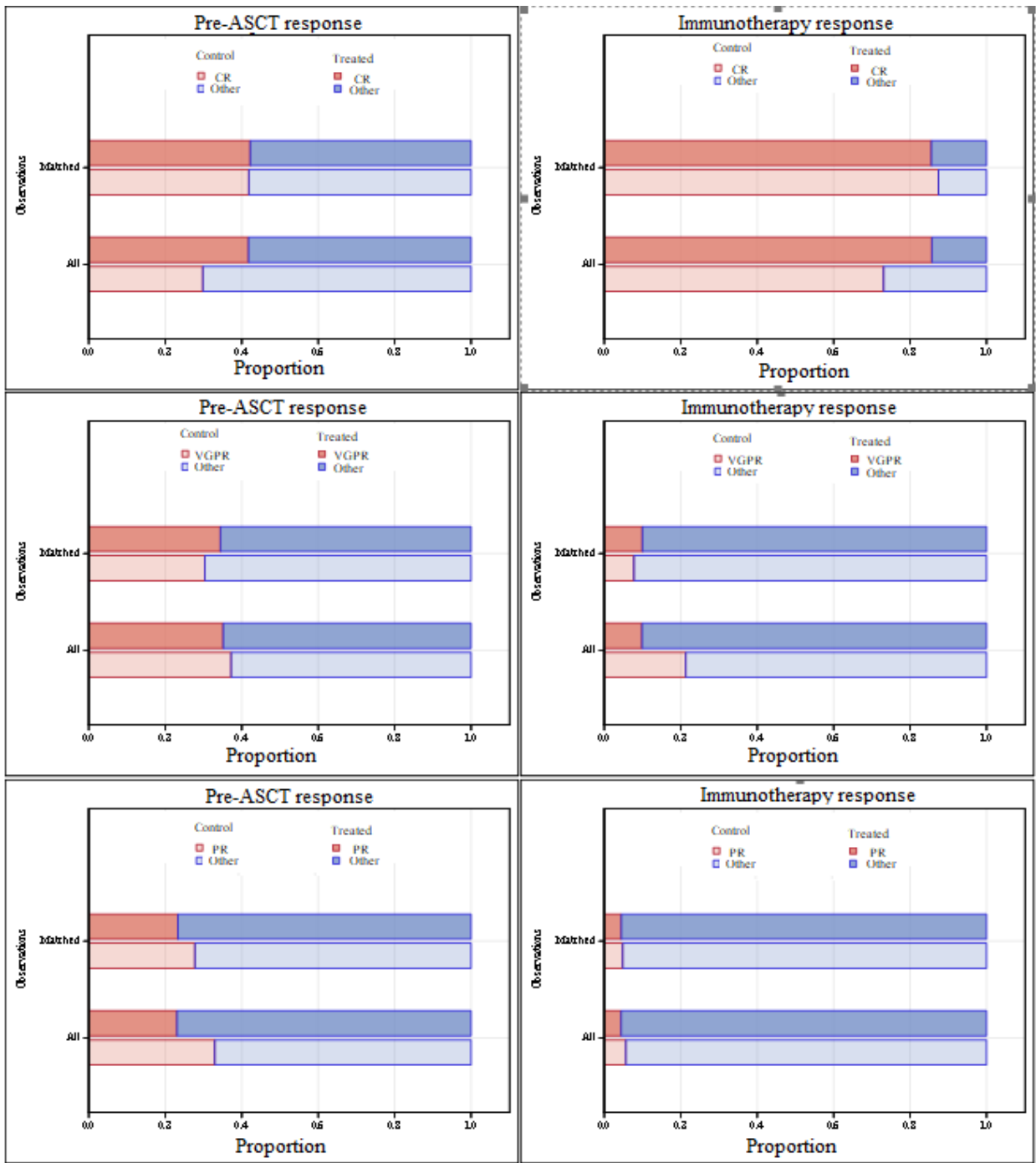


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Given the observed balance achieved by propensity score matching, exploratory subgroup analyses of the primary and key secondary efficacy variables were explored to identify potential factors which could result in a modification of the effect. Subgroups were defined by categories of the covariates included in the propensity score model as well as other measured patient demographics and disease characteristics. Any subgroup with substantially different results may indicate the potential for residual confounding or treatment effect modification. These analyses, considered exploratory, are provided in Table 40.

**Table 40. Subgroup Analyses Using Applicant Proposed Primary Analysis Population and Propensity Score Matching**

| Variables                        | EFS HR (95% CI)   | OS HR (95% CI)    |
|----------------------------------|-------------------|-------------------|
| Sex                              |                   |                   |
| Female (n=149)                   | 0.38 (0.13, 1.08) | 0.15 (0.02, 1.12) |
| Male (n=211)                     | 0.54 (0.27, 1.06) | 0.39 (0.16, 0.92) |
| Age (in months)                  |                   |                   |
| < 18 (n=58)*                     | ---               | ---               |
| ≥ 18 (n=302)                     | 0.49 (0.28, 0.87) | 0.31 (0.14, 0.69) |
| Race                             |                   |                   |
| White (n=316)                    | 0.50 (0.27, 0.92) | 0.29 (0.11, 0.73) |
| Black or African American (n=23) | 0.32 (0.04, 2.53) | 0.23 (0.03, 1.96) |
| Other (n=21)                     | 0.64 (0.08, 5.32) | 0.76 (0.08, 6.98) |
| Pre-ASCT response                |                   |                   |
| CR (n=151)                       | 1.10 (0.49, 2.47) | 0.74 (0.21, 2.66) |
| PR (n=96)                        | 0.20 (0.05, 0.83) | 0.11 (0.02, 0.83) |
| VGPR (n=113)                     | 0.32 (0.11, 0.92) | 0.34 (0.10, 1.13) |
| Transplant type                  |                   |                   |
| Single (n=327)                   | 0.51 (0.29, 0.91) | 0.34 (0.16, 0.76) |

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|                                              |                   |                   |
|----------------------------------------------|-------------------|-------------------|
| Tandem (n=33)*                               | ---               | ---               |
| Stage                                        |                   |                   |
| Stage 4 (n=311)                              | 0.46 (0.26, 0.83) | 0.29 (0.12, 0.67) |
| Other (n=49)                                 | 0.78 (0.09, 6.99) | 0.84 (0.09, 8.39) |
| End of immunotherapy status                  |                   |                   |
| CR (n=313)                                   | 0.54 (0.31, 0.96) | 0.35 (0.16, 0.78) |
| PR/ VGPR (n=47)*                             | ---               | ---               |
| MYCN                                         |                   |                   |
| Not amplified (n=200)                        | 0.57 (0.29, 1.13) | 0.44 (0.19, 1.06) |
| Amplified (n=160)                            | 0.34 (0.12, 0.97) | 0.12 (0.02, 0.87) |
| Time from transplant to immunotherapy (days) |                   |                   |
| < 88 (n=167)                                 | 0.48 (0.20, 1.12) | 0.29 (0.09, 0.95) |
| ≥ 88 (n=193)                                 | 0.48 (0.22, 1.01) | 0.36 (0.13, 1.01) |
| Duration of immunotherapy (days)             |                   |                   |
| < 185 (n=153)                                | 0.45 (0.20, 1.02) | 0.34 (0.12, 0.98) |
| ≥ 185 (n=207)                                | 0.50 (0.23, 1.11) | 0.28 (0.09, 0.91) |
| Diagnosis to end of immunotherapy (days)     |                   |                   |
| < 464 (n=178)                                | 0.44 (0.20, 0.97) | 0.26 (0.08, 0.85) |
| ≥ 464 (n=182)                                | 0.54 (0.24, 1.20) | 0.41 (0.14, 1.17) |

EFS, event-free survival; OS, overall survival; HR, hazard ratio; CR, complete response; PR, partial response; VGPR, very good partial response

\*For subgroups where there were 0 events, the hazard ratio was not estimable

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

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While there were no clear examples of effect modification within the results of these subgroup analyses, the HR results of the exploratory analyses of EFS and OS of 1.10 and 0.74, respectively, in the subgroup of patients who had a pre-ASCT response of complete response were higher than in the Applicant's proposed primary analysis for the overall population. There are limitations associated with small exploratory subgroup results and these results should be interpreted with caution. However, the results of the analyses stratified by pre-ASCT response group may indicate that pre-ASCT response modifies the association between eflornithine and study endpoints, though it is unclear why the exploratory EFS and OS HRs in patients who attained a pre-ASCT response of CR were higher than both the Applicant's proposed primary analysis and those who attained a pre-ASCT response of VGPR or PR in the same exploratory analysis. FDA considers it unlikely that the EFS HR for patients with pre-ASCT response represent a detrimental effect on EFS; however, these results may indicate that patients with a pre-ASCT response of CR experience less benefit from DFMO than patients with pre-ASCT response of PR or VGPR. Given the exploratory nature of these subgroup analyses, results should be interpreted with caution.

Lastly, to assess whether any individual variable was associated with the censoring mechanism for EFS, univariable Cox proportional hazards regression for the censoring indicator were considered. Modelling was conducted for all covariates included in the propensity score model, except for race due to the very small subgroup of patients who were non-White. These univariable model results, provided in Table 41, indicated that age at diagnosis, pre-ASCT response, and tumor stage may be associated with the EFS censoring mechanism. *MYCN* status may also be associated with the EFS censoring mechanism. While differential censoring based on patient characteristics may introduce bias, because the evaluated covariates were reasonably balanced across Study 3(b) and ANBL0032, the potential for bias is likely small.

**Table 41. Assessment of predictors of censoring mechanism for EFS considering censoring an event in the univariable Cox regression model**

| Variables         | HR   | p-value |
|-------------------|------|---------|
| Sex               |      |         |
| Female            | 0.86 | 0.334   |
| Male (reference)  | ---  | ---     |
| Pre-ASCT response |      |         |
| PR                | 2.15 | 0.0002  |

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|                                              |      |         |
|----------------------------------------------|------|---------|
| VGPR                                         | 1.62 | 0.023   |
| CR (reference)                               | ---  | ---     |
| Transplant type                              |      |         |
| Tandem                                       | 0.75 | 0.225   |
| Single (reference)                           | ---  | ---     |
| Stage                                        |      |         |
| Stage 4                                      | 1.95 | 0.006   |
| Other (reference)                            | ---  | ---     |
| End of immunotherapy status                  |      |         |
| PR                                           | 1.35 | 0.345   |
| VGPR                                         | 0.98 | 0.931   |
| CR (reference)                               | ---  | ---     |
| <i>MYCN</i> status                           |      |         |
| Not amplified                                | 1.41 | 0.035   |
| Amplified (reference)                        | ---  | ---     |
| Time from transplant to immunotherapy (days) | 1.0  | 0.292   |
| Age at diagnosis (years)                     | 1.14 | <0.0001 |
| Duration of immunotherapy (days)             | 1.0  | 0.684   |
| Diagnosis to end of immunotherapy (days)     | 1.0  | 0.178   |

HR, hazard ratio; CR, complete response; PR, partial response; VGPR, very good partial response

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

To assess the sensitivity of the results of the Applicant's proposed primary analysis to the potential residual confounders, age at diagnosis, pre-ASCT response, tumor stage, and *MYCN*

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status were included as covariates in outcome model for EFS after propensity score matching. The hazard ratio estimated by the propensity score matched and covariate-adjusted model was 0.45 (95% CI: 0.25, 0.80), which was consistent with the Applicant's proposed primary analysis results. This indicates that while there may be some true association between these confounders and the outcome, the propensity score matching may adequately adjust for this association; therefore, likelihood for residual confounding by these measured covariates is minimal.

***FDA analyses to address potential unmeasured confounding***

The Applicant's proposed primary analysis of EFS adjusted for 11 covariates via matching (propensity score or exact) to control for potential population selection bias and bias due to confounding. These covariates were selected from the available measured covariates in the trial with consideration for clinical meaningfulness and completeness of data. However, there may be other clinical covariates that are not measured that have associations with both treatment and outcome (e.g., confounders), and therefore, there may be concerns for bias due to unmeasured confounding. Specifically, the estimation of treatment effect based on matching or adjustment of these known and measured covariates provides some control of bias due to confounding with respect to these measured factors only and confounding by unmeasured factors (known or unknown) may be responsible for bias on the observed treatment effect.

To assess the impact of unmeasured confounding on the estimation of treatment effect FDA conducted two sensitivity analyses. The first considers the E-value (VanderWeele and Ding, 2017), which provides an estimate of the association an unmeasured confounder would have with both treatment and outcome for the observed results to be fully attributable to that confounder, similar to a tipping point analysis. The second considers a method proposed by Lin et al (1998) which provides the expected effect size for the treatment on outcome given assumptions for the differential prevalence an unmeasured confounder would have in each treatment arm and the expected size of the association of that unmeasured confounder with the outcome (which may or may not be differential by treatment arm).

FDA's analysis indicated that using various assumptions for the underlying true treatment effect, the E-value for EFS ranged from 2.7 to 3.6 and the E-value for OS ranged from 3.8 to 5.7. These results suggest that for an unmeasured confounder to tip the results of the EFS analysis from being positive in favor of DFMO to being totally neutral (HR=1), that variable would have to have a risk ratio of at least 2.7 to 3.6 for both treatment assignment and for EFS outcome. The E-value makes minimal assumptions, particularly regarding the underlying structure of the unmeasured confounders distribution with respect to the treatment or outcome; this is an advantage of the E-value method along with the ease of interpretation of the results. However,

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this approach may also be criticized for being overly simplified and not practically applicable to real-world scenarios.

The method proposed by Lin (1998) requires specification of prevalence of an unmeasured confounder in each treatment arm, as well as the relative risk of the outcome associated with that unmeasured confounder. The analytical solution to the proposed method assumes that the relative risk of outcome for the unmeasured confounder is the same for each treatment arm, that the distributions for unmeasured and measured confounders are approximately independent within each treatment arm, that the outcome event is rare or that the association of the unmeasured confounder with time-to-event outcomes is small, and lastly, that the unmeasured confounder is binary.

FDA analyses using this methodology were conducted in two ways. First, FDA considered a variety of scenarios of unmeasured confounders with varying prevalence and strength of associations with the outcome. Second, FDA identified potential unmeasured confounders with evidence of prevalence and strength of association with outcome that emerged from a thorough literature review.

In the first set of analyses, FDA assumed an array for prevalence of the unmeasured confounder, with values in the DFMO arm ranging from 0% to 50% by 10% and values in the control arm ranging from 0 to 100% by 10%. Additionally, FDA assumed 3 potential strengths of association for the unmeasured confounder with the outcome variable: a moderate association (HR = 1.4), a strong association (HR = 2.0), and a very strong association (HR = 5.0), with the last scenario providing an unlikely extreme example of unmeasured confounding. For each of these strengths of association, the model provided the expected EFS hazard ratio for the effect of DFMO across the array of prevalence of the unmeasured confounder in each arm as presented in Table 42, Table 43, and Table 44.

**Table 42. Adjusted Event-free Survival hazard ratios comparing DFMO vs. NO DFMO adjusting for an unmeasured binary confounder having a hazard ratio of 1.4 and the observed hazard ratio in the current trial of 0.48**

|                      | <b>P<sub>1</sub></b> |             |             |             |      |      |
|----------------------|----------------------|-------------|-------------|-------------|------|------|
| <b>P<sub>0</sub></b> | 0.0                  | 0.1         | 0.2         | 0.3         | 0.4  | 0.5  |
| 0.0                  | <b>0.48</b>          | 0.46        | 0.44        | 0.43        | 0.41 | 0.40 |
| 0.1                  | 0.50                 | <b>0.48</b> | 0.46        | 0.44        | 0.43 | 0.41 |
| 0.2                  | 0.52                 | 0.50        | <b>0.48</b> | 0.46        | 0.44 | 0.43 |
| 0.3                  | 0.54                 | 0.52        | 0.50        | <b>0.48</b> | 0.46 | 0.45 |

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|     |      |      |      |      |             |             |
|-----|------|------|------|------|-------------|-------------|
| 0.4 | 0.56 | 0.54 | 0.52 | 0.50 | <b>0.48</b> | 0.46        |
| 0.5 | 0.58 | 0.56 | 0.54 | 0.52 | 0.50        | <b>0.48</b> |
| 0.6 | 0.60 | 0.58 | 0.56 | 0.53 | 0.52        | 0.50        |
| 0.7 | 0.62 | 0.60 | 0.57 | 0.55 | 0.53        | 0.51        |
| 0.8 | 0.64 | 0.62 | 0.59 | 0.57 | 0.55        | 0.53        |
| 0.9 | 0.67 | 0.64 | 0.61 | 0.59 | 0.57        | 0.55        |
| 1.0 | 0.69 | 0.66 | 0.63 | 0.61 | 0.59        | 0.56        |

Note.  $P_1$  and  $P_0$  are the prevalence of the unmeasured confounder in the DFMO arm and in the control arm, respectively.

Source: FDA analysis based on review of NDA 215500

**Table 43. Adjusted Event-free Survival hazard ratios comparing DFMO vs. NO DFMO adjusting for an unmeasured binary confounder having a hazard ratio of 2.0 and the observed hazard ratio in the current trial of 0.48**

|       | $P_1$       |             |             |             |             |             |
|-------|-------------|-------------|-------------|-------------|-------------|-------------|
| $P_0$ | 0.0         | 0.1         | 0.2         | 0.3         | 0.4         | 0.5         |
| 0.0   | <b>0.48</b> | 0.44        | 0.40        | 0.37        | 0.34        | 0.32        |
| 0.1   | 0.53        | <b>0.48</b> | 0.44        | 0.41        | 0.38        | 0.35        |
| 0.2   | 0.58        | 0.52        | <b>0.48</b> | 0.44        | 0.41        | 0.38        |
| 0.3   | 0.62        | 0.57        | 0.52        | <b>0.48</b> | 0.45        | 0.42        |
| 0.4   | 0.67        | 0.61        | 0.56        | 0.52        | <b>0.48</b> | 0.45        |
| 0.5   | 0.72        | 0.65        | 0.60        | 0.55        | 0.51        | <b>0.48</b> |
| 0.6   | 0.77        | 0.70        | 0.64        | 0.59        | 0.55        | 0.51        |
| 0.7   | 0.82        | 0.74        | 0.68        | 0.63        | 0.58        | 0.54        |
| 0.8   | 0.86        | 0.79        | 0.72        | 0.66        | 0.62        | 0.58        |
| 0.9   | 0.91        | 0.83        | 0.76        | 0.70        | 0.65        | 0.61        |
| 1.0   | 0.96        | 0.87        | 0.80        | 0.74        | 0.69        | 0.64        |

Note.  $P_1$  and  $P_0$  are the prevalence of the unmeasured confounder in the DFMO arm and in the control arm, respectively.

Source: FDA analysis based on review of NDA 215500

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**Table 44. Adjusted Event-free Survival hazard ratios comparing DFMO vs. NO DFMO adjusting for an unmeasured binary confounder having a hazard ratio of 5.0 and the observed hazard ratio in the current trial of 0.48**

|                      | <b>P<sub>1</sub></b> |             |             |             |             |             |
|----------------------|----------------------|-------------|-------------|-------------|-------------|-------------|
| <b>P<sub>0</sub></b> | 0.0                  | 0.1         | 0.2         | 0.3         | 0.4         | 0.5         |
| 0.0                  | <b>0.48</b>          | 0.34        | 0.27        | 0.22        | 0.18        | 0.16        |
| 0.1                  | 0.67                 | <b>0.48</b> | 0.37        | 0.31        | 0.26        | 0.22        |
| 0.2                  | 0.86                 | 0.62        | <b>0.48</b> | 0.39        | 0.33        | 0.29        |
| 0.3                  | 1.06                 | 0.75        | 0.59        | <b>0.48</b> | 0.41        | 0.35        |
| 0.4                  | 1.25                 | 0.89        | 0.69        | 0.57        | <b>0.48</b> | 0.42        |
| 0.5                  | 1.44                 | 1.03        | 0.80        | 0.65        | 0.55        | <b>0.48</b> |
| 0.6                  | 1.63                 | 1.17        | 0.91        | 0.74        | 0.63        | 0.54        |
| 0.7                  | 1.82                 | 1.30        | 1.01        | 0.83        | 0.70        | 0.61        |
| 0.8                  | 2.02                 | 1.44        | 1.12        | 0.92        | 0.78        | 0.67        |
| 0.9                  | 2.21                 | 1.58        | 1.23        | 1.00        | 0.85        | 0.74        |
| 1.0                  | 2.40                 | 1.71        | 1.33        | 1.09        | 0.92        | 0.80        |

Note. P<sub>1</sub> and P<sub>0</sub> are the prevalence of the unmeasured confounder in the DFMO arm and in the control arm, respectively.

Source: FDA analysis based on review of NDA 215500

The results of these analyses indicate that with moderate or strong association between the unmeasured confounder and outcome (HR = 1.4 or 2.0), the EFS hazard ratios remained below 1.0 regardless of the disparity in the prevalence of the unmeasured confounder across treatment arms. For example, assuming a moderate association between the unmeasured confounder and EFS (HR = 1.4), even if the prevalence of the unmeasured confounder in the external control arm is 100% and prevalence in the DFMO arm is 0%, the hazard ratio for EFS comparing DFMO to the external control arm would be expected to be 0.69. Even with the most extreme assumption of very strong association between the unmeasured confounder (HR = 5.0), the hazard ratio for EFS comparing DFMO to the external control arm remains below 0.80 when the prevalence of the unmeasured confounder in the external control arm is less than double the prevalence of the DFMO arm.

Having such extreme differences in the prevalence of the unmeasured confounders would be unlikely, particularly for populations that are derived from the same underlying patient population as >90% of patients on the experimental arm were first enrolled on ANBL0032. The results indicate that the potential impact of an unidentified unmeasured confounding variable on the estimation of the treatment effect of this externally controlled study is likely to be low, in the case of reasonable assumptions of unmeasured confounder association with outcome and

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prevalence across arms. However, a limitation of this method is that it provides estimates for each confounder individually, and the composite effect of various multi-layered confounders on the estimate is unknown.

In the second set of analyses using the Lin et al (1998) method, FDA considered the impact of potential confounding factors that were not measured or available in the externally controlled trial which have a known impact on outcome. These analyses attempt to identify how a difference in prevalence of the potential confounding factor could change the estimated treatment effect. A key issue raised by external clinical experts consulted by FDA during review of the application was the absence of information on SDOH which may impact a family's ability to enroll on a clinical study following frontline therapy. Therefore, patients experiencing household poverty may be underrepresented in Study 3(b) compared to patients in ANBL0032. Further, household poverty been demonstrated in the literature to be associated with inferior EFS (HR = 1.9) in patients with HRNB (Bona, 2021).

FDA's approach to this set of analyses assumed a prevalence rate of the specific confounder published in the literature in the investigational arm and at least double the published prevalence in the control arm to evaluate a scenario for high unmeasured confounding. For the example of household poverty, if it is assumed that 35% of patients in the investigational arm and 70% of patients in the control arm experience household poverty, the resulting EFS HR would be 0.59 (95% CI: 0.53, 0.67).

As shown in Table 45, FDA considered the potential impact of other unmeasured potential confounding factors with a known impact on outcomes (EFS or OS) based on published literature. In certain cases, the control arm prevalence was capped at 100% if double the expected prevalence was greater than 100%, or the control arm prevalence was tripled due to low overall expected prevalence. Overall, the hazard ratios remain consistent with the primary analysis even when considering very large differences in prevalence of the confounding factors. Of note, these are based on individual published studies which provide a reasonable basis for estimates but are subject to individual study limitations.

An important limitation to these approaches is that they evaluate the impact of a single unmeasured confounder of interest. It is possible that there could be multiple unmeasured confounders of interest that may be related to not only the exposure and the endpoint, but also to each other as complex interrelated variables in a real-world setting. These methods provide estimates for each confounder individually, and the composite effect of various multi-layered unknown confounders on the estimate is unknown.

**Table 45. FDA Analysis of Impact of Potential Unmeasured Confounding Factors on Treatment Effect Estimates**

| Potential Unmeasured Confounder              |                                  | Supporting Literature | Association with Outcome | Prevalence in DFMO Arm | Prevalence in Control Arm | Adjusted DFMO HR (95% CI) |
|----------------------------------------------|----------------------------------|-----------------------|--------------------------|------------------------|---------------------------|---------------------------|
| Applicant's Proposed Primary Analysis of EFS |                                  |                       |                          |                        |                           | 0.48<br>(0.27, 0.85)      |
| <i>Social Determinants of Health</i>         | Household poverty                | Bona (2021)           | EFS HR = 1.9             | 35%                    | 70%                       | 0.59<br>(0.53, 0.67)      |
|                                              | Neighborhood & household poverty | Bona (2021)           | EFS HR = 2.2             | 14%                    | 42%*                      | 0.62<br>(0.54, 0.71)      |
| <i>Primary Tumor Location</i>                | Adrenal vs. Non-adrenal          | Vo (2014)             | EFS HR = 1.1             | 47%                    | 94%                       | 0.50<br>(0.48, 0.52)      |
|                                              | Non-thoracic vs. Thoracic        | Vo (2014)             | EFS HR = 1.3             | 85%                    | 100%**                    | 0.50<br>(0.49, 0.50)      |
| Applicant's Proposed Primary Analysis of OS  |                                  |                       |                          |                        |                           | 0.32<br>(0.15, 0.70)      |
| <i>Cytogenetics</i>                          | Chromosome 1p deletion           | Bown (1999)           | OS HR = 1.9              | 47%                    | 94%                       | 0.42<br>(0.33, 0.48)      |
|                                              | Chromosome 17q gain              | Bown (1999)           | OS HR = 3.4              | 54%                    | 100%**                    | 0.47<br>(0.39, 0.52)      |

\*Triple prevalence considered due to low expected prevalence; \*\*If double prevalence exceeds 100%, the prevalence is capped to 100%

Source: FDA analysis

### ***FDA analyses addressing multiple sources of bias simultaneously***

In the above sections, the sensitivity of the treatment effect estimate was examined for individual potential sources of bias. However, practically, it would be expected that multiple sources of bias may exist or impact the estimation to treatment effect concurrently. To address this concern, FDA conducted an analysis of EFS and OS that combined the strategies employed in multiple independent sensitivity analyses presented in the above sections to simultaneously address different sources of bias. In particular, this analysis included only those patients on the external control arm who had contemporary index dates to those on the DFMO arm, excluded patients on the DFMO arm who were BICR ineligible, received cis-RA after index date, received investigational treatment DFMO before index date, or were included in the investigational arm but received DFMO on Stratum 2, excluded patients on the external control arm who received

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DFMO during follow-up period or had an EFS time before 75 days (the 75<sup>th</sup> percentile of observed immortal time), excluded patients in both arms who received fewer than 6 cycles of immunotherapy treatment, and excluded patients from outside of US. Additionally, for the 4 patients with equivocal events preceding an unequivocal event for the same lesion per at least one BICR reader, as described in Table 38, EFS time was updated with time to equivocal recurrence.

The efficacy results from this analysis are presented in Table 46 and Figure 39. Addressing several sources of bias with exclusions and adjustments in a single analysis, particularly when considering the potential “worst-case” scenario for several of these factors, is a very conservative approach to estimation of treatment effect. Additionally, this approach results in an overall smaller sample size and a reduced matching ratio of 1:1, as well as potentially reduced power in the estimation of treatment effect. The point estimates of the estimated treatment effect size remain consistent with the Applicant’s proposed primary analysis despite the rigorous and cautious nature of this conservative sensitivity analysis, improving confidence that there is an observed treatment effect of eflornithine in this ECT.

**Table 46: Sensitivity Analysis of EFS and OS with Simultaneous Adjustment for Multiple Potential Sources of Bias– Propensity Score Matched (1:1)**

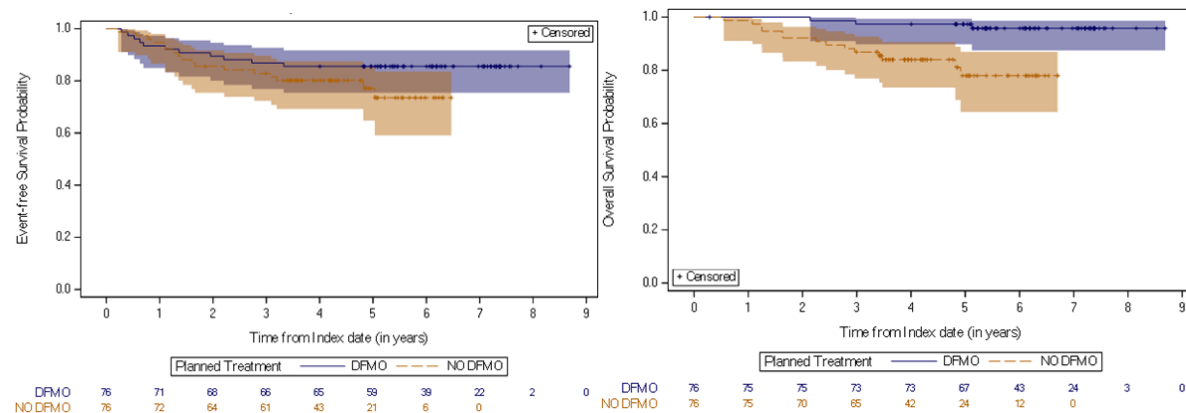
|                                                              | Event-free Survival |                        |                      | Overall Survival |                        |                      |
|--------------------------------------------------------------|---------------------|------------------------|----------------------|------------------|------------------------|----------------------|
|                                                              | DFMO<br>Events/N    | NO<br>DFMO<br>Events/N | HR<br>(95% CI)       | DFMO<br>Events/N | NO<br>DFMO<br>Events/N | HR<br>(95% CI)       |
| Primary Analysis                                             | 14/90               | 79/270                 | 0.48<br>(0.27, 0.85) | 7/90             | 57/270                 | 0.32<br>(0.15, 0.70) |
| Analysis with<br>simultaneous<br>exclusions/adjustment<br>s* | 11/76               | 17/76                  | 0.59<br>(0.28, 1.27) | 3/76             | 14/76                  | 0.16<br>(0.05, 0.57) |

HR, hazard ratio; CI, confidence interval; \*1:1 match due to reduced sample size

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

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**Figure 39. Kaplan-Meier Plots of EFS (left) and OS (right) in the Sensitivity Analysis With Simultaneous Adjustment for Multiple Potential Sources of Bias- Propensity Score Matched (1:1)**

## Data Quality and Integrity

### The Applicant's Position

Data quality and integrity for Study 3b is addressed in Section 8.1.1.

ANBL0032 data were provided under a data transfer agreement with COG. The Applicant performed a comprehensive review of available information to confirm the data were fit for use as an external control to Study 3b. Standard operating procedures related to data management and transfer practices were requested from COG but could not be obtained. To independently verify the integrity of the data, the Applicant used the transferred dataset to replicate the results of the ANBL0032 as most recently published in Yu, 2021 and Desai, 2022 for the randomized and non-randomized patients in the study, respectively. Demographics and outcomes analyses were closely or exactly matched to those in the literature, providing confidence that the integrity of the data was preserved during the transfer to and subsequent handling by the Applicant, enabling reliance on the data for the external control comparisons.

### The FDA's Assessment:

FDA agrees with the Applicant's assessment. Inspections conducted by OSI during the review period did not identify any concerns regarding data quality or integrity.

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In particular, OSI inspected Children’s Oncology Group (COG), the consortium which conducted Study ANBL0032 and maintained the database from which data was transferred to USWM to use as an external control database. Regarding the on-site COG inspection, OSI found that data transfer procedures between COG and BCC were followed as planned. No discrepancies were noted between the Study ANBL0032 data database at COG and the data submitted to the NDA for 40 subjects and variables of interest identified by the review team. Specifically, the following were verified:

- COG’s data collection, handling, and management processes and procedures
- Study ANBL0032 data storage, curation, aggregation, and transfer procedures
- The electronic platforms used to store and transfer the data are in compliance with applicable regulations and password protected
- Study ANBL0032 Data Transfer Agreements between COG and BCC/USWM procedures were followed
- Accuracy of the data submitted to the NDA for 40 subjects and variables of interest identified by the review team.

## **Efficacy Results – Secondary and other relevant endpoints**

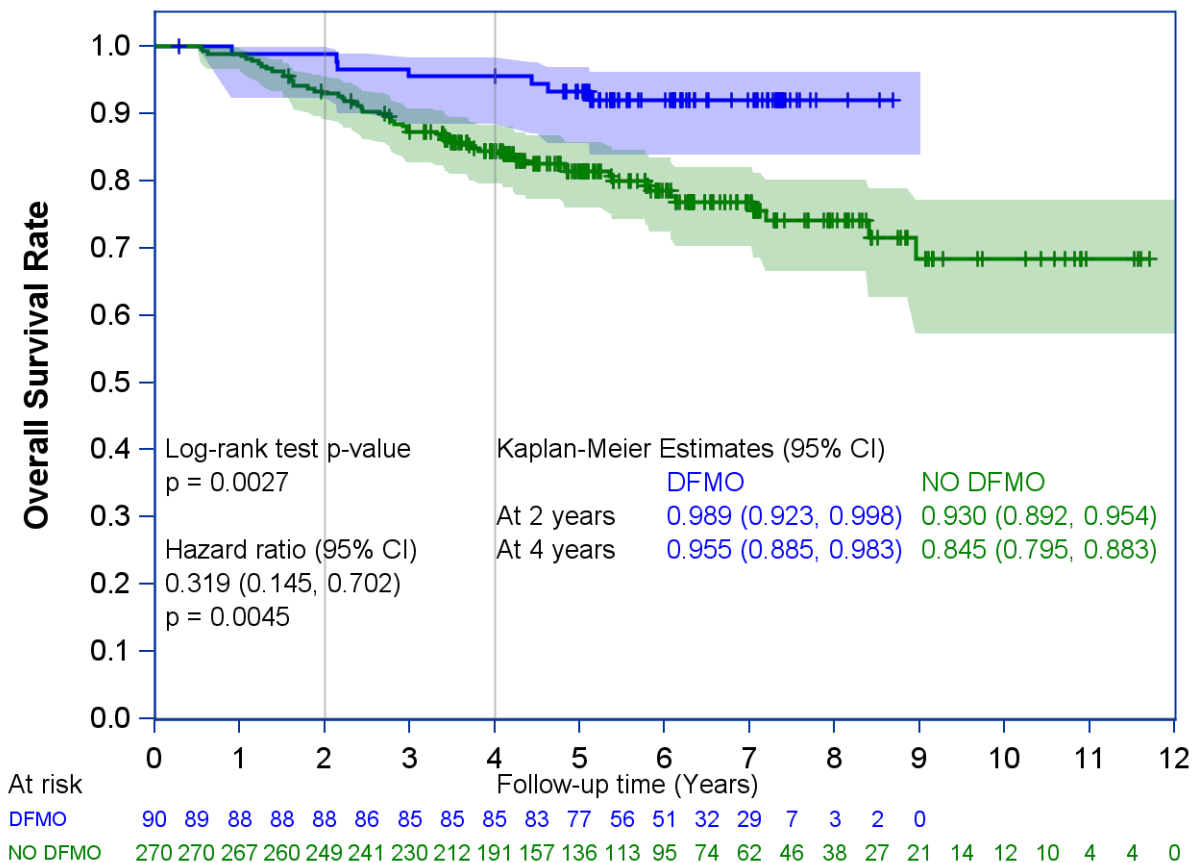
### Data:

#### Key Secondary Endpoint:

Comparison of overall survival in the patients matched for the primary endpoint analysis was a defined key secondary endpoint per the Study 3b vs. ANBL0032 SAP.

Figure 40 presents the results of the overall survival comparison in the same primary Matched groups. The resulting hazard ratio is 0.32 (95% CI 0.145, 0.702) with a p-value of 0.0045.

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**Figure 40: Kaplan-Meier Curve of OS Using PS Matched Samples from DFMO PER COG and NO DFMO (MATCHED) Populations**

Source: Study 3b vs. ANBL0032 Efficacy Report Figure 14.2.1.b

The full complement of sensitivity analyses for the primary EFS analysis were also applied to the overall survival analysis. Results of the OS sensitivity analyses were consistent with the key secondary endpoint results, in terms of hazard ratio and statistical significance.

**Overall Population Comparisons:**

The primary analyses for the comparative analyses employed PSM to address potential sources of bias; however, missing data, primarily in the control database, have the potential to introduce its own source of bias by restricting the eligible matches to those with complete case data. The full explanation for missing covariate data are unknown; however, the most common missing data pattern is for missing MYCN, age, stage, race, and sex. Based on direct exchange with

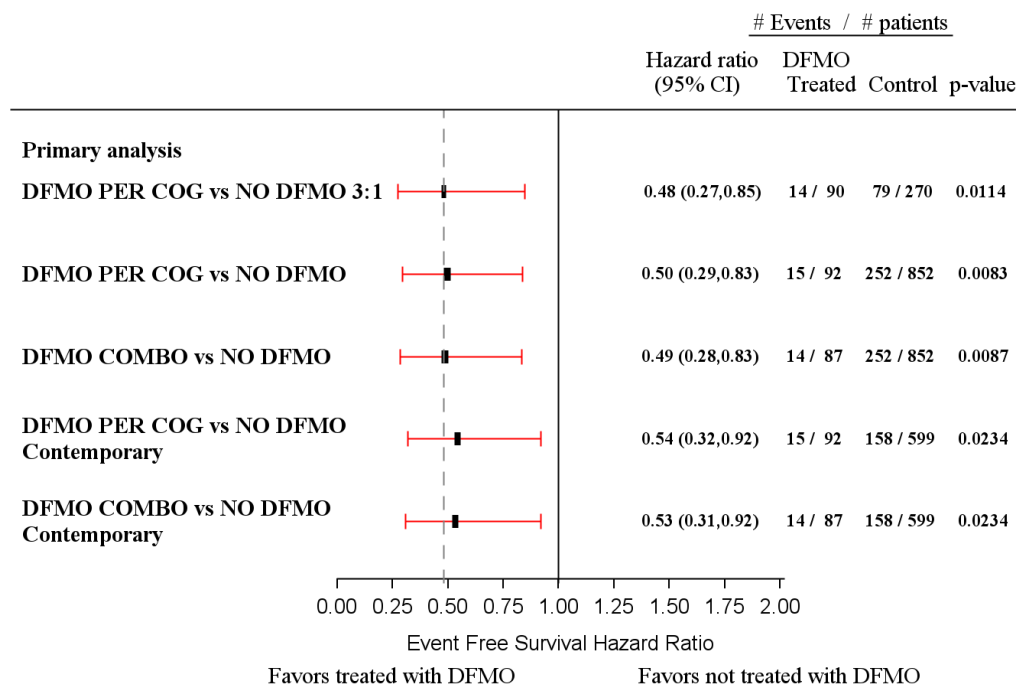
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{Eflornithine [DFMO]}

COG, these covariates were only collected as part of the ANBL00B1 study, a non-interventional biology study for which tumor specimens were collected and characterized. Participation in ANBL00B1 was optional starting with ANBL0032 Amendment 7, and patients that did not participate are missing these five demographic variables. Regardless, all patients included in the NO DFMO group had sufficient data to apply the selection rules and are not missing outcome data. The available data for the overall NO DFMO group supports that the analysis population is consistent with the target patient population for DFMO and all patients in the NO DFMO group had sufficient data to be evaluated against the selection rules for the control analysis population. Thus, comparisons of the overall populations without matching are considered relevant to further characterize the outcome differences between the treated and control groups. EFS outcome comparisons for various combinations of treated and control populations are compared in the forest plot in Figure 41.

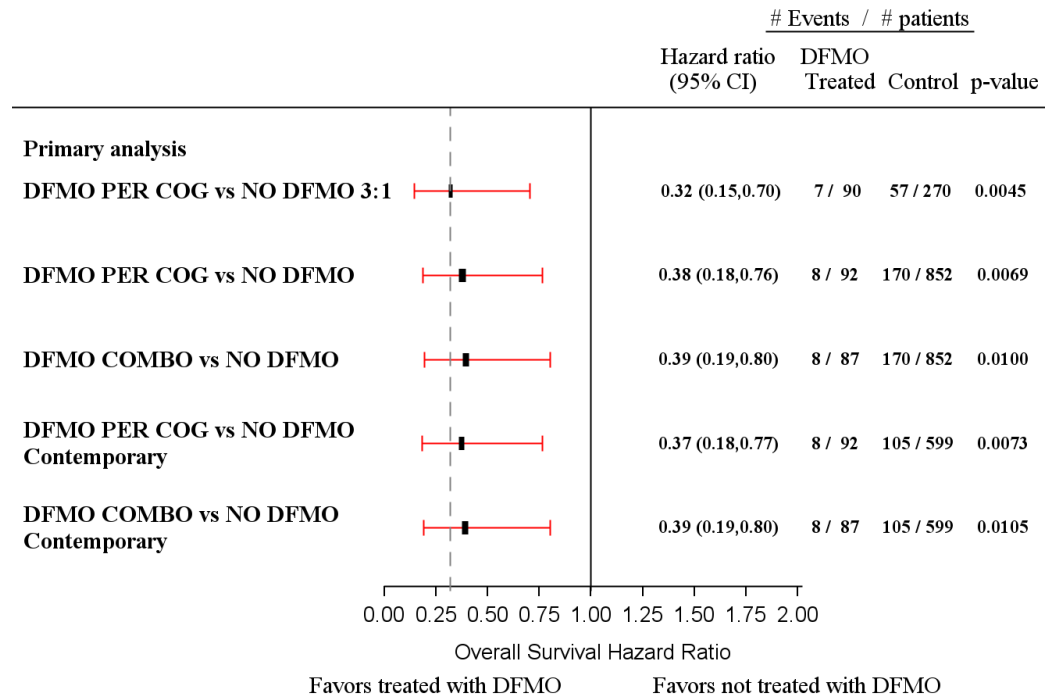
**Figure 41: Forest Plot of Hazard Ratios for Overall Population Comparisons Without Matching (Panel A: Event Free Survival, Panel B: Overall Survival)**

A.



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**B.**

Source: Study 3b vs. ANBL0032 Efficacy Report Figure 14.2.15.7.1 and Figure 14.2.15.7.2

EFS = event free survival; OS = overall survival

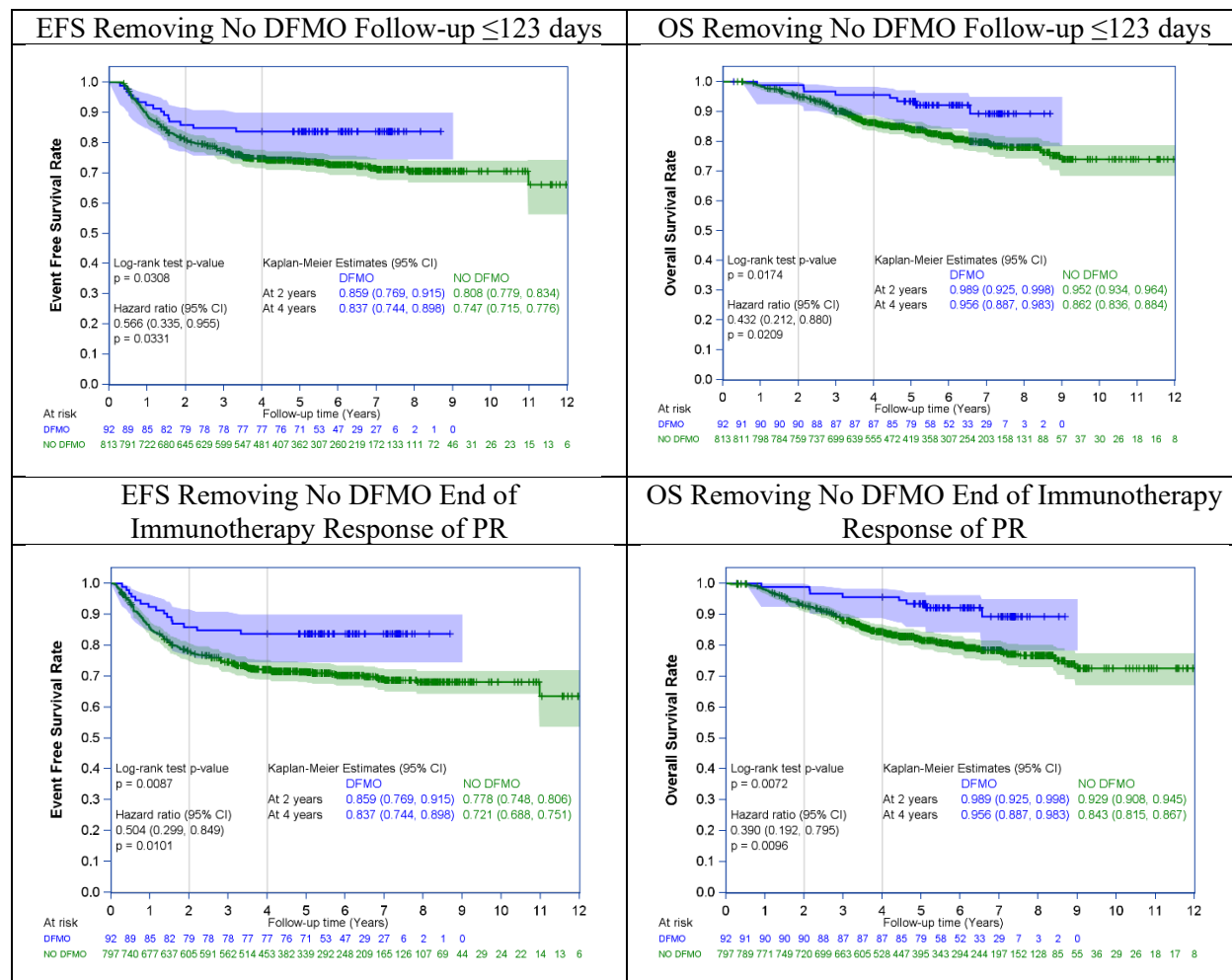
Detailed results from each EFS analyses are presented in Study 3b vs. ANBL0032 Efficacy Report Table 14.2.1.1.1, Table 14.2.14.1.1, Table 14.2.14.2.1, Table 14.2.14.3.1, and Table 14.2.14.4.1. Detailed results from each OS analyses are presented in Table 14.2.1.1.2, Table 14.2.14.1.2, Table 14.2.14.2.2, Table 14.2.14.3.2, and Table 14.2.14.4.2.

In addition to evaluating the overall NO DFMO and DFMO PER COG groups as defined by the primary selection rules, the comparisons were also challenged post-hoc by applying the more conservative VGPR or better end of immunotherapy response and EFS date >123 days modified selection rules to the control group. These comparisons also resulted in hazard ratios of approximately 0.5 (range approximately 0.4 to 0.6) and were statistically significant, as shown in Figure 42.

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**Figure 42: Key Sensitivity Analyses Applied to the Overall Populations Without Matching**

Source: Study 3b vs. ANBL0032 Efficacy Report Figure 14.2.15.5.2.7.a, Figure 14.2.15.5.2.7.b, Figure 14.2.15.5.2.1.a, and Figure 14.2.15.5.2.1.b

In addition to evaluating survival analyses, simple event rate based comparisons were performed and results at 2 and 4 years were consistent with time to event analyses, favoring DFMO.

#### The Applicant's Position:

Secondary comparisons of Study 3b and ANBL0032 included overall survival analyses that

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followed the primary matched analysis and the full complement of sensitivity analyses. Overall survival was higher in DFMO treated patients, an expected long term correlated outcome to reducing the risk of relapse. Outcome analyses in overall population comparisons without matching were again consistent with the PSM analyses.

#### The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the OS results presented in this section. Given the lack of a pre-specified formal testing plan for secondary endpoints, FDA considered all results for the secondary and other relevant endpoints to be exploratory only. In the Applicant's proposed primary analysis of OS (provided in Table 47 and Figure 43), a beneficial effect of eflornithine on overall survival was observed, with a hazard ratio of 0.32 (95% CI: 0.15, 0.70). Given the low number of deaths on each arm of the study, the OS results should be interpreted with caution.

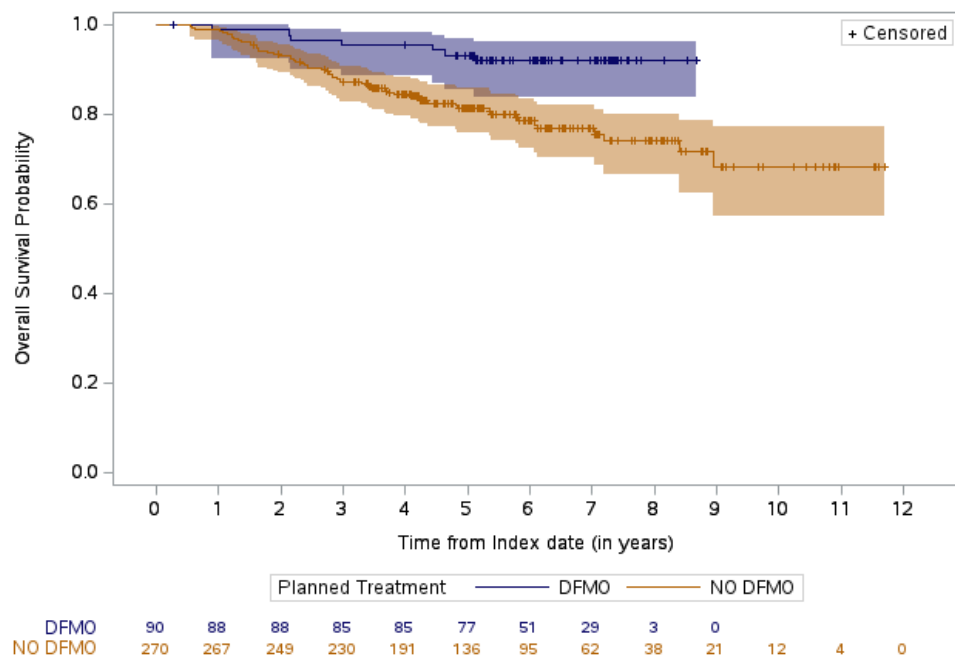
**Table 47.** FDA Analysis of Applicant's Proposed Primary Analysis of OS – Propensity Score Matched (3:1)

|                                            | <b>DFMO</b><br>(N=90) <sup>1</sup> | <b>NO DFMO</b><br>(N=270) <sup>2</sup> |
|--------------------------------------------|------------------------------------|----------------------------------------|
| <b>Overall Survival (OS)<sup>3,4</sup></b> |                                    |                                        |
| Deaths, n (%)                              | 7 (8)                              | 57 (21)                                |
| Censored, n (%)                            | 83 (92)                            | 213 (79)                               |
| Hazard Ratio (95% CI)                      | 0.32 (0.15, 0.70)                  |                                        |

<sup>1</sup>Derived from 91 patients with no missing data out of 92 total eligible patients; <sup>2</sup>Derived from 516 patients with no missing data out of 852 total eligible patients; <sup>3</sup>Final analysis; DCO: Study NMRTC003b, June 2021; Study ANBL0032, June 2019; <sup>4</sup>Descriptive p-value from unstratified log-rank test = 0.0027

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

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**Figure 43. Kaplan-Meier Plots of Applicant's Primary Analysis of OS by Treatment Group - Propensity Score Matched (3:1)**

Receipt of post-relapse therapy would be expected to influence overall survival. Table 48 summarizes the known number of relapses and post-relapse therapies in each arm of the externally controlled trial. Notably, data on post-relapse therapy were limited for patients in the control arm.

**Table 48. FDA Analysis of Post-Relapse Therapies in the Primary Efficacy Populations**

|                          | DFMO arm<br>(N=90) | Control arm<br>(N=270) |
|--------------------------|--------------------|------------------------|
| <b>EFS events, N (%)</b> | <b>14 (16)</b>     | <b>79 (29)</b>         |
| Relapse                  | 14                 | 76                     |
| Death                    | 0                  | 2                      |
| Secondary malignancy     | 0                  | 1                      |

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|                                                                    |          |         |
|--------------------------------------------------------------------|----------|---------|
| <b>Known Relapse Count, N</b>                                      |          |         |
| Single                                                             | 9        | 44      |
| Multiple                                                           | 5        | 22      |
| Missing                                                            | -        | 13      |
| <b>Number of post-relapse therapies, median (range)</b>            | 3 (1, 5) | Unknown |
| Chemotherapy                                                       | 13       | -       |
| Antibody therapy                                                   | 8        | -       |
| Radiation                                                          | 7        | -       |
| Other (e.g., vaccine trial)                                        | 7        | -       |
| <b>Number of patients alive at data cut-off<sup>1</sup>, N (%)</b> | 6 (43)   | 22 (28) |

<sup>1</sup>DFMO data cut-off: 6/30/2021; Control data cut-off: 6/30/2019

Source: Adapted from Applicant analysis submitted in NDA 215500, Module 5.3.5.4, 3bvANBL0032 Efficacy Report Appendix 9

FDA performed several sensitivity analyses of the OS results to assess the impact of factors including differential follow-up, immortal time, variations in treatment administration time around index date, and temporal changes in analysis population in the control arm on the estimation of treatment effect. The results of these analyses are presented along with the sensitivity analyses of EFS under the section on “Efficacy Results – Primary Endpoint (Including Sensitivity Analyses).”. In general, the estimation of treatment effect on OS appeared to be consistent across the range of sensitivity analyses and supportive of the Applicant’s proposed primary analysis of OS.

## Dose/Dose Response

### Data:

None.

### The Applicant’s Position:

Not applicable.

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The FDA's Assessment:

Not applicable.

**Durability of Response**

Data:

None.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

**Persistence of Effect**

Data:

Of the DFMO PER COG group patients remaining in follow up after the end of DFMO therapy visit (30 days from last dose of DFMO), only one patient (of 78 at risk, 1.3%) experienced an EFS event during the long term follow up phase of Study 3b. This result is in contrast to the NO DFMO group, with 63 patients of 645 (9.8%) patients remaining in follow up >24 months from the end of immunotherapy experiencing an event. The low rate of late-occurring events supports persistence of the effect of DFMO treatment over the first two years following completion of upfront therapy

The Applicant's Position:

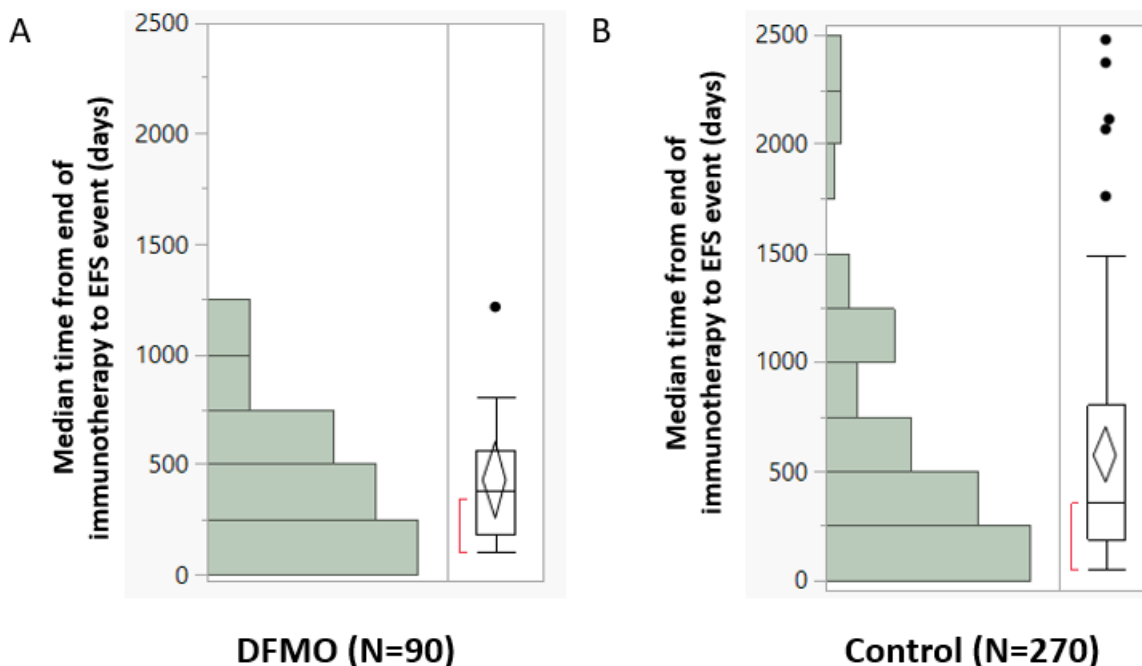
The low rate of late-occurring events supports persistence of the effect of DFMO treatment over the first two years following completion of upfront therapy

The FDA's Assessment:

FDA agrees that most EFS events occurred within the first 2 years after completion of immunotherapy.

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**Figure 44: Histograms of Median Time from End of Immunotherapy to Event-free survival (EFS) Event by Treatment Arm in the Primary Efficacy Population**



Source: FDA analysis using Applicant submitted datasets in NDA 215500

### Efficacy Results – Secondary or exploratory endpoints

#### Data:

Landmark based PSM analyses were performed removing patients in both the DFMO PER COG and NO DFMO groups that were censored or experienced an event prior to the following landmark timepoints: 30 days, 60 days, 90 days, and 120 days from the index date. Explained differently, the index date is shifted to the right by 30, 60, 90 and 120 days ignoring anything to the left of these timepoints for both the matched treated and control groups. EFS and OS comparisons favored DFMO in all analyses with statistically significant results (Study 3b vs ANBL0032 Efficacy Report Section 8.7.2).

Additional exploratory analyses included comparison of overall population NO DFMO and

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DFMO PER COG subgroups by age at diagnosis, sex, race, disease characteristics, treatment response, ASCT type, and antibody treatment duration (Study 3b vs ANBL0032 Efficacy Report Section 8.8). There was no significant difference in the DFMO treatment effect in any of the subgroup analyses conducted.

**The Applicant's Position:**

Exploratory analyses comparing overall and matched analyses consistently supported EFS and OS improvement in DFMO treated patients.

**The FDA's Assessment:**

In general, FDA agrees with the Applicant's descriptions of the landmark analyses of EFS and OS presented in this section. FDA did not independently verify these results and considers these analyses exploratory only. Results from these exploratory analyses should be interpreted with caution.

Results of the FDA assessment of subgroup analyses of EFS and OS are provided in Table 46.

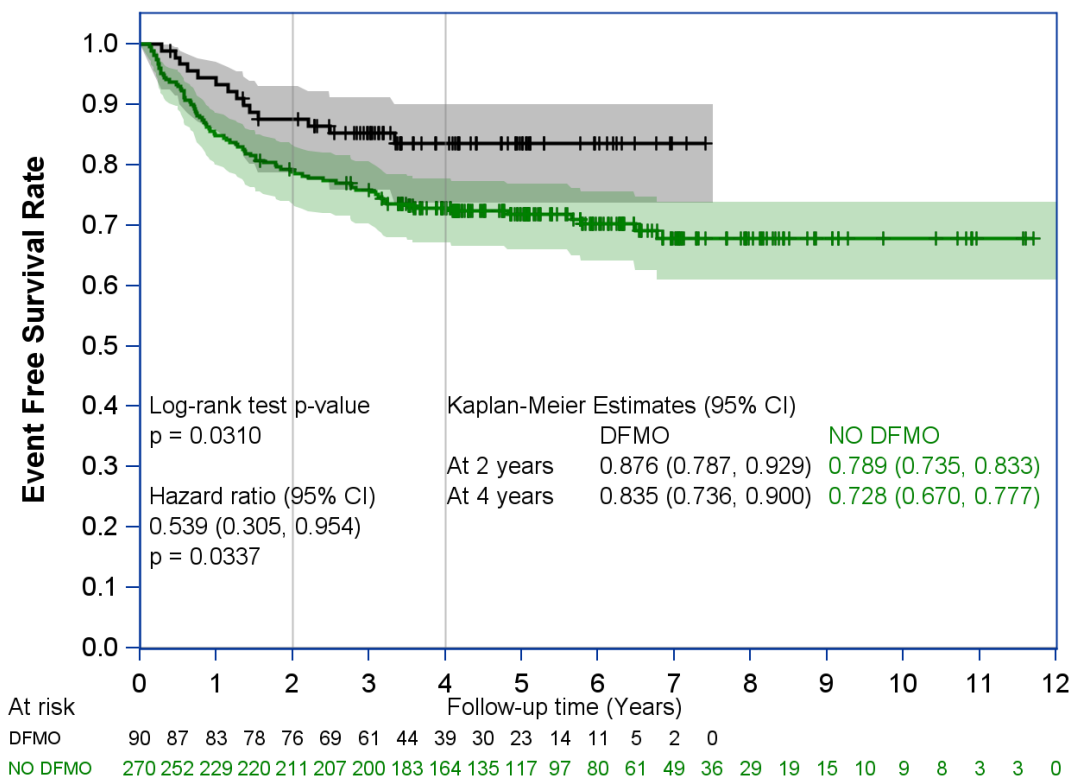
**Additional Analyses Conducted on the Individual Trial**

**Data:**

Independently assessed outcomes for DFMO PER COG patients from the W2218 BICR study were used in additional comparative analyses to ANBL0032. The DFMO PER COG-BICR group was identical to the DFMO PER COG group, thus the same 90 treated patients and the same 270 control patients selected by the primary PSM analysis for Study 3b vs. ANBL0032 are compared, only using BICR reported outcomes rather than LE reported outcomes for the treated patients. Analyses were conducted based on outcomes determined from imaging obtained only during the two year on therapy period and separately for outcomes determined from imaging obtained through the long term follow up period (during which no further imaging studies were required but were often conducted per standard of care), the "Full BICR Period". The results of the Full BICR Period comparative BICR analysis were consistent with the LE outcome-based analyses, as expected given near-perfect agreement between LE and IR determined EFS events (Figure 45).

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**Figure 45: BICR Reported Outcomes – Event Free Survival Using Propensity Score Matched Samples, Full BICR Period, DFMO PER COG BICR and NO DFMO Populations**



Source: Figure 14.2.5.2.1.1 BICR

BICR = blinded independent central review; CI = confidence interval; LE = local evaluator

Note: includes all available follow-up data for the NO DFMO patients.

BICR outcome data were analyzed in a variety of PSM based sensitivity analyses, with all but the most conservative handling of the outcomes resulting in consistent results favoring DFMO treatment. Notably, the analysis which handled IR determined final outcomes of “Equivocal” as an EFS event resulted in the conversion of 9 no event outcomes to EFS events (increasing the total from 15 to 24 events in 92 patients; Table 14.2.5.11.1.1 BICR) for the treated arm of the comparison which effectively diminished any difference between the groups.

#### The Applicant’s Position:

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Comparative analyses utilizing BICR reported outcomes for treated patients matched to the ANBL0032 external control favored DFMO across the majority of SAP-defined analyses. In the Full BICR Period analyses, DFMO PER COG patients without an EFS event are censored at date of the last imaging visit available for review in the BICR. By contrast, full follow up data are maintained in the analysis for the NO DFMO group, although imaging was not required beyond 3 years and EFS events would have been reported based on standard of care, which may or may not have included further imaging as consistent with the LE reporting of EFS events for Study 3b. The hazard ratio resulting from the comparison is consistent with that reported based on the LE outcomes; and despite the more conservative censoring applied to the DFMO PER COG treatment group, the result remains statistically significant.

The only sensitivity analyses with unfavorable results were applying worst-case handling to IR reported Equivocal outcomes. The Applicant performed a thorough review of Equivocal reporting outcomes which support that such determinations by IRs in the W2218 study were consistent with benign observations that would be noted in clinical practice and which would not be considered to be evidence of recurrence of neuroblastoma or occurrence of new secondary malignancies. Thus, the worst-case handling of BICR outcomes as requested by the Agency and planned accordingly in the SAP are assessed by the Applicant to be unhelpful to the assessment of efficacy.

The consistency in the results across the vast majority of planned analyses utilizing BICR reported outcomes allow robust characterization of the positive treatment effect of DFMO. More importantly, high concordance between BICR and local evaluator outcomes addressed potential concerns of Investigator reporting bias, supporting the reliability of the Study 3b LE outcomes utilized in extensive analyses of EFS and OS presented in earlier Section 8.1.3.

#### The FDA's Assessment:

Refer to analyses of BICR outcomes under the section on “Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)”.

In addition to the many sensitivity analyses presented in the above sections, FDA conducted several supportive analyses outlined in this section. In particular, a second approach to balancing the treatment arms by using inverse probability of treatment weighting (IPTW) was explored, allowing for all patients to contribute information to the efficacy analysis rather than just patients in the matched cohort. These analyses considered two target populations for the causal estimand. The first considers the overall population and is represented by the average treatment effect (ATE). Notably, this is the same target population and causal estimand as the propensity score

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matching approach used for the primary analysis. The second considers the treated population (e.g., the population of Study 3(b) as the target population and is provided in the results for the average treatment effect on the treated (ATT). These IPTW analyses were conducted for the overall patient population, the patients who have contemporaneous index dates across arms (index dates of March 22, 2012 or later), and in the same population as that in Table 41 which provides the sensitivity analysis with simultaneous adjustment for multiple potential sources of bias.

These analyses are provided in Table 49 through Table 52 and Figure 46 through Figure 49. Overall, the observed results of the analyses using IPTW to balance with both the same and alternative estimand (corresponding to the different target population), were generally supportive of the results observed in the Applicant's proposed primary analyses as well as the several sensitivity analyses conducted by the Applicant and the FDA.

**Table 49. Inverse Probability of Treatment Weighting Analysis of EFS and OS in the Overall Complete Case Population Meeting Eligibility Criteria**

|                           | DFMO<br>(n=90)    | NO DFMO<br>(n=494) |
|---------------------------|-------------------|--------------------|
| Effective sample size     |                   |                    |
| ATE                       | 595.43            | 584.5              |
| ATT                       | 90.00             | 90.50              |
| Event free survival (EFS) |                   |                    |
| Events, n (%)             | 14 (16)           | 141 (29)           |
| Censored, n (%)           | 76 (84)           | 353 (71)           |
| IPTW-ATE HR (95% CI)      | 0.39 (0.30, 0.52) |                    |
| IPTW-ATT HR (95% CI)      | 0.50 (0.26, 0.96) |                    |
| Overall Survival (OS)     |                   |                    |
| Deaths, n (%)             | 7 (8)             | 93 (19)            |

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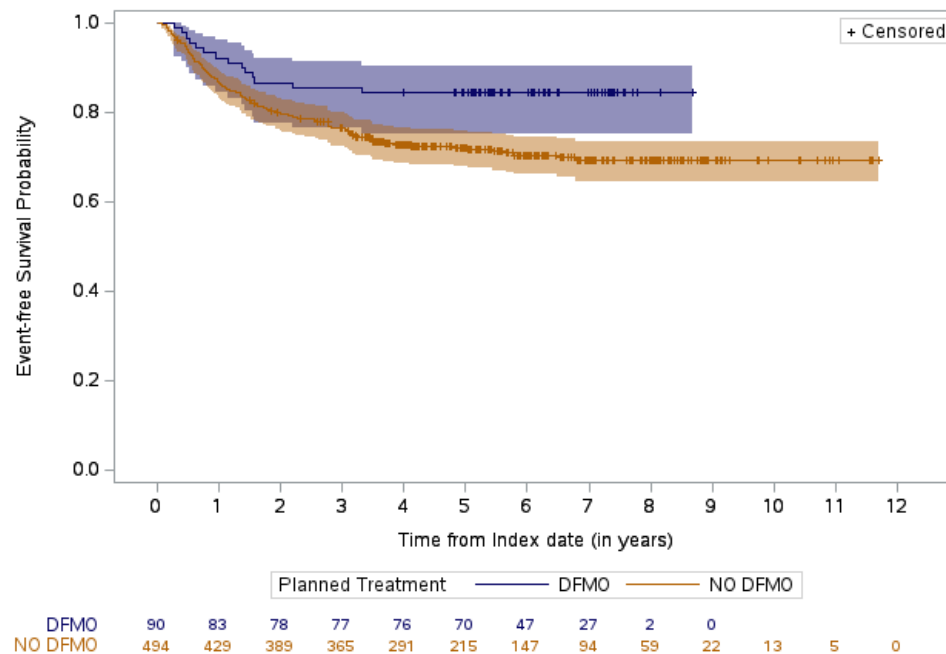
{Eflornithine [DFMO]}

|                      |                   |          |
|----------------------|-------------------|----------|
| Censored, n (%)      | 83 (92)           | 401 (81) |
| IPTW-ATE HR (95% CI) | 0.34 (0.24, 0.49) |          |
| IPTW-ATT HR (95% CI) | 0.38 (0.16, 0.92) |          |

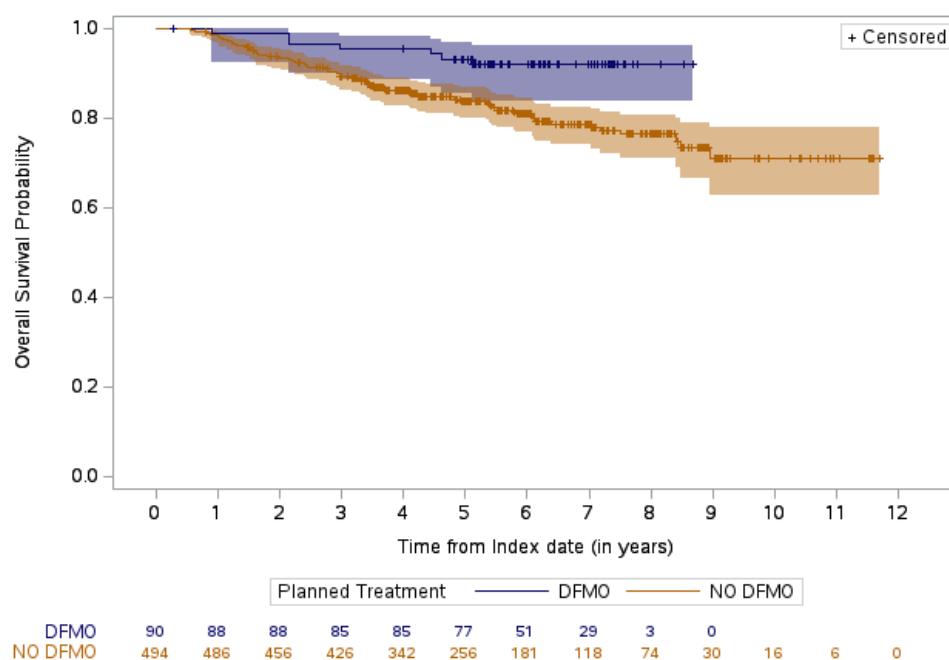
HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting; ATE, average treatment effect; ATT, average treatment effect for the treated

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

**Figure 46. Kaplan-Meier Plots of Inverse Probability of Treatment Weighting Analysis for EFS in the Overall Complete Case Population Meeting Eligibility Criteria (ATE)**



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**Figure 47. Kaplan-Meier Plots of Inverse Probability of Treatment Weighting Analysis for OS in the Overall Complete Case Population Meeting Eligibility Criteria (ATE)****Table 50. Inverse Probability of Treatment Weighting Analysis of EFS and OS in the Contemporaneous Complete Case Population Meeting Eligibility Criteria**

|                           | DFMO<br>(n=91) | NO DFMO<br>(n=302) |
|---------------------------|----------------|--------------------|
| Effective sample size     |                |                    |
| ATE                       | 399.67         | 390.82             |
| ATT                       | 91.00          | 88.82              |
| Event free survival (EFS) |                |                    |
| Events, n (%)             | 15 (16)        | 75 (25)            |
| Censored, n (%)           | 76 (84)        | 227 (75)           |

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|                       |                   |          |
|-----------------------|-------------------|----------|
| IPTW-ATE HR (95% CI)  | 0.53 (0.38, 0.73) |          |
| IPTW-ATT HR (95% CI)  | 0.62 (0.32, 1.19) |          |
| Overall Survival (OS) |                   |          |
| Deaths, n (%)         | 8 (9)             | 45 (15)  |
| Censored, n (%)       | 83 (91)           | 257 (85) |
| IPTW-ATE HR (95% CI)  | 0.45 (0.30, 0.70) |          |
| IPTW-ATT HR (95% CI)  | 0.44 (0.18, 1.09) |          |

HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting; ATE, average treatment effect; ATT, average treatment effect for the treated

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

**Table 51. Inverse Probability of Treatment Weighting Analysis of EFS and OS in the Contemporaneous Complete Case Population Meeting Eligibility Criteria and with Simultaneous Adjustment for Multiple Potential Sources of Bias**

|                           | DFMO<br><br>(n=76) | NO DFMO<br><br>(n=237)* |
|---------------------------|--------------------|-------------------------|
| Effective sample size     |                    |                         |
| ATE                       | 326.3              | 311.2                   |
| ATT                       | 76.0               | 74.1                    |
| Event free survival (EFS) |                    |                         |
| Events, n (%)             | 11 (14)            | 53 (23)                 |
| Censored, n (%)           | 65 (86)            | 179 (77)                |
| IPTW-ATE HR (95% CI)      | 0.48 (0.32, 0.72)  |                         |
| IPTW-ATT HR (95% CI)      | 0.64 (0.30, 1.39)  |                         |
| Overall Survival (OS)     |                    |                         |
| Deaths, n (%)             | 3 (4)              | 35 (15)                 |

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|                      |                   |          |
|----------------------|-------------------|----------|
| Censored, n (%)      | 73 (96)           | 202 (85) |
| IPTW-ATE HR (95% CI) | 0.19 (0.10, 0.37) |          |
| IPTW-ATT HR (95% CI) | 0.22 (0.06, 0.80) |          |

HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting; ATE, average treatment effect; ATT, average treatment effect for the treated

\*EFS calculations are based on 232 patients in the NO DFMO arm because 5 patients were excluded due to an EFS time within the immortal time period used in this analysis. Effective sample size is 627.9 (321.8 in DFMO arm, and 306.1 in no DFMO arm) for ATE and 150.1 (76 in DFMO arm, and 74.1 in no DFMO arm) for ATT analysis of EFS.

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

**Figure 48. Kaplan-Meier Plots of Inverse Probability of Treatment Weighting Analysis of EFS in the Contemporaneous Complete Case Population Meeting Eligibility Criteria and with Simultaneous Adjustment for Multiple Potential Sources of Bias (ATE)**

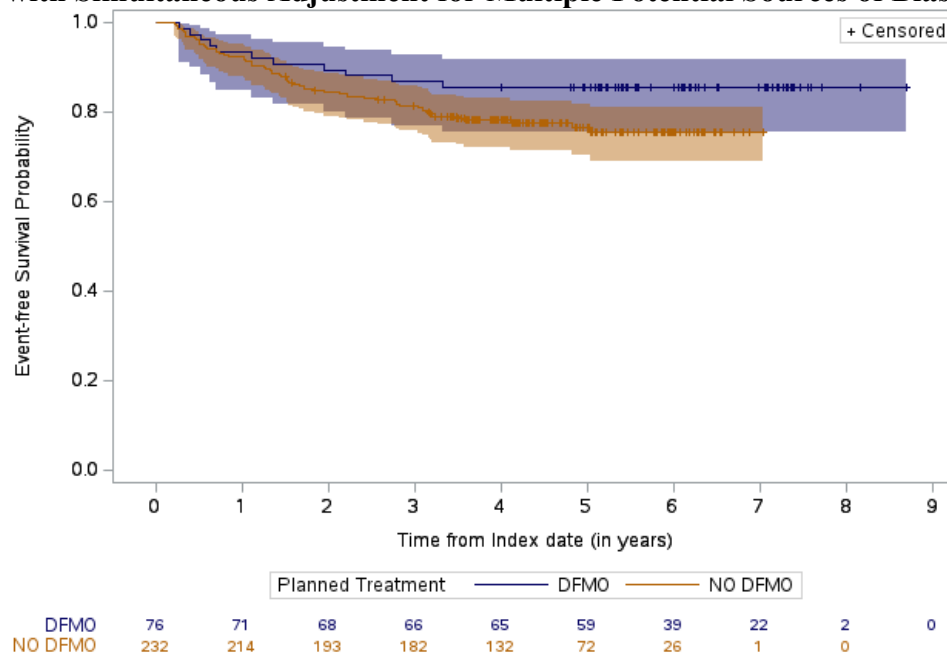
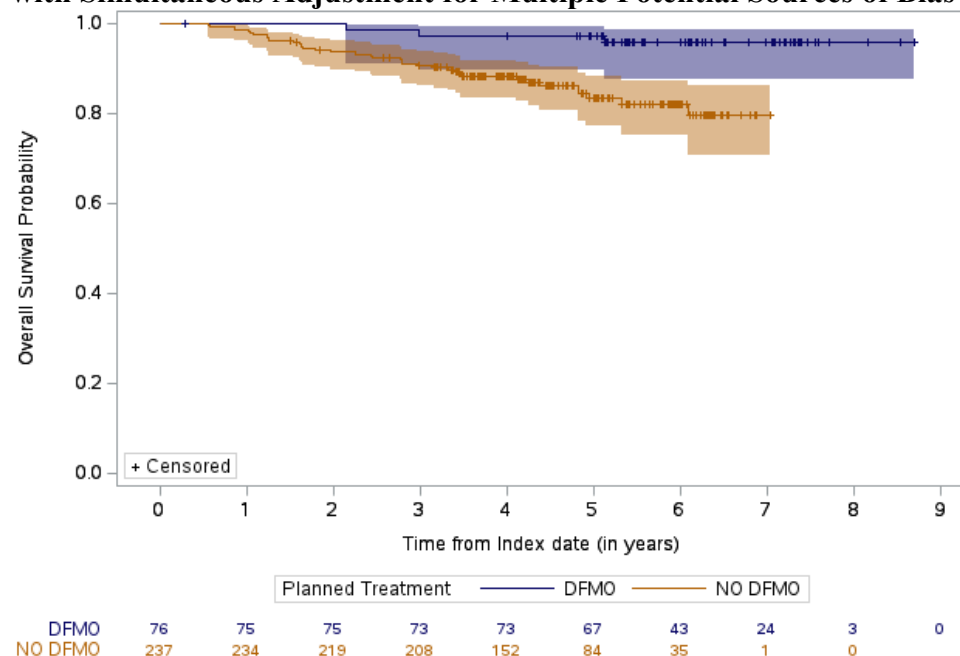


**Figure 49. Kaplan-Meier Plots of Inverse Probability of Treatment Weighting Analysis of OS in the Contemporaneous Complete Case Population Meeting Eligibility Criteria and**

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**with Simultaneous Adjustment for Multiple Potential Sources of Bias (ATE)**

FDA also used a doubly robust estimation method to estimate the treatment effect of DFMO in this ECT. When considering this type of data, it is never certain that a given model for the treatment assignment mechanism or a model for the counterfactual data is correct; therefore, it is important to assess the robustness of the results to misspecification of these models. An estimator is considered doubly robust if it remains consistent when either a model for the treatment assignment mechanism or a model for the distribution of the counterfactual data is correctly specified. Efficacy results (Table 49) from these analyses were supportive of the results from the Applicant's proposed primary analysis and from other alternative statistical approaches.

**Table 52. Doubly Robust Analysis of EFS and OS in the Overall Complete Case Population Meeting Eligibility Criteria**

|  | Propensity Score Matching |                 | Propensity Score Weighting (ATT) |                  | Propensity Score Weighting (ATE) |                   |
|--|---------------------------|-----------------|----------------------------------|------------------|----------------------------------|-------------------|
|  | DFMO (N=90)               | NO DFMO (N=270) | DFMO (N=90)                      | NO DFMO (N=90.5) | DFMO (N=595.4)                   | NO DFMO (N=584.5) |

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|                              |                      |                      |                      |
|------------------------------|----------------------|----------------------|----------------------|
| EFS hazard ratio<br>(95% CI) | 0.45<br>(0.25, 0.80) | 0.50<br>(0.26, 0.97) | 0.40<br>(0.30, 0.53) |
| OS hazard ratio<br>(95% CI)  | 0.30<br>(0.14, 0.67) | 0.36<br>(0.15, 0.90) | 0.36<br>(0.25, 0.51) |

EFS, event-free survival; OS, overall survival; CI, confidence interval; ATE, average treatment effect; ATT, average treatment effect for the treated

Source: FDA Analysis based on Applicant submitted data: 3bvanbl0032 ADTTE

### 8.1.5. Integrated Review of Effectiveness

Not populated. Applicant addressed in Section 8.1.7.

#### The FDA's Assessment:

In addition to the single ECT, the Applicant submitted supportive data as part of the NDA. The supportive data included non-clinical data (summarized in Section 5) and data from activity-estimating studies of eflornithine in related populations; a summary of these studies is provided below. The supportive clinical data for DFMO in patients with neuroblastoma is generally limited by several factors including the small number of patients, inability to isolate the effect of DFMO, and lack of objective responses attributable to DFMO. While generally supportive, given the limitations of the clinical data, the team did not consider this data to be sufficiently strong to serve as confirmatory evidence to establish substantial evidence of effectiveness.

**Study NMTRC002** (NCT 01059071) was a multi-center, single-arm, dose-escalation study of DFMO monotherapy for one cycle followed by DFMO plus oral etoposide, enrolled between 2010 and 2014 (Saulnier Sholler et al, 2015). A total of 21 patients were treated with DFMO, with 4 patients at 500 mg/m<sup>2</sup>, five patients at 750 mg/m<sup>2</sup>, three patients at 1000 mg/m<sup>2</sup>, and nine patients at 1500 mg/m<sup>2</sup>. There were no confirmed DLTs. The study enrolled 18 evaluable pediatric patients. Three patients had partial responses, although only one was actively progressing at the time of enrollment. Three patients had either bone marrow positivity or PET avid disease at study entry which improved after 1 cycle of DFMO alone; however, all these patients subsequently progressed. There are 3 long-term survivors from this study. The contribution of any anti-tumor effect of DFMO in this study is challenging to interpret given that it was primarily administered as part of a combination regimen and the patients had received multiple prior therapies.

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**Study NMTRC003(b)** also included Stratum 2, as described in Section 8.1.1. This stratum enrolled 35 patients with HRNB in remission after any previous relapse or refractory therapy (Table 53). Patients received a median of 1 prior anti-cancer therapy (range 1-3) with a median of approximately 1 month between completion of last anti-cancer treatment and start of DFMO (range 4 to 124 days). Most patients (63%) had experienced one relapse, with fewer (11% and 3%, respectively) having experienced two or three relapses. Patients in Study 3(b) Stratum 2 initiated DFMO between June 2012 and February 2016. In the Stratum 2 cohort, EFS at 2 years was 46% (95% CI: 29, 61) for patients treated with DFMO compared to a pre-specified historical control rate of 10%. The historical control rate was based on a published analysis of 91 patients with newly diagnosed HRNB enrolled on studies at a single institution between 1991 and 2002 (Santana, 2008). The calculated historical control rate used a weighted average of EFS rates at 2 years considering median times from first relapse to second relapse, and second relapse to third relapse reported in the publication.

Given the lack of contemporaneity of Study 3b and data analyzed in the reference publication, FDA requested further justification for the control EFS rate of 10%. The Applicant provided reported outcomes from two studies conducted in a similar timeframe to Study 3b to evaluate maintenance therapies for patients in second or later remission, including NCT00072358 and NCT00911560, both of which reported 5-year progression-free survival (PFS) rates of 32-33% (Kushner, 2015; Cheung, 2021). Both studies were conducted at a highly specialized single center and the outcomes may reflect both a potential treatment effect of the investigational treatments and an improvement due to highly specialized care that is not widely available. Therefore, the appropriateness of these studies to serve as a historical benchmark for Stratum 2 of Study 3(b) is uncertain.

FDA also considered that the combination of dinutuximab, irinotecan, and temozolomide is a commonly used relapse regimen for patients with HRNB since the initial publication of the results of ANBL1221 (Mody, 2017; Mody, 2020). This study enrolled patients with HRNB at the time of first relapse or first designation of refractory disease between 2013 and 2015, with results published in 2017 and 2020. Patients who received dinutuximab, irinotecan and temozolomide had a 1-year PFS rate of 68% (95% CI: 55, 81) and the Kaplan-Meier curves (Figure 2) in the publication demonstrate a PFS rate of approximately 40% at 2 years. Given the timing of enrollment, patients on Study 3(b) initiated DFMO prior to the publication of the results of ANBL1221; however, it is not clear whether patients could have received dinutuximab, irinotecan, and temozolomide (on Study ANBL1221 or according to the study protocol) prior to enrollment on Study 3(b) (Stratum 2) since prior therapies are not known.

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Due to limitations of data capture in ANBL0032 after initial relapse, a historical control rate for patients in a second or later remission after relapse from the ANBL0032 dataset cannot be reliably estimated. Based on the outcomes reported in published literature in more recent studies, it is possible that the proposed historical control rate of EFS at 2 years of 10% is lower than what would be currently observed in the US population, but the anticipated EFS rate in a contemporary population is unclear. Therefore, the EFS results of Study 3(b) Stratum 2 are difficult to interpret.

**Table 53: Study 3(b) Stratum 2 Demographics and Disease Characteristics**

|                                                 |                                   | DFMO (N=35)            |
|-------------------------------------------------|-----------------------------------|------------------------|
| <b>Age at diagnosis (years), median (range)</b> |                                   | 3.5 years (0.4 - 11.6) |
| <b>Sex, %</b>                                   | Male                              | 66                     |
|                                                 | Female                            | 34                     |
| <b>Race, %</b>                                  | White                             | 83                     |
|                                                 | Black, African American, or Other | 17                     |
| <b>MYCN status, %</b>                           | Amplified                         | 26                     |
|                                                 | Not amplified                     | 66                     |
|                                                 | Missing                           | 8                      |
| <b>Histology, %</b>                             | Favorable                         | 17                     |
|                                                 | Unfavorable                       | 60                     |
|                                                 | Missing                           | 23                     |
| <b>Stage at diagnosis, %</b>                    | 4                                 | 89                     |
|                                                 | Other (2, 3, 4S)                  | 11                     |
| <b>Disease status, %</b>                        | Relapsed                          | 80                     |

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|                                                 |                                       |                       |
|-------------------------------------------------|---------------------------------------|-----------------------|
|                                                 | Refractory                            | 20                    |
| <b>Tumor Cytogenetics, %</b>                    | Chromosomal aberration (1p, 11q, 17q) | 17                    |
|                                                 | ALK mutation                          | 3                     |
|                                                 | Missing                               | 80                    |
| <b>Primary Tumor Location, %</b>                | Adrenal                               | 31                    |
|                                                 | Non-adrenal                           | 14                    |
|                                                 | Missing                               | 54                    |
| <b>Single vs. Tandem Transplant, %</b>          | Single                                | 69                    |
|                                                 | Tandem                                | 11                    |
|                                                 | Missing                               | 20                    |
| <b>Cycles of immunotherapy, %</b>               | < 6 cycles                            | 8                     |
|                                                 | 6 cycles                              | 83                    |
|                                                 | Missing                               | 8                     |
| <b>Anti-GD2 immunotherapy, %</b>                | Ch 14.18                              | 77                    |
|                                                 | 3F8                                   | 9                     |
|                                                 | Missing                               | 14                    |
| <b>End of immunotherapy overall response, %</b> | CR                                    | 63                    |
|                                                 | VGPR or PR                            | 14                    |
|                                                 | SD                                    | 3                     |
|                                                 | PD                                    | 11                    |
|                                                 | Missing                               | 9                     |
| <b>Dates of end of immunotherapy (range)</b>    |                                       | May 2005 – April 2015 |

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| Dates of DFMO initiation (range)                                      |                                     | June 2012 – February 2016 |
|-----------------------------------------------------------------------|-------------------------------------|---------------------------|
| Number of Prior Relapses <sup>a</sup> , %                             | 1                                   | 63                        |
|                                                                       | 2                                   | 11                        |
|                                                                       | 3                                   | 3                         |
|                                                                       | Missing                             | 3                         |
|                                                                       | Not applicable (refractory disease) | 20                        |
| Days from last anti-cancer treatment to start of DFMO, median (range) |                                     | 37 (4 – 124)              |
| Days from end of immunotherapy to start of DFMO, median (range)       |                                     | 532 (17 – 3591)           |

<sup>a</sup> Number and type of prior anti-cancer therapies not reported

Source: Datasets submitted to NDA 215500

**Study NMTRC006** (NCT03581240) is an ongoing expanded access study of DFMO in patients with relapsed rare tumors with increased LIN28 expression, MYCN amplification, or upregulation of ornithine decarboxylase, including high-risk neuroblastoma. As of January 2023, a total of 97 patients were enrolled, including 27 patients with HRNB in remission, defined as being either in remission following upfront therapy (n=13) or in subsequent remission following refractory or relapse disease (n=14). In this expanded access study, there were no defined response criteria. Of the 13 patients with HRNB in initial remission, 12 (92%) remained in remission at the data cut-off, with eight completing two years of DFMO therapy and four continuing on DFMO therapy (range 180 to 629 days on therapy); one patient relapsed after 453 days on DFMO therapy. Of 15 patients with HRNB in remission after therapy for relapsed/refractory disease, 10 (67%) remained in remission at the data cut-off, with five patients completing 2 years of DFMO therapy; one patient stopped DFMO after 86 days; three patients continue on DFMO therapy (range 285 to 685 days on therapy); and five patients relapsed during DFMO therapy (start of DFMO therapy to relapse: 49 to 170 days). The expanded access data regarding tumor responses or duration of remission in HRNB and related tumor types are challenging to interpret given the lack of pre-specified response criteria and lack of a control arm.

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Forty-one patients with HRNB with active disease received DFMO on the expanded access study. Outcomes for patients treated with DFMO as part of a combination regimen with other products are difficult to interpret given the lack of isolation of effect of each of the components of the regimen. Fifteen patients received DFMO as a single agent and 8 had described decreases in PET or MIBG avidity or decreases in lesion size. However, there were no standardized response criteria; therefore, interpretation of this potential supportive clinical evidence is limited by the small number of patients in the study and the lack of prespecified, standardized response criteria in the expanded access program.

### ***Additional Neuroblastoma Trials Evaluating DFMO***

There are several ongoing trials with DFMO in patients with neuroblastoma, for which efficacy data was not provided in this application. To FDA's knowledge, there have not been any negative trials of DFMO in neuroblastoma populations.

Study NMTRC014 (NCT02679144) is an ongoing multi-center, open label trial of DFMO monotherapy in patients with HRNB in remission after up-front (Strata 1/1b/2) or relapse/refractory (Strata 3/4) therapy. The primary endpoint is EFS rate at 4 years compared to a historical control rate. This study supports the safety evaluation for this application; however, at the time of NDA submission, efficacy data were not available. Since the design of Study 14 is similar to Study 3b, efficacy results which replicate findings from Study 3b could provide support for the proposed indication. However, in the absence of a comparator arm, interpretation of the findings of Study 14 would be limited by its single arm nature. Further, use of data from ANBL0032 as a comparator for Study 14 may be less appropriate given the non-overlapping time periods in which the studies were conducted, as well as other potential differences. This study began enrollment in February 2016 and has enrolled 280 of 441 planned patients at 37 sites in the US and Canada as of June 30, 2021.

Two additional randomized studies for which data have not been provided in the current application are ongoing in the newly diagnosed and relapsed/refractory setting:

- Study NMTRC012 (NCT02559778) is an open-label, randomized trial which evaluates immunotherapy (e.g., anti-GD2 antibody) alone vs. immunotherapy with DFMO in the post-consolidation phase of upfront treatment, with a primary endpoint of EFS. Following this randomized period during immunotherapy, all patients receive DFMO for 2 years in the post-immunotherapy setting; therefore, the study is not designed to evaluate

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the efficacy of DFMO in the maintenance setting. The trial is expected to complete enrollment in 2-5 years.

- COG Study ANBL1821 (NCT03794349) is an open label, randomized (1:1) trial of irinotecan, temozolomide and dintuxutimab with or without DFMO in patients with relapsed/refractory HRNB. The study is anticipated to be complete in 2024.

#### *Non-Neuroblastoma Trials Evaluating DFMO*

The lack of robust efficacy and anti-tumor activity data in other adult oncology disease settings despite decades of study was discussed by members of the ODAC on October 4, 2023, and was considered by FDA to be a limitation of this application.

The results of completed clinical studies of eflornithine across other tumor types have largely not been submitted to the FDA to support marketing applications. To date, there are no approved oncology indications for DFMO. To further evaluate existing data regarding eflornithine in oncology populations, as recommended by ODAC panel members, FDA conducted a literature search of ongoing and completed clinical investigations of eflornithine in non-neuroblastoma populations (Table 54).

The review team noted that LIN28 overexpression is observed in multiple tumor types, and there have been multiple negative trials of eflornithine in adults with cancer, however the *ODCI* and *MYCN* genes are largely not considered major drivers of tumors in which studies of eflornithine were negative. In contrast, these genes are particularly relevant in neuroblastoma and aberrations of *ODC* and *MYCN* are correlated with poor prognosis in this disease. In addition, pediatric solid tumors have largely different ontogeny and biology from adult tumors, with the latter being more likely to have substantially higher mutational burdens and multiple driver mutations (Langenberg et al, 2021). Pediatric cancers are frequently defined by a single driver gene as opposed to the multiple cancer-driving mutations identified in adults, and driver mutations are more exclusive in specific tumor types while adult cancers more frequently share mutations (Grober et al, 2018). Thus, the lack of activity reported in other adult tumor types was not felt to necessarily portend a lack of activity in pediatric neuroblastoma, and the non-clinical data and results from relevant animal models were felt to provide confirmatory evidence necessary to support substantial evidence of an improvement in EFS.

(b) (4), (b) (5)

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(b) (4), (b) (5)

DFMO is being investigated for the treatment of adult patients with high grade glioma, (b) (4)

a

randomized (1:1) study of patients with anaplastic glioma who received procarbazine, CCNU, and vincristine with or without DFMO after completion of radiation therapy for newly diagnosed disease (Levin, 2003). (b) (4)

a randomized trial of lomustine with or without DFMO is ongoing in patients with anaplastic astrocytoma with recurrence after prior irradiation and treatment with temozolomide (STELLAR Study, NCT02796261). The study is closed to enrollment with results anticipated in 2023 according to clinicaltrials.gov.

**Table 54: Ongoing and Completed Studies of DFMO in oncology populations other than neuroblastoma as per clinicaltrials.gov review**

| NCT Number  | Study Title                                                                                    | Study Status as per clinicaltrials.gov on September 22, 2023 | Publication available per clinicaltrials.gov on September 22, 2023 | Study Results, if published; Study Status, if not published                                                                                                                                                                                      |
|-------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NCT00118365 | Eflornithine and Sulindac in Preventing Colorectal Cancer in Patients With <b>Colon Polyps</b> | Completed                                                    | Thompson et al (2010)                                              | Eflornithine 500 mg once daily + sulindac vs. placebo (1:1) for up to 36 months (N = 375); Colorectal adenoma recurrence was lower in the eflornithine + sulindac group (12%) compared to placebo (41%) with risk ratio 0.30 (95% CI 0.18, 0.49) |

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|             |                                                                                                                        |                       |                      |                                                                                                                         |
|-------------|------------------------------------------------------------------------------------------------------------------------|-----------------------|----------------------|-------------------------------------------------------------------------------------------------------------------------|
| NCT05717153 | Intratumoral Extracellular Metabolic Impact of DFMO and AMXT 1501 in Patients With <b>Diffuse or High-Grade Glioma</b> | Recruiting            | None                 | None (study started in August 2023, estimated completion date September 2027)                                           |
| NCT00003814 | Eflornithine in Treating Patients With <b>Bladder Cancer</b>                                                           | Completed             | Messing et al (2006) | Eflornithine vs. placebo (1:1) for up to 1 year (N = 454); 2-year recurrence-free rates similar (49% vs. 57%, p = 0.30) |
| NCT05879367 | Evaluation of Eflornithine Plus Temozolomide in Patients With Newly Diagnosed <b>Glioblastoma</b>                      | Recruiting            | None                 | None (study started in July 2023, estimated completion date December 2024)                                              |
| NCT04091022 | Topical Diclofenac and Topical DFMO Chemoprevention Trial in Subjects With a <b>History of Skin Cancer</b>             | Recruiting            | None                 | None (study started in January 2021, estimated completion date December 2024)                                           |
| NCT00204789 | Difluoromethylornithine (DFMO) Chemoprevention of <b>Skin Cancer</b> in Organ Transplant Recipients                    | Completed             | None                 | No results posted (52 participants enrolled; actual study completion date December 2007)                                |
| NCT02796261 | Study to Evaluate Eflornithine + Lomustine vs Lomustine in Recurrent <b>Anaplastic Astrocytoma (AA)</b> Patients       | Active not recruiting | None                 | None (study started in July 2016, estimated completion date June 2023)                                                  |
| NCT05500508 | Oral AMXT 1501 Dicaprte in Combination With IV DFMO in <b>Advanced Solid Tumors or DIPG/DMG</b>                        | Recruiting            | None                 | None (study started in November 2022, estimated completion date September 2024)                                         |
| NCT01245816 | A Trial of Low Dose Sulindac Combined With Eflornithine in Patients With <b>Familial Adenomatous Polyposis (FAP)</b>   | Withdrawn             | None                 | No results posted (0 participants enrolled; actual study completion date June 2013)                                     |
| NCT00006079 | Eflornithine To Prevent Cervical Cancer in Patients With <b>Cervical Intraepithelial Neoplasia</b>                     | Completed             | None                 | No results posted (150 participants enrolled; actual study completion date April 2004)                                  |

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|             |                                                                                                                               |                       |                       |                                                                                                                                                                                                                           |
|-------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NCT00033371 | Celecoxib With or Without Eflornithine in Preventing Colorectal Cancer in Patients With <b>Familial Adenomatous Polyposis</b> | Completed             | Lynch et al (2016)    | Eflornithine + celecoxib vs. celecoxib (1:1) for up to 6 months (N = 205); mean percent change in adenoma count over 6 months similar (-13% vs. -1%, p = 0.69)                                                            |
| NCT00021294 | Eflornithine With or Without Triamcinolone in Preventing Nonmelanoma Skin Cancer in Patients With <b>Actinic Keratosis</b>    | Completed             | Bartels et al (2014)  | Eflornithine + triamcinolone vs. eflornithine + placebo vs. triamcinolone + placebo (1:1:1) for up to 6 months (N=102); similar decline in nuclear abnormality value for all intervention arms compared to double placebo |
| NCT02636569 | Topical Chemoprevention of <b>Skin Cancer</b> Biomarkers                                                                      | Active not recruiting | None                  | None (study started in October 2017, estimated completion date December 2024)                                                                                                                                             |
| NCT04696029 | DFMO as Maintenance Therapy for Molecular High/Very High Risk and Relapsed <b>Medulloblastoma</b>                             | Recruiting            | None                  | None (study started in March 2021, estimated completion date March 2029)                                                                                                                                                  |
| NCT00086736 | Neoadjuvant Eflornithine and Bicalutamide in Patients With Localized <b>Prostate Cancer</b>                                   | Completed             | None                  | No results posted (34 participants enrolled; actual study completion date November 2003)                                                                                                                                  |
| NCT00983580 | Acetylsalicylic Acid and Eflornithine in Treating Patients at High Risk for <b>Colorectal Cancer</b>                          | Completed             | None                  | Eflornithine + aspirin vs. placebo (1:1) for up to 1 year (N = 85); Rate of adenoma recurrence at 1-year follow-up colonoscopy similar (60% vs. 58%, p = 0.448) per clincialtrials.gov study results                      |
| NCT00006101 | Eflornithine in Treating Patients At High Risk of Developing <b>Prostate Cancer</b>                                           | Completed             | Simoneau et al (2008) | Eflornithine vs. placebo (1:1) for up to 1 year (N = 81); Smaller increase in prostate volume in eflornithine arm (0.14 cm <sup>3</sup> ) vs. placebo (2.95 cm <sup>3</sup> ) at 1 year (p=0.03)                          |
| NCT03536728 | Oral AMXT 1501 Dicaprte in Combination With DFMO in <b>Advanced Solid Tumors</b>                                              | Completed             | None                  | No results posted (56 participants enrolled; actual study completion date April 2023)                                                                                                                                     |

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|             |                                                                                                                                                                                               |                       |                     |                                                                                                                                                                                                                         |
|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NCT02794428 | Chemoprevention of <b>Gastric Carcinogenesis</b>                                                                                                                                              | Active not recruiting | None                | None (study started in September 2016, estimated completion date December 2023)                                                                                                                                         |
| NCT01483144 | Trial of Eflornithine Plus Sulindac in Patients With <b>Familial Adenomatous Polyposis (FAP)</b>                                                                                              | Completed             | Burke et al (2020)  | Eflornithine + sulindac vs. eflornithine vs. sulindac (1:1:1) for up to 2 years (N = 171); Disease progression rates similar (32% vs. 40% vs. 38%), HR 0.71 (95% CI: 0.4, 1.3) for eflornithine + sulindac vs. sulindac |
| NCT00003076 | Eflornithine to Prevent Cancer in Patients With <b>Barrett's Esophagus</b>                                                                                                                    | Completed             | None                | No results posted (152 participants enrolled; actual study completion date October 2005)                                                                                                                                |
| NCT01349881 | S0820, Trial of Eflornithine and Sulindac to Prevent Recurrence of High Risk <b>Adenomas</b> and Second Primary <b>Colorectal Cancers</b> in Patients With Stage 0-III Colon or Rectal Cancer | Recruiting            | None                | None (study started in March 2013, estimated completion date February 2032)                                                                                                                                             |
| NCT00005884 | Eflornithine to Prevent Skin Cancer in Patients With Previously Treated Early-Stage <b>Skin Cancer</b>                                                                                        | Completed             | Bailey et al (2010) | Eflornithine vs. placebo (1:1) for up to 5 years (N = 291); Rate of new NMSCs similar (260 vs. 363 cancers, p = 0.069)                                                                                                  |

NCT: National Clinical Trial, DIPG: diffuse intrinsic pontine glioma, DMG: diffuse midline glioma, NMSC: non-melanoma skin cancer

Source: Clinicaltrials.gov, accessed September 22, 2023

### *Other Supportive Data*

**Biomarker data:** On September 20, 2023, the Applicant submitted results from a small subgroup of 21 patients in Study 3(b) who had urine polyamine analyses performed. The Applicant stated that treatment with DFMO led to a reduction in excreted polyamines found in the urine. However, these data are challenging to interpret given that only 21 patients in Study 3(b) were included, some of whom were in remission after upfront therapy alone and others who had relapsed/refractory disease. While urine polyamines may be quantitatively decreased in patients receiving DFMO, it is unclear whether this finding correlates with anti-tumor activity or survival outcomes.

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The Applicant also submitted plasma Let-7 microRNA expression analyses for 33 patients treated with DFMO in Study NMTRC012. The Applicant stated that the results showed a trend for increased Let-7 expression in patients with HRNB treated with DFMO, with an average increase from pre-DFMO to post-DFMO samples of approximately 3-fold across the evaluated patients, suggesting that interactions between reduced polyamine and Let-7 balance restoration may occur with adequate ODC inhibition. These data are challenging to interpret given that only 33 patients were included, and there is no comparison to non-DFMO treated patients to evaluate expected Let-7 expression at similar time periods. “Pre vs. Post” DFMO changes in the same patient may reflect intra-patient variability independent of DFMO.

**SIOPEN data:** On September 20, 2023, the Applicant submitted a comparative analysis of a cohort of DFMO-treated patients in remission after upfront therapy on SIOPEN trial HRNBL1 (rather than COG up-front therapy), which includes dinutuximab-beta as the anti-GD2 antibody used in the immunotherapy phase. The Applicant noted that the 2- and 4-year EFS estimates for the DFMO per SIOPEN group are generally similar to those reported for the primary analysis DFMO group, suggesting preliminary support for consistency of outcomes with DFMO maintenance after upfront treatment across two treatment paradigms (COG and SIOPEN). There are challenges interpreting these data, including the lack of statistical methods to ensure balance across important clinical covariates. In particular, comparisons of the DFMO per SIOPEN vs. DFMO per COG primary analysis population are limited by potential confounding factors in the SIOPEN cohort which influenced survival outcomes independent of DFMO. For instance, this small group of patients (N=47) received different up-front therapy (European regimen including rapid COJEC and dinutuximab-beta) and had lower rates of CR/VGPR compared to the ECT DFMO patients. In addition, comparisons of the DFMO per SIOPEN (N=47) vs. SIOPEN alone (N=319) population are limited by differences in disease and treatment-related characteristics (e.g., more patients in the DFMO group had a CR pre-immunotherapy compared to the SIOPEN group [70.2 vs. 55.6%]).

#### 8.1.6. Assessment of Efficacy Across Trials

##### Primary Endpoints

Data:

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EFS outcomes in DFMO treated patients are improved when compared to both published historical rates and patient level data from external control database, ANBL0032. Extensive testing of the external control database was performed to characterize the range of the treatment effect, with results being consistent in both magnitude and statistical significance across the range of analytical approaches designed with FDA input.

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### The Applicant's Position:

Event free survival is a well-established, clinically meaningful endpoint in oncology. Patients enrolled in Study 3b study were determined to be in remission following completion of multiagent, multimodality therapy. Patients were followed through routine clinic visits with imaging assessments to monitor for disease recurrence as the risk of relapse in high-risk neuroblastoma is well established. EFS analyses as prospectively defined in Study 3b for comparison to published historical rates and through extensive analyses vs. patient level data in ANBL0032, a natural extension of the hypothesis testing for Study 3b, consistently favored DFMO. EFS events were considered to be the first occurrence of progressive disease, relapse, secondary cancer or death due to any cause. Because the patients selected for comparison had completed therapy and were considered to be in remission, the endpoint is of particular clinical importance. EFS analyses separate groups of patients that remain disease free and engaged in normal childhood activities with groups of patients that experience a devastating diagnosis of recurrent disease. The latter group of patients are subjected to seriously toxic therapy and have dramatically reduced odds of survival into adulthood. The magnitude and consistency of the treatment effect size across the Study 3b and Study 3b vs ANBL0032 analyses, including those which utilize BICR reported outcomes, characterize a meaningful clinical benefit associated with DFMO treatment. Generally, hazard ratios across the external control comparisons range between 0.4 and 0.6, supporting that DFMO treatment reduces the risk of an EFS event by approximately half at any point in the follow up.

### The FDA's Assessment:

Not applicable. This section applies to applications that are supported by multiple clinical trials.

### **Secondary and Other Endpoints**

#### Data:

Secondary endpoints for overall survival consistently favored DFMO, across both the prospective Study 3b analyses and the Study 3b vs. ANBL0032 analyses, including extensive sensitivity analyses for the matched comparison and overall population comparisons. Hazard ratios across the external control comparisons generally range between 0.3 and 0.4, supporting that DFMO treatment reduces the risk of death to approximately one third that of control patients at any point in the follow up.

### The Applicant's Position:

Deaths were reported exclusively for patients with preceding non-death (i.e., relapse) EFS events in the treated group and, with few exceptions, in the control group. Because the EFS rate was

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lower in the treated population and relapse puts patients at a higher risk of mortality, the overall survival differences can reasonably be attributed to the primary benefit of DFMO, reducing the risk of relapse. Anticancer therapy following an EFS event in both treated and control patients was also evaluated by the Applicant with no clear differences between the groups that would have been expected to influence overall survival other than having a smaller proportion of treated patients that experience relapse events and therefore had no requirement for any post relapse therapy.

**The FDA's Assessment:**

Not applicable. This section applies to applications that are supported by multiple clinical trials.

**Subpopulations**

**Data:**

Subpopulations based on demographic and disease characteristics were evaluated in the Study 3b and Study 3b vs. ANBL0032 EFS and OS analyses. No subgroups were identified with notable differences in treatment effect.

**The Applicant's Position:**

There are no specific subgroups with the target population that appear to benefit more or less from DFMO therapy.

**The FDA's Assessment:**

Not applicable. This section applies to applications that are supported by multiple clinical trials.

**Additional Efficacy Considerations**

**The FDA's Assessment:**

Not applicable. This section applies to considerations on benefit in the postmarket setting or other relevant benefits.

**8.1.7. Integrated Assessment of Effectiveness**

**Data:**

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DFMO treatment produced meaningful improvement in event free survival rates in HRNB patients that completed multimodality treatment. This claim is supported by the prospective evaluations in Study 3b, the patient level comparisons to a fit-for-purpose external control database, ANBL0032, and independent evaluation of the outcomes for treated patients based on a blinded independent central review of imaging. The conclusions are consistent with the originally reported outcomes for the Study 3b as reported by [Saulnier Sholler 2018](#) and when compared to a separate, BCC-developed control database as reported by [Lewis 2020](#). The reported efficacy is consistent with the mechanistic and nonclinical scientific evidence supporting the role of DFMO as a chemopreventative agent in neuroblastoma and specific effects on key pathways necessary for the survival of cancer stem cells believed to have an important role in HRNB relapse. Overall survival is also improved in patients receiving DFMO treatment compared to historical control rates and external control patient outcomes.

#### The Applicant's Position:

The evaluation of DFMO as a treatment to reduce the risk of relapse in patients that complete multiagent, multimodality therapy is primarily supported by EFS outcome comparisons for patients treated with DFMO in Study 3b to similar patients not receiving DFMO therapy in the external control database, ANBL0032. Pivotal analyses of treatment effect are investigated in terms of hazard ratio which requires reliance on time to event data. Time to EFS event data are reliable for the reported analyses, and suitable to serve as the basis for the efficacy conclusions. Event free survival events were defined identically between Study 3b and ANBL0032 and the index date for the analyses was harmonized to the common treatment point prior to the introduction of the DFMO intervention, the end of immunotherapy. Timely and reliable determination of relapse in HRNB patients requires consistent monitoring of patients through clinic visits, imaging assessments, and/or regular follow up contact. Good compliance with follow up was established in both Study 3b and ANBL0032 which utilized very comparable surveillance procedures and schedules. EFS outcomes for treated patients are reliable, based on high concordance with independent outcome determinations assessed in BICR W2218. While conducting a BICR for the control patients was not feasible, there is no reasonable expectation that clinical outcome determination would be different when the implications for a relapse diagnosis of HRNB are so severe. Additionally, with regard to the potential for outcome bias, ANBL0032 had as much or more potential for outcome bias given that approximately 1200 patients enrolled in the open label, non-randomized portion of the study that followed the [Yu, 2010](#) publication concluding EFS improvement with dinutuximab treatment. Such potential bias in the control arm would lead to under or delayed EFS event determination which would only work against establishing a DFMO treatment effect. Sufficient information must be available to definitively determine relapse has occurred, but such caution must be balanced with the timely initiation of relapse therapy to optimize chances of treatment success. For patients that do not

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experience EFS events, there is sufficient data to characterize those patients, supporting interpretability of the time to event data. The majority of censored patients in the analysis remain ongoing in follow up as a result of the long follow up periods in both studies. Few patients, especially in the treated arm of the comparisons, are lost to follow up. Further, the extent of follow up data available provides adequate opportunity across the populations to observe and report EFS events within the follow up period where such events are most likely to be observed; and treated patients have longer follow up duration than control patients, giving confidence that there was more than equal opportunity for sites to report EFS events in treated patients than would have or still could be reported in the control patients.

EFS time-to event analyses are further supported by simple, event rate comparisons which are consistent with the time to event analyses. Overall survival time to event analyses are also supportive. Overall survival reporting is more objective, though reliable reporting again depends primarily on maintaining regular contact with patient families. There was good reporting compliance during the long term follow up for both groups of patients and the extent of long term survival follow up is again longer in treated patients compared to controls.

By regulation, an uncontrolled study is insufficient on its own to support efficacy claims. Study 3b is a single arm study that through the design of statistically robust comparisons to ANBL0032 as an external control (or a historical control, a control category recognized by CFR 314.126) enables it to meet the regulatory requirements for an adequate and well controlled study. The comparative analyses were prospectively documented prior to receipt of the final control database and, more importantly, were consistent with the original stated objectives and analysis plans for Study 3b (the study was designed for comparison to the published results of ANBL0032), again consistent with the criteria in CFR 314.126. The selection of patients for inclusion in the analysis populations for overall and matched comparisons were designed with input from FDA to assure comparability of the groups, and the resulting balance across demographic and disease characteristics supports that the selected groups are similar, both representing the target HRNB patient population. Efficacy assessment procedures and outcome measures were clearly defined by the protocol and were consistent with both the procedures and outcome definitions in ANBL0032 and with determination of clinical events of recurrence per the standard of care in HRNB surveillance. Further, the BICR conducted by the Applicant is an adequate measure to address the potential for bias in the outcome data reported in Study 3b, for the DFMO PER COG group, with the results supporting that the outcome data by Study 3b reporting was essentially free of bias. The methods and criteria for determining outcomes of EFS and OS were well defined in both studies contributing outcome data to the efficacy comparisons. Finally, robust statistical analyses fully characterize the treatment effect and address remaining potential biases and/or known or unknown differences between the treated and control patients across multiple pertinent variables. The results across the full range of EFS and OS analyses

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clearly meet the regulatory threshold of demonstrating substantial effectiveness of DFMO for its proposed use in reducing the risk of relapse in HRNB patients completing multiagent, multimodality therapy, particularly in the context of the severity of HRNB an indication for which no other treatments are available (consistent with the criteria of CFR 312.84).

#### The FDA's Assessment:

According to the 1962 Kefauver-Harris amendment to the Federal Food, Drug, & Cosmetic Act, a drug's effectiveness must be established by "substantial evidence," which is defined as: "evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof (U.S. Food and Drug Administration. Guidance Document: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Draft Guidance for Industry)."

In this NDA, the Applicant submitted one externally controlled trial (ECT) with potential supportive clinical and non-clinical data. To determine whether the results of the ECT with confirmatory evidence support a determination of substantial evidence of effectiveness of DFMO for the proposed indication, the review team considered the following critical issues:

- Whether the external control is appropriate for use,
- Whether the single ECT is adequate and well-controlled, and
- Whether the submitted supportive data provides confirmatory evidence.

#### ***Appropriateness of External Control***

An ECT compares a group of patients receiving the test treatment with a group of patients external to the trial, rather than to an internal control group consisting of patients from the same trial population assigned to a different treatment.

The FDA Substantial Evidence of Effectiveness Guidance states that while there can be limitations, "strong support for effectiveness can emerge from externally controlled trials"<sup>12</sup>, especially when the points listed here are true:

- The natural history of a disease is well defined,

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- The external control population is very similar to that of the treatment group
- The concomitant treatments that affect the primary endpoint are not substantially different between the external control population and the trial population, and
- The results provide compelling evidence of a change in the established progression of disease.

The review team considered the following with regard to the evaluation of these criteria for the externally controlled trial submitted in the NDA:

- The natural history and poor prognosis of patients with HRNB are well-defined and reported in the published literature, as summarized in Section 2.
- The external control population is generally similar to the treatment group, although there are potential unmeasured confounders as discussed in Section 8.1.4. The external control data is derived from a single source with patient-level data from one large clinical trial conducted by the major pediatric oncology cooperative group at >150 sites in the US. Notably, Study 3b was originally designed based on the historical control rate derived from ANBL0032 and 95% of patients in the investigational arm were first treated on ANBL0032. Since dinutuximab was not approved until 2015, Study ANBL0032 provided the only access to dinutuximab for the majority of the time Study 3(b) was open.
- There are no other available treatments in this setting (i.e., maintenance treatment for patients in remission after up-front therapy). Patients in the control arm were observed until the time of relapse, so differences in concomitant therapy would be primarily limited to supportive care treatments, which could differ by site and time period.
- The definition and ascertainment of endpoints and other key covariates were comparable across populations. However, there are several key distinctions: the primary endpoint of EFS was determined by local evaluator and BICR assessment was only available for the DFMO arm; the assessment frequency for EFS may be different in later times of follow-up; and some potentially relevant clinical characteristics were not collected in ANBL0032.
- Based on the Applicant's proposed primary analysis, the estimated treatment effect is large, with an EFS HR of 0.48 (95% CI: 0.27, 0.85), and an OS HR 0.32 (95% CI 0.15, 0.70). Although the historical EFS rate of 70% limits the observable magnitude of effect in this maintenance setting, these results are supported by the numerous sensitivity and supportive analyses conducted by the Applicant and FDA.

While a randomized controlled trial may have been feasible in this population and disease setting

prior to the publication of Study 3(b) results in 2018, it would likely be challenging to conduct at this time given the widespread knowledge of the Study 3(b) results within the pediatric oncology patient community and the lack of any other approved or available therapies in the maintenance setting to serve as a comparator arm. Two clinical SGEs, both academic investigators in this field, stated that investigators may be willing to participate in a randomized trial, but they were less sure about the acceptance within the patient community. It is possible there would be limited enrollment and drop-out of patients randomized to a control arm. Given these considerations, the review team finds the use of an ECT to be appropriate in this specific and unique circumstance.

### ***Determination of an Adequate and Well-Controlled Trial***

As described in 21 CFR 314.126, “the purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation...Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is ‘substantial evidence’ to support the claims of effectiveness for new drugs. An adequate and well-controlled study has the following characteristics:

- There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results.
- The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect...Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).
- The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.
- The method of assigning patients to treatment and control groups minimizes bias and ...adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data.
- The methods of assessment of subjects’ response are well-defined and reliable.

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- There is an analysis of the results of the study adequate to assess the effects of the drug.”

The review team considered each of the points outlined in the regulation in its determination of whether this single externally controlled trial is an adequate and well-controlled trial:

- There is a clear statement of objectives. While Study 3(b) was not initially designed to support a marketing application and the ECT was designed post-hoc, the pre-specified statistical analysis plan was developed through discussions with FDA.
- There appears to be a valid comparison to the external control and its use is appropriate in this setting given the high and predictable mortality after relapse.
- All patients had the disease being studied (HRNB in remission after up-front therapy); in addition, 95% of patients on the investigational arm completed up-front therapy on same clinical trial as patients on the control arm. The remaining 5% of patients received the same therapy, but not on the ANBL0032 clinical trial.
- Attempts were made to minimize bias through detailed selection rules. However, it is challenging to control for potential biases related to unmeasured and residual differences between arms given the design of a non-randomized trial.
- The response criteria and tumor assessments used in the trial are appropriate for the disease. While imaging after 2 years was conducted per institutional standard, >80% of patients on both arms had imaging completed through 5 years.
- The primary statistical analysis of the results of the study and multiple sensitivity and supportive analyses conducted by the Applicant and FDA appear adequate to assess the effects of the drug.

#### ***Determination of Substantial Evidence of Effectiveness with a Single Externally Controlled Trial and Confirmatory Evidence***

The FDA Substantial Evidence of Effectiveness Guidance states that “in general, substantiation of a drug’s effectiveness obtained with two trials, especially with complementary design, will provide more convincing evidence of effectiveness than would a single trial.”

FDA did not consider this ECT to be capable of establishing substantial evidence of effectiveness on its own. The quality of clinical evidence to establish effectiveness and the resulting level of certainty about the demonstration of substantial evidence is impacted by the selection of trial design, and the uncertainties inherent in a non-randomized design increase the potential of false positive conclusions.

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The Food and Drug Administration Modernization Act (FDAMA) of 1997 amended the statutory provision on substantial evidence of effectiveness such that “under certain circumstances and consistent with FDAMA, FDA can conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness,” taking into consideration the persuasiveness of the single trial, robustness of the confirmatory evidence, and the seriousness of the disease.

FDA considers a number of factors when determining whether reliance on a single adequate and well-controlled clinical investigation plus confirmatory evidence is appropriate, including the following:

- Persuasiveness of the single trial
- Robustness of the confirmatory evidence
- Seriousness and rarity of the disease, particularly where there is an unmet medical need
- Whether it is ethical and practicable to conduct more than one adequate and well-controlled investigation

In this application, the external control data was of high quality due to its provenance and the large set of individual patient-level trial data, the magnitude of treatment effect was large, and the results of sensitivity analyses were generally consistent with the Applicant’s primary analysis.

Considering the seriousness of the disease, HRNB is a rare and life-threatening disease with a high unmet need. Prognosis after relapse is poor and there are no available therapies in the proposed disease setting.

In many oncology applications, the evidentiary package is supported by dose-dependent tumor response data in early-stage studies with or without additional clinical data showing early activity or efficacy in other cancer indications. Given the suggested cytostatic mechanism of action of DFMO as a single agent in this application, response rate data are not expected in this clinical setting.

The 2019 Substantial Evidence draft guidance states that “compelling mechanistic evidence in the setting of well-understood disease pathophysiology, may be sufficient to provide substantial evidence of effectiveness of a new drug or a new indication.” Such mechanistic evidence would generally be obtained from clinical testing using a relevant and well understood pharmacodynamic endpoint; however, the guidance states it could also be collected from other sources such as animal studies.

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In this application, confirmatory evidence providing strong mechanistic support was derived from the well-understood pathophysiology of *ODC* and *MYCN* in neuroblastoma, the mechanism of action of eflornithine in vitro, and evidence of in vivo tumor preventative activity in two well-established, relevant animal models of neuroblastoma which showed that eflornithine prevents or delays tumor formation in mice who have no initial evidence of disease. While LIN28 overexpression is observed in multiple tumor types, and there have been negative trials of eflornithine in adults with cancer, the *ODC1* and *MYCN* genes are not major drivers of those tumors. In contrast, these genes are particularly relevant in neuroblastoma and aberrations of *ODC* and *MYCN* are correlated with poor prognosis in this disease. In addition, pediatric solid tumors have largely different ontogeny and biology from adult tumors, the latter being more likely to have substantially higher mutational burdens and multiple driver mutations. Thus, the lack of activity in other adult tumor types does not necessarily portend a lack of activity in neuroblastoma.

Given the complex nature of this application, an Oncology Drugs Advisory Committee meeting was held on October 4, 2023. Regarding the voting question, “Has the Applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?”, 14 members voted yes, and 6 members voted no. The discussion was robust, highlighting both strengths and limitations of the application.

While there are limitations of non-randomized trials as previously described, FDA may exert regulatory flexibility where appropriate and rely on study designs that produce less certainty in some circumstances when a better design is not feasible. The 2019 FDA guidance on Demonstrating Substantial Evidence of Effectiveness states that “in certain settings, a somewhat greater risk (compared to placebo-controlled or other randomized superiority trials) of false positive conclusions – and therefore less certainty about effectiveness – may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy...for an unmet medical need. The data supporting effectiveness could, despite the greater risk of error, support a conclusion that there is substantial evidence of effectiveness.”

Based on the strength of the evidence in the ECT and the confirmatory nonclinical data, FDA determined that application contains substantial evidence of effectiveness to conclude that DFMO reduces the risk of relapse in patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy. In the context of the strength of the scientific evidence, the feasibility of a randomized trial, and the unmet medical need in this pediatric patient population with a life-threatening disease, the review team considered it appropriate to rely upon the results of the ECT

as the primary basis of the evidence of effectiveness.

## 8.2. Review of Safety

### Data:

The safety evaluation used is based on analysis of a safety population comprised of 311 patients enrolled into either Study 3b (Strata 1 & 2) or Study 14 (all strata except 1b) who received the to-be-marketed DFMO drug product at a dose of 1500 mg/m<sup>2</sup>/day and for whom full safety data are available. The Study 3b CSR reports safety data for an additional 49 patients with partial safety data collected as a result of transition to NMTRC003b from the predecessor study at varying points in treatment. Safety data collected after transfer to NMTRC003b are available, but represent partial safety data at varying start points on therapy and potentially confound interpretation when combined with patients for whom complete data are available and are therefore excluded from the safety population used to inform the proposed label. Missing baseline assessments notwithstanding, there was no evidence to indicate the transfer patients experienced significant differences in adverse events, SAE's, or discontinuation of study drug.

The Applicant also has very limited data for a small subset of patients with exposures at a higher dose level, 5000 mg/m<sup>2</sup>/day from Study 14 Stratum 1b; at the time of data cutoff only 3 of the Study 14 Stratum 1b patients had received at least 1 year of DFMO dosing.

In addition to the pediatric studies, DFMO has also been assessed in a food effect study conducted in healthy adult volunteers.

### The Applicant's Position:

These safety data allow for an informed assessment of the safety profile of DFMO in the intended patient population (i.e., subjects who achieve remission following multiagent, multimodality therapy for HRNB).

### The FDA's Assessment:

FDA considered the **pooled safety population** to include the 360 pediatric patients with newly diagnosed or relapsed/refractory high-risk neuroblastoma who received eflornithine as a single agent taken orally twice daily, dose ranging 192 - 768 mg, based on body surface area (BSA), until disease progression or unacceptable toxicity for a maximum of 2 years in Study 3b (n=101; NCT02679144) and Study 14 (n=259; NCT02679144).

The **primary safety population** included a subset of 85 patients who received eflornithine at the proposed dose of eflornithine in Study 3(b) Stratum 1 (in which the population was reflective of the proposed indication) for whom safety data was available.

### 8.2.1. Safety Review Approach

#### The Applicant's Position:

The data presented herein is an integrative analysis of safety data relevant to the use of DFMO in pediatric patients who achieve remission following upfront or relapse therapy for HRNB.

Data for the safety population are presented both by study as well as both studies pooled together to support comparisons between studies. Although the safety population is comprised only of the patients treated with the proposed label dose of 1500 mg/m<sup>2</sup>/day, data for Study 14 Stratum 1b (5000 mg/m<sup>2</sup>/day) are also presented separately and pooled with all subjects from both studies overall. Since the Applicant is seeking approval for the 1500 mg/m<sup>2</sup>/day dose level, discussion of safety findings focuses on the pooled data for subjects enrolled into the 1500 mg/m<sup>2</sup>/day dose strata across both Study 3b and Study 14. Safety data for Study 14 Stratum 1b are only discussed if there were clinically noteworthy findings.

Both studies captured AEs per Common Terminology Criteria for Adverse Events (CTCAE) version 4. Study 3b captured new or worsening AEs of CTCAE Grade 2 or higher each visit after administration of study drug, while Study 14 captured new or worsening AEs of CTCAE Grade 3 or higher each visit after administration of study drug. Study 14 allowed the reporting of Grade 2 AEs in the event the AE resulted in either discontinuation from the study or dose modifications (discussed further in Section 8.2.4). The difference in AE reporting requirements between the studies led to a higher total incidence of AEs and AESIs reported for Study 3b, which, as expected, is primarily driven by differences in the number of Grade 2 AEs. To address differences in AE collection between the two studies, AE tables also include one column containing all AEs reported for Study 3b and then a column of Grade 3 or higher AEs in Study 3b to enable appropriate comparison to Study 14 AE rates. The pooled 1500 mg/m<sup>2</sup> group does not include Study 3b AEs < Grade 3.

The integrated safety analysis (Module 2.7.4) also presents all safety data by disease history (i.e., remission after initial upfront treatment or after relapse or refractory disease) to assess whether the greater exposure to toxic oncolytic treatments experienced by patients achieving remission after relapse or refractory disease may have contributed to higher incidence of safety events in that group. None of the differences between these two groups were determined to be clinically significant, therefore safety data will not be presented by disease history in this Assessment Aid.

Previous clinical experience with indicate that the most common AEs related to DFMO administration include diarrhea, headache, nausea, hearing loss, tinnitus, and asthenia. Other common toxicities (each accounting for 2 to 3% of all AEs reported) were epigastric pain, flatulence, dyspepsia, anemia, dizziness and skin rash. Due to reports of hearing loss during



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administration of high doses of DFMO (ORNIDYL 1990, Croghan 1991), audiograms were included as a safety assessment in Study 3b and Study 14. Changes in hearing were observed through audiograms and AE reporting, as described further in Section 8.2.5.

#### The FDA's Assessment:

FDA agrees with the Applicant's approach to pool safety data from Study 3(b) and Study 14 for the patients who received the proposed dose of eflornithine.

Safety data were limited in both clinical studies. Study 3(b) collected Grade 2 or higher AEs and no laboratory data. Study 14 collected Grade 3 or higher AEs.

In addition to the safety data provided in the initial NDA submission, the Applicant submitted a Day 120 Safety Update Report. A data cutoff of June 30, 2022 was used for this update and provided 12 months of additional follow-up information beyond the original data cutoff of June 30, 2021. The 120-day safety update included an additional 12 months of safety data for the 62 patients in Study 14 who were ongoing in treatment at the time of the NDA data cutoff and data from 40 patients enrolled after the NDA data cutoff. Of the 40 new patients, 28 received eflornithine at a higher dose than the proposed dose (2500 mg/m<sup>2</sup> BID) in Study 14 Stratum 1b. No additional data from Study 3(b) was collected after the original NDA data cutoff because all patients had completed treatment and safety data were not collected in the long-term follow-up phase of the study.

### **Overall Exposure**

#### The Applicant's Position:

Overall, 381 patients received DFMO and 159 patients completed DFMO therapy (Module 2.7.4 Table 6, ISS Table 14.1.1.1.1). Across both Study 3b (Strata 1 and 2) and Study 14 (All Strata except 1b), 360 patients received the projected labeled dose of 1500 mg/m<sup>2</sup> and 21 patients in Study 14 (Stratum 1b) received 5000 mg/m<sup>2</sup>, which is higher than the intended dose for the proposed indication (750 ± 250 mg/m<sup>2</sup> twice a day [BID]). In Study 14 (Stratum 1b), none of the patients have completed the full 2 years of DFMO at the time of data cutoff as the study is ongoing, however only 1 patient has stopped DFMO early and the other 20 (95.2%) patients were continuing to receive DFMO therapy at the time of data cutoff.

**Table 55: Safety Population**

| Study    |                                | Prior supply of DFMO | Current supply of DFMO | CSR       | Safety Population SCS | Total Safety Population SCS |
|----------|--------------------------------|----------------------|------------------------|-----------|-----------------------|-----------------------------|
| Study 3b | Transfer patients <sup>1</sup> | 49                   | 49                     | 3b CSR    | No                    | 0                           |
|          | Direct enrolled                | 0                    | 52                     | 3b CSR    | Yes                   | 52                          |
| Study 14 | Direct enrolled                | 0                    | 259                    | PK report | Yes                   | 259                         |
| Total    |                                | 49                   | 360                    |           |                       | 311                         |

<sup>1</sup>Safety data were contractually inaccessible to the Applicant for 49 patients who initiated treatment under a trial that preceded NMTRC003b (NMTRC003) and later transferred into Study 3b. Safety data collected after transfer to NMTRC003b are available, but represent partial safety data at varying start points on therapy, and potentially confound interpretation when combined with patients for whom complete data are available and therefore are excluded from the safety population. (See Module 2.7.4 Section 1.2 for additional information).

In Study 3b, the majority of patients (63.5%) completed 2 years of DFMO therapy as compared to 19 (36.5%) of the patients stopping DFMO early. In Study 14 (All Strata Except 1b), 126 (48.6%) patients completed DFMO therapy with 35.1% discontinuing early which is very similar to the discontinuation rate in study 3b (36.5%); 42 (16.2%) patients are still ongoing with DFMO therapy.

Reasons for stopping DFMO early was consistent across both studies with the primary reason for stopping for the 1500 mg/m<sup>2</sup> dose, related to relapse of disease or diagnosis of a secondary cancer (Module 2.7.4 Table 6).

After completing or stopping DFMO early, patients continue for long-term follow-up. Although the majority of Study 3b patients are ongoing (73.1%), of the patients who discontinued the study early, the most frequent cause for study discontinuation was death (19.2%). This contrasts slightly with Study 14 discontinuations (11.2%); however, a greater number of patients remain ongoing in Study 14 (88.8%). Pooling studies 3b and 14, however, resulted in a similar number of patients discontinuing due to death (11.7%). Of those discontinuing the study due to death the reason for death was due to relapse of disease (Module 2.7.4 Table 6).

#### The FDA's Assessment:

FDA agrees that all patients in the pooled safety population received the proposed dose of eflornithine as a single agent taken orally twice daily, with doses ranging from 192 - 768 mg, based on body surface area (BSA), until disease progression or unacceptable toxicity for a maximum of 2 years.

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While 49 “transfer patients” in Study 3(b) had partial safety data collected as a result of transition from NMTRC003 to NMTRC003b, FDA considered the available safety data derived from these patients to be informative, particularly given that there are no other approved indications for this formulation of eflornithine to help inform the assessment of safety. Therefore, these patients were included in the pooled safety population.

### Relevant characteristics of the safety population:

#### Data:

Overall, the mean age (SD) of patients was 5.2 (3.04). The majority of patients were male (55.7%), white (76.5%), and were in the  $\geq 18$  months to  $< 6$  years age group (64.5%).

Across both studies (1500 mg/m<sup>2</sup>) pooled, the majority of subjects had a disease history of remission (i.e., NED/NAD) after initial upfront treatment than a disease history of remission after relapse or refractory disease (71.7% versus 28.3%). This trend was also observed when disease history was assessed by study, with 78.8% of Study 3b subjects and 70.3% of Study 14 All Strata except 1b subjects having a disease history of remission after initial upfront treatment.

A summary of baseline demographic and disease characteristics is provided in Table 49.

**Table 56: Summary of Patient Baseline Demographic and Disease Characteristics by Study and Dose – Safety Population**

| Parameter                             | Statistics  | Study 3b<br>(Strata 1 & 2)<br>(1500 mg/m <sup>2</sup> )<br>(N=52)<br>n (%) | Study 14,<br>All Strata<br>except 1b<br>(1500 mg/m <sup>2</sup> )<br>(N=259)<br>n (%) | Both Studies<br>(1500 mg/m <sup>2</sup> )<br>Pooled<br>(N=311)<br>n (%) | Study 14<br>Stratum 1b<br>(5000 mg/m <sup>2</sup> )<br>(N=21)<br>n (%) | All DFMO<br>(N=332)<br>n (%) |
|---------------------------------------|-------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------|
| Age (year) at Enrollment              | n (missing) | 52 (0)                                                                     | 259 (0)                                                                               | 311 (0)                                                                 | 21 (0)                                                                 | 332 (0)                      |
|                                       | Mean (SD)   | 5.2 (2.95)                                                                 | 5.3 (3.10)                                                                            | 5.2 (3.07)                                                              | 4.0 (2.31)                                                             | 5.2 (3.04)                   |
|                                       | Median      | 4.0                                                                        | 5.0                                                                                   | 5.0                                                                     | 3.0                                                                    | 4.0                          |
|                                       | Q1, Q3      | 3.0, 7.0                                                                   | 3.0, 6.0                                                                              | 3.0, 6.0                                                                | 3.0, 4.0                                                               | 3.0, 6.0                     |
|                                       | Min, Max    | 1, 14                                                                      | 1, 19                                                                                 | 1, 19                                                                   | 2, 11                                                                  | 1, 19                        |
| <b>Age Group (year) at Enrollment</b> |             |                                                                            |                                                                                       |                                                                         |                                                                        |                              |
| 0 to $< 18$ Months                    | n (%)       | 0                                                                          | 2 (0.8)                                                                               | 2 (0.6)                                                                 | 0                                                                      | 2 (0.6)                      |
| $\geq 18$ Months to $< 6$ Years       | n (%)       | 33 (63.5)                                                                  | 163 (62.9)                                                                            | 196 (63.0)                                                              | 18 (85.7)                                                              | 214 (64.5)                   |
| $\geq 6$ Years                        | n (%)       | 19 (36.5)                                                                  | 94 (36.3)                                                                             | 113 (36.3)                                                              | 3 (14.3)                                                               | 116 (34.9)                   |
| <b>BSA (m<sup>2</sup>) Group</b>      |             |                                                                            |                                                                                       |                                                                         |                                                                        |                              |
| $< 0.25$                              | n (%)       | 0                                                                          | 0                                                                                     | 0                                                                       | 0                                                                      | 0                            |
| 0.25 to $< 0.5$                       | n (%)       | 1 (1.9)                                                                    | 8 (3.1)                                                                               | 9 (2.9)                                                                 | 0                                                                      | 9 (2.7)                      |

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| Parameter                                 | Statistics | Study 3b<br>(Strata 1 &<br>2)<br>(1500 mg/m <sup>2</sup> )<br>(N=52)<br>n (%) | Study 14,<br>All Strata<br>except 1b<br>(1500 mg/m <sup>2</sup> )<br>(N=259)<br>n (%) | Both Studies<br>(1500 mg/m <sup>2</sup> )<br>Pooled<br>(N=311)<br>n (%) | Study 14<br>Stratum 1b<br>(5000 mg/m <sup>2</sup> )<br>(N=21)<br>n (%) | All DFMO<br>(N=332)<br>n (%) |
|-------------------------------------------|------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------|
| 0.5 to <0.75                              | n (%)      | 31 (59.6)                                                                     | 149 (57.5)                                                                            | 180 (57.9)                                                              | 16 (76.2)                                                              | 196 (59.0)                   |
| 0.75 to <1.0                              | n (%)      | 14 (26.9)                                                                     | 70 (27.0)                                                                             | 84 (27.0)                                                               | 3 (14.3)                                                               | 87 (26.2)                    |
| 1.0 to <1.25                              | n (%)      | 5 (9.6)                                                                       | 19 (7.3)                                                                              | 24 (7.7)                                                                | 2 (9.5)                                                                | 26 (7.8)                     |
| 1.25 to <1.50                             | n (%)      | 1 (1.9)                                                                       | 8 (3.1)                                                                               | 9 (2.9)                                                                 | 0                                                                      | 9 (2.7)                      |
| ≥1.5                                      | n (%)      | 0                                                                             | 5 (1.9)                                                                               | 5 (1.6)                                                                 | 0                                                                      | 5 (1.5)                      |
| <b>Gender</b>                             |            |                                                                               |                                                                                       |                                                                         |                                                                        |                              |
| Female                                    | n (%)      | 23 (44.2)                                                                     | 115 (44.4)                                                                            | 138 (44.4)                                                              | 9 (42.9)                                                               | 147 (44.3)                   |
| Male                                      | n (%)      | 29 (55.8)                                                                     | 144 (55.6)                                                                            | 173 (55.6)                                                              | 12 (57.1)                                                              | 185 (55.7)                   |
| <b>Race</b>                               |            |                                                                               |                                                                                       |                                                                         |                                                                        |                              |
| American Indian or Alaska Native          | n (%)      | 0                                                                             | 1 (0.4)                                                                               | 1 (0.3)                                                                 | 0                                                                      | 1 (0.3)                      |
| Asian                                     | n (%)      | 1 (1.9)                                                                       | 18 (6.9)                                                                              | 19 (6.1)                                                                | 2 (9.5)                                                                | 21 (6.3)                     |
| Black or African American                 | n (%)      | 3 (5.8)                                                                       | 16 (6.2)                                                                              | 19 (6.1)                                                                | 3 (14.3)                                                               | 22 (6.6)                     |
| Native Hawaiian or Other Pacific Islander | n (%)      | 0                                                                             | 1 (0.4)                                                                               | 1 (0.3)                                                                 | 0                                                                      | 1 (0.3)                      |
| White                                     | n (%)      | 45 (86.5)                                                                     | 195 (75.3)                                                                            | 240 (77.2)                                                              | 14 (66.7)                                                              | 254 (76.5)                   |
| More than One Race                        | n (%)      | 3 (5.8)                                                                       | 9 (3.5)                                                                               | 12 (3.9)                                                                | 0                                                                      | 12 (3.6)                     |
| Unknown/ Not Reported                     | n (%)      | 0                                                                             | 19 (7.3)                                                                              | 19 (6.1)                                                                | 2 (9.5)                                                                | 21 (6.3)                     |
| Other                                     | n (%)      | 0                                                                             | 0                                                                                     | 0                                                                       | 0                                                                      | 0                            |
| <b>Disease History</b>                    |            |                                                                               |                                                                                       |                                                                         |                                                                        |                              |
| NED/NAD After Initial Upfront Treatment   | n (%)      | 41 (78.8)                                                                     | 182 (70.3)                                                                            | 223 (71.7)                                                              | 21 (100)                                                               | 244 (73.5)                   |
| NED/NAD After Relapse or Refractory       | n (%)      | 11 (21.2)                                                                     | 77 (29.7)                                                                             | 88 (28.3)                                                               | 0                                                                      | 88 (26.5)                    |

BSA = body surface area; Max = maximum; Min = minimum; MR = minimal response; NAD = no active disease; NED = no evidence of disease; Q1 = first quartile; Q3 = third quartile.

Notes:

Percentages (in parentheses) are based on the total number of patients in each column.

Source: ISS Table 14.1.3.1.1

### The Applicant's Position:

Overall, the demographics and baseline disease characteristics of subjects treated in the clinical program reflect the intended target population.

### The FDA's Assessment:

FDA agrees that the demographics of the safety populations are generally similar to the intended use population.

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In the **pooled safety population (N=360)**, the median age of patients was 4 years (range: 1 to 19); 56% male; 78% White, 7% Black, 5% Asian; 9% Hispanic or Latino; 85% had International Neuroblastoma Staging System Stage 4 disease; 39% had neuroblastoma with known MYCN-amplification.

In the **primary safety population (N=85)**, the median age of patients was 4 years (range: 1 to 17); 59% male; 85% White, 7% Black, 1% Asian; 8% Hispanic or Latino; 87% had International Neuroblastoma Staging System Stage 4 disease; 47% had neuroblastoma with known MYCN-amplification.

### **Adequacy of the safety database:**

#### Data:

The safety population includes 311 patients treated with DFMO from two phase 2 trials. Across the safety population, 287 (92.3%) patients remained on treatment for  $\geq 3$  months, 257 (82.6%) patients remained on treatment for  $\geq 6$  months, 216 (69.5%) patients remained on treatment for  $\geq 1$  year, 195 (62.7%) patients remained on treatment for  $\geq 1.5$  years, and 159 (51.1%) patients remained on treatment for  $\geq 2$  years. At the time of data cutoff, 51.1% of patients had completed DFMO therapy, with 13.5% ongoing and 35.1% discontinued.

#### The Applicant's Position:

The size of the safety database for this program is considered adequate to support the benefit-risk assessment for the use of DFMO in pediatric patients who achieve remission following upfront or relapse therapy for HRNB.

#### The FDA's Assessment:

FDA agrees that the safety population studied in Study 3(b) and Study 14 adequately represents the target population, including demographics, disease and other baseline characteristics. The safety narratives were also adequate to allow further assessment of relevant safety signals.

## **8.2.2. Adequacy of Applicant's Clinical Safety Assessments**

### **Issues Regarding Data Integrity and Submission Quality**

#### Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety.

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**The FDA’s Assessment:**

FDA agrees that there do not appear to be any data quality or integrity concerns. The Applicant provided all the datasets and supporting documentation as requested.

**Categorization of Adverse Events**

**The Applicant’s Position:**

The safety evaluation of DFMO included the following:

- Treatment emergent adverse events (TEAEs) defined as any AE that developed or worsened in intensity or frequency after initiation of DFMO. For the pooled data, AEs with a start date up to 30 days after stopping DFMO will be assessed for being a TEAE which was a requirement for reporting by both study protocols
- Serious TEAEs
- Adverse events leading to discontinuation or modification of study drug
- Laboratory and vital sign values recorded as adverse events
- Aes of special interest (AESIs) including hearing and vestibular disorders, renal impairment, hepatic disorders, and gastrointestinal abnormalities

Both studies captured Aes per Common Terminology Criteria for Adverse Events (CTCAE) version 4. Study 3b captured new or worsening Aes of CTCAE Grade 2 or higher each visit after administration of study drug, while Study 14 captured new or worsening Aes of CTCAE Grade 3 or higher each visit after administration of study drug. Study 14 allowed the reporting of Grade 2 Aes in the event the AE resulted in either discontinuation from the study or dose modifications. The difference in AE reporting requirements between the studies led to a higher total incidence of Aes and AESIs reported for Study 3b, which, as expected, is primarily driven by differences in the number of Grade 2 Aes. To address differences in AE collection between the two studies, AE tables also include one column containing all AEs reported for Study 3b and then a column of Grade 3 or higher Aes in Study 3b to enable appropriate comparison to Study 14 AE rates. The pooled 1500 mg/m<sup>2</sup> group does not include Study 3b Aes < Grade 3.

**The FDA’s Assessment:**

FDA agrees with the Applicant’s assessment.

**Routine Clinical Tests**

**The Applicant’s Position:**

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The clinical safety assessments performed for Study 3b and Study 14 are listed in Table 50.

**Table 57: Clinical Safety Assessments Performed in Study 3b and Study 14**

| Clinical Assessments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Study 3b                                                                                                                                                                                                                            | Study 14                                                                                                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical Chemistry and Hematology Labs <sup>1</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Laboratory testing was performed for Study 3b, however the lab results only exist in source at clinical sites (i.e., not entered into EDC). Study 3b lab results meeting CTCAE 4.0 Grade 2 or higher criteria were captured as Aes. | Performed at screening, every 30 days for the first 6 months of treatment, every 90 days for the remaining 1.5 years of treatment, and end of maintenance therapy. |
| Vital Signs <sup>2</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Vitals were measured at Screening, Day 1 of each cycle, Day 15 of Cycle 1, and end of therapy                                                                                                                                       | Vitals were measured at Screening, every 30 days for the first 6 months of DFMO therapy, every 60 days for the last 18 months of DFMO therapy, and end of therapy  |
| ECGs <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | ECGs were not required per the Study 3b protocol                                                                                                                                                                                    | A single ECG was performed at Screening and at 3 hours postdose on Days 1, 91, and 181 (each in triplicate) to correspond with PK sample collection.               |
| Audiograms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Screening, after 6 months of treatment, after 12 months of treatment, at end of DFMO maintenance therapy, and as otherwise clinically indicated                                                                                     | Screening, after 6 months of treatment, after 12 months of treatment, at end of DFMO maintenance therapy, and as otherwise clinically indicated                    |
| <sup>1</sup> Clinical chemistries included: blood urea nitrogen, electrolytes, creatinine, bilirubin, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase. Hematology labs included: complete blood count (white blood cell, absolute neutrophil count, hemoglobin, platelets) with differentials<br><sup>2</sup> Vital signs collected in both studies included: temperature, heart rate, resting blood pressure, BSA, weight, and height.<br><sup>3</sup> ECG parameters included ventricular rate, PR interval, and QT, and QRS. |                                                                                                                                                                                                                                     |                                                                                                                                                                    |

#### The FDA's Assessment:

FDA agrees with the Applicant's assessment.

### 8.2.3. Safety Results

#### Deaths

#### The Applicant's Position:

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During DFMO administration, there were no adverse events leading to death in either Study 3b or Study 14 (ISS Listing 16.2.1.2). Deaths associated with relapse post-DFMO administration are reported in the efficacy analyses for event-free survival (EFS) and overall survival (OS) (2.7.3 Summary of Clinical Efficacy, Section 3.3.1.1 and Section 3.3.1.2).

**The FDA's Assessment:**

FDA agrees with the Applicant's assessment. There were no Grade 5 treatment-emergent adverse events reported in Study 3(b) or Study 14.

**Serious Adverse Events****The Applicant's Position:**

In Study 3b, there were no SAEs that were reported in more than one patient. The SAEs in Study 14 except Stratum 1b that were reported in more than one patient were pneumonia, bacteremia, device related infection (catheter related infection), skin infection, upper respiratory tract infection, otitis media, dehydration, hypoglycemia, vomiting, pyrexia, hypoxia, and blood creatinine increased. In Study 14 Stratum 1b, the SAE of anemia was reported in 2 (9.5%) patients.

**Table 58: Summary of Serious Adverse Events Reported in >1 Patient by SOC and PT by Study and Dose – Safety Population**

| System Organ Class Preferred Term     | Study 3b (Strata 1 & 2) (1500 mg/m <sup>2</sup> ) (N=52) n (%) | Study 14, All Strata except 1b (1500 mg/m <sup>2</sup> ) (N=259) n (%) | Both Studies (1500 mg/m <sup>2</sup> ) Pooled (N=311) n (%) | Study 14 Stratum 1b (5000 mg/m <sup>2</sup> ) (N=21) n (%) | All DFMO (N=332) n (%) |
|---------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------|------------------------------------------------------------|------------------------|
| Number of Patients with Serious TEAEs | 6 (11.5)                                                       | 46 (17.8)                                                              | 52 (16.7)                                                   | 3 (14.3)                                                   | 55 (16.6)              |
| Infections and infestations           | 1 (1.9)                                                        | 23 (8.9)                                                               | 24 (7.7)                                                    | 0                                                          | 24 (7.2)               |
| Pneumonia                             | 0                                                              | 4 (1.5)                                                                | 4 (1.3)                                                     | 0                                                          | 4 (1.2)                |
| Bacteremia                            | 0                                                              | 3 (1.2)                                                                | 3 (1.0)                                                     | 0                                                          | 3 (0.9)                |
| Device related infection              | 0                                                              | 3 (1.2)                                                                | 3 (1.0)                                                     | 0                                                          | 3 (0.9)                |
| Skin infection                        | 1 (1.9)                                                        | 2 (0.8)                                                                | 3 (1.0)                                                     | 0                                                          | 3 (0.9)                |
| Upper respiratory tract infection     | 0                                                              | 3 (1.2)                                                                | 3 (1.0)                                                     | 0                                                          | 3 (0.9)                |
| Otitis media                          | 0                                                              | 2 (0.8)                                                                | 2 (0.6)                                                     | 0                                                          | 2 (0.6)                |
|                                       |                                                                |                                                                        |                                                             |                                                            |                        |
| Metabolism and nutrition disorders    | 2 (3.8)                                                        | 12 (4.6)                                                               | 14 (4.5)                                                    | 0                                                          | 14 (4.2)               |
| Dehydration                           | 0                                                              | 7 (2.7)                                                                | 7 (2.3)                                                     | 0                                                          | 7 (2.1)                |

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| System Organ Class<br>Preferred Term                    | Study 3b<br>(Strata 1 & 2)<br>(1500 mg/m <sup>2</sup> )<br>(N=52)<br>n (%) | Study 14,<br>All Strata<br>except 1b<br>(1500 mg/m <sup>2</sup> )<br>(N=259)<br>n (%) | Both Studies<br>(1500 mg/m <sup>2</sup> )<br>Pooled<br>(N=311)<br>n (%) | Study 14<br>Stratum 1b<br>(5000<br>mg/m <sup>2</sup> )<br>(N=21)<br>n (%) | All DFMO<br>(N=332)<br>n (%) |
|---------------------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------|
| Hypoglycemia                                            | 1 (1.9)                                                                    | 3 (1.2)                                                                               | 4 (1.3)                                                                 | 0                                                                         | 4 (1.2)                      |
| Hyponatremia                                            | 1 (1.9)                                                                    | 1 (0.4)                                                                               | 2 (0.6)                                                                 | 0                                                                         | 2 (0.6)                      |
|                                                         |                                                                            |                                                                                       |                                                                         |                                                                           |                              |
| Gastrointestinal disorders                              | 2 (3.8)                                                                    | 8 (3.1)                                                                               | 10 (3.2)                                                                | 0                                                                         | 10 (3.0)                     |
| Vomiting                                                | 0                                                                          | 6 (2.3)                                                                               | 6 (1.9)                                                                 | 0                                                                         | 6 (1.8)                      |
| Diarrhea                                                | 1 (1.9)                                                                    | 1 (0.4)                                                                               | 2 (0.6)                                                                 | 0                                                                         | 2 (0.6)                      |
|                                                         |                                                                            |                                                                                       |                                                                         |                                                                           |                              |
| General disorders and administration site<br>conditions | 1 (1.9)                                                                    | 7 (2.7)                                                                               | 8 (2.6)                                                                 | 0                                                                         | 8 (2.4)                      |
| Pyrexia                                                 | 1 (1.9)                                                                    | 7 (2.7)                                                                               | 8 (2.6)                                                                 | 0                                                                         | 8 (2.4)                      |
|                                                         |                                                                            |                                                                                       |                                                                         |                                                                           |                              |
| Respiratory, thoracic and mediastinal<br>disorders      | 0                                                                          | 5 (1.9)                                                                               | 5 (1.6)                                                                 | 0                                                                         | 5 (1.5)                      |
| Hypoxia                                                 | 0                                                                          | 3 (1.2)                                                                               | 3 (1.0)                                                                 | 0                                                                         | 3 (0.9)                      |
|                                                         |                                                                            |                                                                                       |                                                                         |                                                                           |                              |
| Investigations                                          | 0                                                                          | 4 (1.5)                                                                               | 4 (1.3)                                                                 | 0                                                                         | 4 (1.2)                      |
| Blood creatinine increased                              | 0                                                                          | 2 (0.8)                                                                               | 2 (0.6)                                                                 | 0                                                                         | 2 (0.6)                      |
|                                                         |                                                                            |                                                                                       |                                                                         |                                                                           |                              |
| Blood and lymphatic system disorders                    | 0                                                                          | 2 (0.8)                                                                               | 2 (0.6)                                                                 | 2 (9.5)                                                                   | 4 (1.2)                      |
| Anemia                                                  | 0                                                                          | 0                                                                                     | 0                                                                       | 2 (9.5)                                                                   | 2 (0.6)                      |

TEAE = treatment-emergent adverse event.

Notes:

Adverse event terms are coded using MedDRA version 23.1.

Percentages (in parentheses) are based on the total number of patients in each column.

Data are sorted by descending All DFMO descending Both Studies pooled descending Study 14 Stratum 1b SOC PT

Source: ISS Table 14.3.1.6.1

**The FDA's Assessment:**

In the **pooled safety population (N=360)**, serious adverse reactions occurred in 16% of patients who received eflornithine. Serious adverse reactions in >1% of patients included pyrexia (2.2%), vomiting (1.9%), dehydration (1.9%), pneumonia (1.4%), skin infection (1.4%), and hypoglycemia (1.1%).

In the **primary safety population (N=85)**, serious adverse reactions occurred in 12% of patients who received eflornithine. Serious adverse reactions in > 1 patient included skin infection (3 patients).

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## **Dropouts and/or Discontinuations Due to Adverse Effects**

### The Applicant's Position:

Study 3b CRFs did not offer differentiation of permanent drug withdrawal (i.e., discontinuation of study drug) versus temporary withdrawal (i.e., drug interruptions). The 9 patients that had drug withdrawn as the action taken due to an AE were manually reviewed to determine whether the action taken was a permanent discontinuation of study drug versus an interruption, as described further in Module 2.7.4 Section 2.2.1 and the Study 3b CSR.

In Study 14 All Strata except 1b, 13 (5.0%) patients had a TEAE that led to treatment discontinuation. The TEAEs that led to discontinuation of study drug in more than one patient were hypoacusis, platelet count decreased, and headache (ISS Table 14.3.1.8.1).

### The FDA's Assessment:

In the **pooled safety population (N=360)**, permanent discontinuation of eflornithine due to an adverse reaction occurred in 7% of patients. Adverse reactions which resulted in permanent discontinuation of eflornithine in > 1 patient included hearing loss, thrombocytopenia, increased AST/ALT, headache, and musculoskeletal pain.

In the **primary safety population (N=85)**, permanent discontinuation of eflornithine due to an adverse reaction occurred in 11% of patients. Adverse reactions which resulted in permanent discontinuation of eflornithine in > 1 patient included hearing loss.

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## **Dose Interruption/Reduction Due to Adverse Effects**

### The Applicant's Position:

For Study 14, dose modifications due to adverse events included dose reductions and/or study drug temporarily withheld (i.e., drug interruption). In Study 14 All Strata except 1b, 28 (10.8%) patients had a TEAE that led to dose modification. The TEAEs that led to dose modification in more than one patient in Study 14 All Strata except 1b were: alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased, hypoacusis, vomiting, anemia, and pyrexia. (ISS Table 14.3.1.9.1). The incidence of AEs of anemia leading to dose modification was notably higher in Study 14 Stratum 1b (14.3%) compared to Study 14 All Strata except 1b (0.8%). At the time of the data cutoff 4 of the 5 anemia events leading to dose modifications resolved with either a dose reduction or dose interruption.

In Study 14 all Strata except 1b, dosing of the study drug was interrupted in 26 (10.0%) patients (ISS Table 14.3.1.16). TEAEs that led to drug interruptions in more than one patient were: alanine aminotransferase increased (8 patients [3.1%]), hypoacusis (8 patients [3.1%]), aspartate aminotransferase increased (4 patients [1.5%]), anemia (2 patients [0.8%]), and vomiting (2 patients [0.8%]). Anemia and platelet count decreased TEAEs led to drug interruptions more frequently in Stratum 1b compared to Study 14 all strata except 1b. The higher incidence of drug interruptions due to anemia and platelet count decreased in Study 14 Stratum 1b is consistent with the higher incidence of these TEAEs in Study 14 Stratum 1b and hematological changes that have been reported to occur with higher doses of DFMO ([Saulnier Sholler 2018](#), [ORNIDYL 1990](#)).

### The FDA's Assessment:

In the **pooled safety population (N=360)**, dose modifications (reductions or interruptions) of eflornithine due to an adverse reaction occurred in 10% of patients. Adverse reactions which required dose modification in > 1 patient included hearing loss, increased AST/ALT, anemia, neutropenia, thrombocytopenia, pyrexia, and vomiting.

No dose interruptions were recorded in Study 3(b). In the **primary safety population (N=85)**, dose reductions of eflornithine due to an adverse reaction occurred in 8% of patients. Adverse reactions which required dose reductions in > 1 patient included hearing loss.

## **Significant Adverse Events**

### The Applicant's Position:

The significant AEs reported are described in other sections of the document (see Serious

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Adverse Events and Adverse Events of Special Interest).

**The FDA's Assessment:**

Refer to Section 8.2.4.

**Treatment Emergent Adverse Events and Adverse Reactions****The Applicant's Position:**

An overall summary of adverse events is presented in Table 59. The most common treatment emergent adverse events (reported in  $\geq 5\%$  of patients) are presented by SOC and PT in Table 60.

Across both Study 3b and Study 14, 45.3% of patients receiving the proposed labeled dose (1500 mg/m<sup>2</sup>) reported a TEAE, and 19.9% reported a TEAE related to the study drug.

Across both studies (1500 mg/m<sup>2</sup> dose) pooled, 45.3% of patients experienced at least one TEAE, the most frequently reported TEAEs were alanine aminotransferase increased (11.9%) and hypoacusis (11.9%).

**Table 59: Overall Summary of Adverse Events – Safety Population**

|                                                     | Study 3b<br>(Strata 1<br>& 2)<br>(1500<br>mg/m <sup>2</sup> )<br>(N=52)<br>n (%) | Study 3b<br>(Strata 1<br>& 2)<br>(1500<br>mg/m <sup>2</sup> )<br>Grade 3 or<br>higher<br>(N=52)<br>n (%) | Study 14,<br>All Strata<br>except 1b<br>(1500<br>mg/m <sup>2</sup> )<br>(N=259)<br>n (%) | Both<br>Studies<br>(1500<br>mg/m <sup>2</sup> )<br>Pooled<br>(N=311)<br>n (%) | Study 14<br>Stratum<br>1b<br>(5000<br>mg/m <sup>2</sup> )<br>(N=21)<br>n (%) | All DFMO<br>(N=332)<br>n (%) |
|-----------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------|
| Number of TEAEs                                     | 290                                                                              | 54                                                                                                       | 339                                                                                      | 393                                                                           | 36                                                                           | 429                          |
| Patients with at least one                          |                                                                                  |                                                                                                          |                                                                                          |                                                                               |                                                                              |                              |
| Adverse event                                       | 42 (80.8)                                                                        | 21 (40.4)                                                                                                | 120 (46.3)                                                                               | 141 (45.3)                                                                    | 9 (42.9)                                                                     | 150 (45.2)                   |
| Adverse events related to the study medication      | 19 (36.5)                                                                        | 12 (23.1)                                                                                                | 50 (19.3)                                                                                | 62 (19.9)                                                                     | 8 (38.1)                                                                     | 70 (21.1)                    |
| Serious adverse events                              | 6 (11.5)                                                                         | 5 (9.6)                                                                                                  | 46 (17.8)                                                                                | 51 (16.4)                                                                     | 3 (14.3)                                                                     | 54 (16.3)                    |
| Serious related adverse events                      | 1 (1.9)                                                                          | 1 (1.9)                                                                                                  | 5 (1.9)                                                                                  | 6 (1.9)                                                                       | 2 (9.5)                                                                      | 8 (2.4)                      |
| Adverse events leading to dose modification         | 5 (9.6)                                                                          | 2 (3.8)                                                                                                  | 28 (10.8)                                                                                | 30 (9.6)                                                                      | 4 (19.0)                                                                     | 34 (10.2)                    |
| Adverse events leading to treatment discontinuation | 9 (17.3)                                                                         | 8 (15.4)                                                                                                 | 13 (5.0)                                                                                 | 21 (6.8)                                                                      | 0                                                                            | 21 (6.3)                     |
| Adverse events of special interest                  | 23 (44.2)                                                                        | 9 (17.3)                                                                                                 | 77 (29.7)                                                                                | 86 (27.7)                                                                     | 1 (4.8)                                                                      | 87 (26.2)                    |
| Toxicity Grade 1                                    | 0                                                                                |                                                                                                          | 3 (1.2)                                                                                  | 3 (1.0)                                                                       | 2 (9.5)                                                                      | 5 (1.5)                      |

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|                                                   | Study 3b<br>(Strata 1<br>& 2)<br>(1500<br>mg/m <sup>2</sup> )<br>(N=52)<br>n (%) | Study 3b<br>(Strata 1<br>& 2)<br>(1500<br>mg/m <sup>2</sup> )<br>Grade 3 or<br>higher<br>(N=52)<br>n (%) | Study 14,<br>All Strata<br>except 1b<br>(1500<br>mg/m <sup>2</sup> )<br>(N=259)<br>n (%) | Both<br>Studies<br>(1500<br>mg/m <sup>2</sup> )<br>Pooled<br>(N=311)<br>n (%) | Study 14<br>Stratum<br>1b<br>(5000<br>mg/m <sup>2</sup> )<br>(N=21)<br>n (%) | All DFMO<br>(N=332)<br>n (%) |
|---------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------|
| Toxicity Grade 2                                  | 42 (80.8)                                                                        |                                                                                                          | 8 (3.1)                                                                                  | 8 (2.6)                                                                       | 1 (4.8)                                                                      | 9 (2.7)                      |
| Toxicity Grade 3                                  | 21 (40.4)                                                                        | 21 (40.4)                                                                                                | 112 (43.2)                                                                               | 133 (42.8)                                                                    | 9 (42.9)                                                                     | 142 (42.8)                   |
| Toxicity Grade 4                                  | 1 (1.9)                                                                          | 1 (1.9)                                                                                                  | 22 (8.5)                                                                                 | 23 (7.4)                                                                      | 2 (9.5)                                                                      | 25 (7.5)                     |
| Toxicity Grade 5                                  | 0                                                                                | 0                                                                                                        | 0                                                                                        | 0                                                                             | 0                                                                            | 0                            |
| Toxicity Grades 3, 4, and 5<br>(Maximum Toxicity) | 21 (40.4)                                                                        | 21 (40.4)                                                                                                | 115 (44.4)                                                                               | 136 (43.7)                                                                    | 9 (42.9)                                                                     | 145 (43.7)                   |
| TEAEs leading to Death                            | 0                                                                                | 0                                                                                                        | 0                                                                                        | 0                                                                             | 0                                                                            | 0                            |

AE = adverse event; TEAE = treatment-emergent adverse event.

Notes:

Percentages (in parentheses) are based on the total number of patients in each column.

Adverse events of special interest include: hearing and vestibular disorders, acute renal failures, hepatic disorders, and gastrointestinal abnormalities.

‘Both Studies’ column is the summation of ‘Study 3b Grade 3 or higher’ column and ‘Study 14 except 1b’ column.

‘All DFMO’ column is the summation of ‘Both Studies’ column and ‘Study 14 Stratum 1b’ column.

The Toxicity Grade 3, 4, and 5 (maximum toxicity) row may not equal the sum of the Toxicity Grade 3, Toxicity Grade 4, and Toxicity Grade 5 rows. The Toxicity Grade 1, 2, 3, 4, and 5 rows report the number of patients with AEs of their respective Grades. For example, a patient with at least one Grade 3 AE, and at least one Grade 4 AE, will be counted once in both Toxicity Grade 3 and Toxicity Grade 4 rows. That patient will only be counted once in the Toxicity Grade 3, 4, and 5 (maximum toxicity) row.

Source: ISS Table 14.3.1.1.1

**Table 60: Adverse Events in ≥5% of Patients by Study and Dose – Safety Population**

| System Organ Class<br>Preferred Term | Study 3b<br>(Strata 1 &<br>2)<br>(1500<br>mg/m <sup>2</sup> )<br>(N=52) <sup>1</sup><br>N (%) | Study 3b<br>(Strata 1 &<br>2)<br>(1500<br>mg/m <sup>2</sup> )<br>Grade 3 or<br>higher<br>(N=52) <sup>1</sup><br>n (%) | Study 14,<br>All Strata<br>except 1b<br>(1500<br>mg/m <sup>2</sup> )<br>(N=259)<br>n (%) | Both<br>Studies<br>(1500<br>mg/m <sup>2</sup> )<br>Pooled<br>(N=311)<br>n (%) | Study 14<br>Stratum 1b<br>(5000<br>mg/m <sup>2</sup> )<br>(N=21)<br>n (%) | All DFMO<br>(N=332)<br>n (%) |
|--------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------|
| Number of patients with any<br>TEAEs | 42 (80.8)                                                                                     | 21 (40.4)                                                                                                             | 120 (46.3)                                                                               | 141 (45.3)                                                                    | 9 (42.9)                                                                  | 150 (45.2)                   |
| Investigations                       | 11 (21.2)                                                                                     | 6 (11.5)                                                                                                              | 50 (19.3)                                                                                | 56 (18.0)                                                                     | 2 (9.5)                                                                   | 58 (17.5)                    |

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{Eflornithine [DFMO]}

| <b>System Organ Class Preferred Term</b> | <b>Study 3b (Strata 1 &amp; 2) (1500 mg/m<sup>2</sup>) (N=52)<sup>1</sup> N (%)</b> | <b>Study 3b (Strata 1 &amp; 2) (1500 mg/m<sup>2</sup>) Grade 3 or higher (N=52)<sup>1</sup> n (%)</b> | <b>Study 14, All Strata except 1b (1500 mg/m<sup>2</sup>) (N=259) n (%)</b> | <b>Both Studies (1500 mg/m<sup>2</sup>) Pooled (N=311) n (%)</b> | <b>Study 14 Stratum 1b (5000 mg/m<sup>2</sup>) (N=21) n (%)</b> | <b>All DFMO (N=332) n (%)</b> |
|------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------|
| Alanine aminotransferase increased       | 5 (9.6)                                                                             | 3 (5.8)                                                                                               | 34 (13.1)                                                                   | 37 (11.9)                                                        | 0                                                               | 37 (11.1)                     |
| Aspartate aminotransferase increased     | 4 (7.7)                                                                             | 3 (5.8)                                                                                               | 18 (6.9)                                                                    | 21 (6.8)                                                         | 0                                                               | 21 (6.3)                      |
| Neutrophil count decreased               | 5 (9.6)                                                                             | 4 (7.7)                                                                                               | 7 (2.7)                                                                     | 11 (3.5)                                                         | 0                                                               | 11 (3.3)                      |
| Platelet count decreased                 | 0                                                                                   | 0                                                                                                     | 4 (1.5)                                                                     | 4 (1.3)                                                          | 2 (9.5)                                                         | 6 (1.8)                       |
| Blood alkaline phosphatase increased     | 3 (5.8)                                                                             | 1 (1.9)                                                                                               | 4 (1.5)                                                                     | 5 (1.6)                                                          | 0                                                               | 5 (1.5)                       |
|                                          |                                                                                     |                                                                                                       |                                                                             |                                                                  |                                                                 |                               |
| Ear and labyrinth disorders              | 6 (11.5)                                                                            | 6 (11.5)                                                                                              | 34 (13.1)                                                                   | 40 (12.9)                                                        | 0                                                               | 40 (12.0)                     |
| Hypacusis                                | 5 (9.6)                                                                             | 5 (9.6)                                                                                               | 32 (12.4)                                                                   | 37 (11.9)                                                        | 0                                                               | 37 (11.1)                     |
|                                          |                                                                                     |                                                                                                       |                                                                             |                                                                  |                                                                 |                               |
| Infections                               | 33 (63.5)                                                                           | 5 (9.6)                                                                                               | 30 (11.6)                                                                   | 35 (11.3)                                                        | 1 (4.8)                                                         | 36 (10.8)                     |
| Skin infection                           | 4 (7.7)                                                                             | 3 (5.8)                                                                                               | 3 (1.2)                                                                     | 6 (1.9)                                                          | 0                                                               | 6 (1.8)                       |
| Pneumonia                                | 8 (15.4)                                                                            | 1 (1.9)                                                                                               | 4 (1.5)                                                                     | 5 (1.6)                                                          | 1 (4.8)                                                         | 6 (1.8)                       |
| Otitis media                             | 20 (38.5)                                                                           | 1 (1.9)                                                                                               | 3 (1.2)                                                                     | 4 (1.3)                                                          | 0                                                               | 4 (1.2)                       |
| Upper respiratory tract infection        | 7 (13.5)                                                                            | 0                                                                                                     | 4 (1.5)                                                                     | 4 (1.3)                                                          | 0                                                               | 4 (1.2)                       |
| Urinary tract infection                  | 5 (9.6)                                                                             | 1 (1.9)                                                                                               | 3 (1.2)                                                                     | 4 (1.3)                                                          | 0                                                               | 4 (1.2)                       |
| Sinusitis                                | 10 (19.2)                                                                           | 0                                                                                                     | 1 (0.4)                                                                     | 1 (0.3)                                                          | 0                                                               | 1 (0.3)                       |
| Conjunctivitis                           | 5 (9.6)                                                                             | 0                                                                                                     | 0                                                                           | 0                                                                | 0                                                               | 0                             |
| Eye infection                            | 3 (5.8)                                                                             | 0                                                                                                     | 0                                                                           | 0                                                                | 0                                                               | 0                             |
|                                          |                                                                                     |                                                                                                       |                                                                             |                                                                  |                                                                 |                               |
| Blood and lymphatic system disorders     | 4 (7.7)                                                                             | 2 (3.8)                                                                                               | 12 (4.6)                                                                    | 14 (4.5)                                                         | 8 (38.1)                                                        | 22 (6.6)                      |
| Anemia                                   | 3 (5.8)                                                                             | 2 (3.8)                                                                                               | 10 (3.9)                                                                    | 12 (3.9)                                                         | 8 (38.1)                                                        | 20 (6.0)                      |
|                                          |                                                                                     |                                                                                                       |                                                                             |                                                                  |                                                                 |                               |
| Gastrointestinal disorders               | 17 (32.7)                                                                           | 3 (5.8)                                                                                               | 16 (6.2)                                                                    | 19 (6.1)                                                         | 1 (4.8)                                                         | 20 (6.0)                      |
| Vomiting                                 | 6 (11.5)                                                                            | 0                                                                                                     | 8 (3.1)                                                                     | 8 (2.6)                                                          | 0                                                               | 8 (2.4)                       |
| Diarrhea                                 | 9 (17.3)                                                                            | 3 (5.8)                                                                                               | 3 (1.2)                                                                     | 6 (1.9)                                                          | 1 (4.8)                                                         | 7 (2.1)                       |
| Constipation                             | 3 (5.8)                                                                             | 0                                                                                                     | 0                                                                           | 0                                                                | 0                                                               | 0                             |
| Nausea                                   | 3 (5.8)                                                                             | 0                                                                                                     | 0                                                                           | 0                                                                | 0                                                               | 0                             |

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{Eflornithine [DFMO]}

| <b>System Organ Class Preferred Term</b>             | <b>Study 3b (Strata 1 &amp; 2) (1500 mg/m<sup>2</sup>) (N=52)<sup>1</sup> N (%)</b> | <b>Study 3b (Strata 1 &amp; 2) (1500 mg/m<sup>2</sup>) Grade 3 or higher (N=52)<sup>1</sup> n (%)</b> | <b>Study 14, All Strata except 1b (1500 mg/m<sup>2</sup>) (N=259) n (%)</b> | <b>Both Studies (1500 mg/m<sup>2</sup>) Pooled (N=311) n (%)</b> | <b>Study 14 Stratum 1b (5000 mg/m<sup>2</sup>) (N=21) n (%)</b> | <b>All DFMO (N=332) n (%)</b> |
|------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------|
| General disorders and administration site conditions | 13 (25.0)                                                                           | 1 (1.9)                                                                                               | 13 (5.0)                                                                    | 14 (4.5)                                                         | 1 (4.8)                                                         | 15 (4.5)                      |
| Pyrexia                                              | 10 (19.2)                                                                           | 0                                                                                                     | 13 (5.0)                                                                    | 13 (4.2)                                                         | 1 (4.8)                                                         | 14 (4.2)                      |
| Respiratory, thoracic, and mediastinal disorders     | 16 (30.8)                                                                           | 2 (3.8)                                                                                               | 9 (3.5)                                                                     | 11 (3.5)                                                         | 1 (4.8)                                                         | 12 (3.6)                      |
| Rhinitis allergic                                    | 6 (11.5)                                                                            | 0                                                                                                     | 0                                                                           | 0                                                                | 1 (4.8)                                                         | 1 (0.3)                       |
| Cough                                                | 7 (13.5)                                                                            | 0                                                                                                     | 0                                                                           | 0                                                                | 0                                                               | 0                             |
| Skin and subcutaneous tissue disorders               | 8 (15.4)                                                                            | 2 (3.8)                                                                                               | 3 (1.2)                                                                     | 5 (1.6)                                                          | 0                                                               | 5 (1.5)                       |
| Rash maculo-papular                                  | 3 (5.8)                                                                             | 1 (1.9)                                                                                               | 0                                                                           | 1 (0.3)                                                          | 0                                                               | 1 (0.3)                       |
| Musculoskeletal and connective tissue disorders      | 5 (9.6)                                                                             | 0                                                                                                     | 2 (0.8)                                                                     | 2 (0.6)                                                          | 0                                                               | 2 (0.6)                       |
| Pain in extremity                                    | 4 (7.7)                                                                             | 0                                                                                                     | 2 (0.8)                                                                     | 2 (0.6)                                                          | 0                                                               | 2 (0.6)                       |

TEAE = treatment-emergent adverse event.

<sup>1</sup> The Applicant obtained efficacy data from a retrospective chart review protocol, BCC001, that included efficacy data from patients who were treated under a trial that preceded NMTRC003b (NMTRC003). Safety data were contractually inaccessible to the Applicant for 40 patients treated solely under the predecessor trial. An additional 49 patients who initiated treatment under the predecessor trial later transferred into Study 3b. The transfer patients initiated treatment under the predecessor trial for which data were inaccessible. Safety data collected after transfer to NMTRC003b are available, but represent partial safety data at varying start points on therapy, and potentially confound interpretation when combined with patients for whom complete data are available and therefore are excluded from the safety population. (See Module 2.7.4 Section 1.2 for additional information). Collection of the data comprising the BCC001 database is governed by the BCC001 protocol (3b CSR, Appendix 16.1.1).

Notes:

Adverse event terms are coded using MedDRA version 23.1.

Percentages (in parentheses) are based on the total number of patients in each column.

‘Both Studies’ column is the summation of ‘Study 3b Grade 3 or higher’ column and ‘Study 14 except 1b’ column.

‘All DFMO’ column is the summation of ‘Both Studies’ column and ‘Study 14 Stratum 1b’ column.

SOCs are only provided when a preferred term within the SOC occurred in &gt;5% of patients.

Source: Module 2.7.4 Table 17

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**The FDA's Assessment:**

In the **pooled safety population (N=360)**, the most common ( $\geq 5\%$ ) adverse reactions, were hearing loss (11%), otitis media (10%), pyrexia (7%), pneumonia (5%), and diarrhea (5%).

In the **primary safety population (N=85)**, the most common ( $\geq 5\%$ ) adverse reactions were otitis media, diarrhea, cough, sinusitis, pneumonia, upper respiratory tract infection, conjunctivitis, vomiting, pyrexia, allergic rhinitis, hearing loss, skin infection, and urinary tract infection (Table 61).

Clinically relevant adverse reactions in  $<5\%$  of patients who received eflornithine included rash, extremity pain, and alopecia.

**Table 61: Adverse Reactions ( $\geq 5\%$ ) in Patients with HRNB Who Received Eflornithine in Study 3(b)**

| Adverse Reaction <sup>a</sup>     | Eflornithine (n=85)              |                 |
|-----------------------------------|----------------------------------|-----------------|
|                                   | All Grades <sup>b,c</sup><br>(%) | Grade 3*<br>(%) |
| <b>Infections</b>                 |                                  |                 |
| Otitis media                      | 32                               | 2.4             |
| Sinusitis                         | 13                               | 0               |
| Pneumonia                         | 12                               | 1.2             |
| Upper respiratory tract infection | 11                               | 0               |
| Conjunctivitis                    | 11                               | 0               |
| Skin infection                    | 7                                | 4.7             |
| Urinary tract infection           | 6                                | 1.2             |
| <b>Gastrointestinal Disorders</b> |                                  |                 |
| Diarrhea <sup>d</sup>             | 15                               | 3.5             |
| Vomiting                          | 11                               | 1.2             |

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|                                    |    |     |
|------------------------------------|----|-----|
| <b>Respiratory Disorders</b>       |    |     |
| Cough                              | 15 | 0   |
| Allergic rhinitis                  | 11 | 0   |
| <b>General Disorders</b>           |    |     |
| Pyrexia                            | 11 | 1.2 |
| <b>Ear and Labyrinth Disorders</b> |    |     |
| Hearing loss                       | 7  | 7   |

a Adverse Reactions were graded using CTCAE Version 4.03.

b Grade 1 adverse events were not comprehensively collected in Study 3b.

c No Grade 4 or 5 events were reported.

d Diarrhea include diarrhea and colitis.

In the 120-day safety update, the Applicant provided a revised summary of safety, including an additional 12 months of safety data for the 62 patients in Study 14 who were ongoing in treatment at the time of the NDA data cutoff (June 30, 2021) and data from 40 patients enrolled after the NDA data cutoff (Table 55). Of the 40 new patients, 28 received eflornithine at a higher dose than the proposed dose (2500 mg/m<sup>2</sup> BID) in Study 14 Stratum 1b. No additional data from Study 3(b) was collected after the original NDA data cutoff because all patients had completed treatment and safety data were not collected in the long-term follow-up phase of the study.

In the updated population of patients who received the proposed dose of eflornithine, the adverse event profile is similar to that of the original pooled safety population. In the population of patients who received the higher dose of eflornithine (2500 mg/m<sup>2</sup> BID), there were more patients who experienced high-grade and serious SAEs as well as dose modifications. No AEs leading to death were reported in the NDA or in the safety update. Overall, no new safety signals were identified in the updated safety population.

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**Table 62:** Overall Summary of Adverse Events by Study and Dose in 120-Day Safety Update

|                                                                                            | Study 3b<br>(Strata 1<br>& 2)<br>(1500<br>mg/m <sup>2</sup> )<br>All Grades<br>(N=52)<br>n (%) | Study 3b<br>(Strata 1<br>& 2)<br>(1500<br>mg/m <sup>2</sup> )<br>Grade 3 or<br>higher<br>(N=52)<br>n (%) | Study 14,<br>All Strata<br>except 1b<br>(1500<br>mg/m <sup>2</sup> )<br>(N=271)<br>n (%) | Both<br>Studies<br>(1500<br>mg/m <sup>2</sup> )<br>Pooled<br>(N=323)<br>n (%) | Study 14<br>Stratum<br>1b<br>(5000<br>mg/m <sup>2</sup> )<br>(N=49)<br>n (%) | All DFMO<br>(N=372)<br>n (%) |
|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------|
| Number of TEAEs                                                                            | 290                                                                                            | 54                                                                                                       | 381                                                                                      | 435                                                                           | 146                                                                          | 581                          |
| Patients with at least one                                                                 |                                                                                                |                                                                                                          |                                                                                          |                                                                               |                                                                              |                              |
| Adverse event                                                                              | 42 (80.8)                                                                                      | 21 (40.4)                                                                                                | 136 (50.2)                                                                               | 157 (48.6)                                                                    | 30 (61.2)                                                                    | 187 (50.3)                   |
| Adverse events related to the study medication                                             | 19 (36.5)                                                                                      | 12 (23.1)                                                                                                | 56 (20.7)                                                                                | 68 (21.1)                                                                     | 25 (51.0)                                                                    | 93 (25.0)                    |
| Serious adverse events                                                                     | 6 (11.5)                                                                                       | 5 (9.6)                                                                                                  | 53 (19.6)                                                                                | 58 (18.0)                                                                     | 12 (24.5)                                                                    | 70 (18.8)                    |
| Serious related adverse events                                                             | 1 (1.9)                                                                                        | 1 (1.9)                                                                                                  | 5 (1.8)                                                                                  | 6 (1.9)                                                                       | 2 (4.1)                                                                      | 8 (2.2)                      |
| Adverse events leading to dose modification                                                | 5 (9.6)                                                                                        | 2 (3.8)                                                                                                  | 32 (11.8)                                                                                | 34 (10.5)                                                                     | 24 (49.0)                                                                    | 58 (15.6)                    |
| Adverse events leading to treatment discontinuation per CRF                                | 9 (17.3) <sup>1</sup>                                                                          | 8 (15.4) <sup>1</sup>                                                                                    | 11 (4.1)                                                                                 | 19 (5.9)                                                                      | 1 (2.0)                                                                      | 20 (5.4)                     |
| Adverse events leading to treatment discontinuation per Sponsor determination <sup>2</sup> | 3 (5.8)                                                                                        | 2 (3.8)                                                                                                  | 11 (4.1)                                                                                 | 13 (4.0)                                                                      | 2 (4.1)                                                                      | 15 (4.0)                     |
| Adverse events of special interest                                                         | 23 (44.2)                                                                                      | 9 (17.3)                                                                                                 | 88 (32.5)                                                                                | 97 (30.0)                                                                     | 21 (42.9)                                                                    | 118 (31.7)                   |
| Toxicity Grade 1                                                                           | 0                                                                                              |                                                                                                          | 8 (3.0)                                                                                  | 8 (2.5)                                                                       | 7 (14.3)                                                                     | 15 (4.0)                     |
| Toxicity Grade 2                                                                           | 42 (80.8)                                                                                      |                                                                                                          | 15 (5.5)                                                                                 | 15 (4.6)                                                                      | 13 (26.5)                                                                    | 28 (7.5)                     |
| Toxicity Grade 3                                                                           | 21 (40.4)                                                                                      | 21 (40.4)                                                                                                | 126 (46.5)                                                                               | 147 (45.5)                                                                    | 28 (57.1)                                                                    | 175 (47.0)                   |
| Toxicity Grade 4                                                                           | 1 (1.9)                                                                                        | 1 (1.9)                                                                                                  | 23 (8.5)                                                                                 | 24 (7.4)                                                                      | 7 (14.3)                                                                     | 31 (8.3)                     |
| Toxicity Grade 5                                                                           | 0                                                                                              | 0                                                                                                        | 0                                                                                        | 0                                                                             | 0                                                                            | 0                            |

## Laboratory Findings

### Data:

ALT was one of the laboratory values with the largest change in values and trends (ISS Table 14.3.4.1.1.1), however the number of patients with increased ALT levels meeting criteria for CTCAE (Grade 1-4) decreased over the course of the study (31.7% at baseline to 10.4% at the

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last visit) (Module 2.7.4 Table 24). Patients with increased AST meeting criteria for CTCAE (Grade 1-4) demonstrated a similar trend, decreasing from 24.7% at baseline to 14.7% at the last visit. Other liver function metrics were generally unremarkable. Parameters related to kidney function were either unchanged or improved during the course of treatment except values meeting CTCAE criteria for creatinine increase, which increased over the course of the study (from 4.2% at baseline to 8.9% at last visit). No trends were observed in the exposure-response relationship for any of the clinical chemistry parameters investigated.

Hematology values remained generally unchanged throughout the course of study (ISS Table 14.3.4.1.2.1). Although higher doses of DFMO (used in [Saulnier Sholler 2018](#)) as well as for ORNIDYL, 1990 to treat African Sleeping Sickness) have been known to drive neutropenia and thrombocytopenia, a significant downward trend in neutrophils was not observed in Study 14 All Strata Except 1b (1500 mg/m<sup>2</sup> dose) patients, and there was a marked reduction in the number of subjects with values meeting CTCAE criteria (Grade 1-4) of platelet counts decreased and WBC counts decreased from baseline to the last visit (Module 2.7.4 Table 25). All other blood parameters were completely unaffected by treatment with DFMO for 24 months in patients receiving 1500 mg/m<sup>2</sup> and no trends were observed in the exposure-response relationship for any of the clinical chemistry parameters investigated in this group or patients

Notably, the incidence of the TEAE of anemia was strikingly higher at the highest dose tested in this study (5000 mg/m<sup>2</sup>, Stratum 1b, 38.1%) compared to the lower, proposed dose (3.9% in both studies [1500 mg/m<sup>2</sup>] pooled) (Module 2.7.4 Table 17). The higher incidence of anemia in Stratum 1b is consistent with laboratory findings, including decreases in mean hemoglobin and hematocrit compared to baseline in these patients across all timepoints (Module 2.7.4 Table 26); the trending decrease in hemoglobin and hematocrit was not observed in Study 14 All Strata except 1b (1500 mg/m<sup>2</sup>).

Table 56 presents potentially clinically significant laboratory tests Grades 3-4 by worst value at any post baseline time point that occurred in ≥1% of patients in Study 14 All Strata Except 1b. Potentially clinically significant laboratory test results were determined by applying CTCAE Laboratory Toxicity Grade thresholds to the available laboratory data. The potentially clinically significant laboratory tests determined by this approach did not necessarily meet requirements for adverse event reporting as the CTCAE Laboratory Toxicity Grade criteria for some parameters also require that the patient be symptomatic or that hospitalization be indicated.

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**Table 63: Potentially Clinically Significant Laboratory Tests Reported in ≥1% of Patients in Study 14 All Strata Except 1b**

| Visit<br>Parameter                          | Study 14 All Strata except 1b (1500<br>mg/m <sup>2</sup> )<br>N=259 |
|---------------------------------------------|---------------------------------------------------------------------|
|                                             | Grades 3-4 <sup>1</sup><br>n (%)                                    |
| Worst value at any post baseline time point |                                                                     |
| Clinical Chemistries                        |                                                                     |
| Alanine aminotransferase increased          | 6.6                                                                 |
| Aspartate aminotransferase increased        | 3.1                                                                 |
| Blood bilirubin increased                   | 2.7                                                                 |
| Hypocalcemia                                | 2.3                                                                 |
| Hyperkalemia                                | 1.5                                                                 |
| Hypermagnesemia                             | 1.5                                                                 |
| Hypokalemia                                 | 1.2                                                                 |
| Hematology                                  |                                                                     |
| Neutrophil count decreased                  | 4.7                                                                 |
| Platelet count decreased                    | 1.2                                                                 |

<sup>1</sup> per NCI CTCAE v4.03

Notes:

There were no Grade 5 events in the patient population.

Laboratory testing was performed at screening, every 30 days for the first 6 months of treatment, every 90 days for the remaining 1.5 years of treatment, and end of maintenance therapy.

Source: ISS Table 14.3.4.2.1.1 and ISS Table 14.3.4.2.2.1

**The Applicant's Position:**

Laboratory assessments indicated a good safety profile in patients treated with DFMO for 24 months at the indicated dose level of 1500 mg/m<sup>2</sup>.

**The FDA's Assessment:**

Laboratory data were not recorded in the datasets for Study 3(b). Therefore, FDA relied upon the assessment of adverse events to identify lab abnormalities. This method likely underestimates the occurrence of the observed laboratory abnormalities.

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In the **pooled safety population (N=360)**, the most common ( $\geq 2\%$ ) Grade 3 or 4 laboratory abnormalities were increased ALT (11%), increased AST (6%), decreased neutrophils (4.2%), and decreased hemoglobin (3.3%).

In the **primary safety population (N=85)**, the most common ( $\geq 2\%$ ) Grade 3 or 4 laboratory abnormalities were increased ALT, decreased neutrophils, increased AST, increased alkaline phosphatase, decreased hemoglobin, decreased potassium, decreased glucose, decreased sodium, and decreased white blood cells (Table 57).

**Table 64: Select Laboratory Abnormalities ( $\geq 1\%$ ) in Patients with HRNB Who Received Eflornithine in Study 3b**

| Laboratory Abnormality <sup>a</sup> | Eflornithine<br>(n=85)           |                     |
|-------------------------------------|----------------------------------|---------------------|
|                                     | All Grades <sup>b,c</sup><br>(%) | Grade 3 or 4<br>(%) |
| <b>Chemistry</b>                    |                                  |                     |
| Increased ALT                       | 9                                | 7*                  |
| Increased AST                       | 8                                | 6*                  |
| Increased alkaline phosphatase      | 4.7                              | 2.4*                |
| Decreased potassium                 | 2.4                              | 2.4*                |
| Decreased glucose                   | 2.4                              | 1.1                 |
| Decreased sodium                    | 2.4                              | 2.4*                |
| Increased potassium                 | 1.2                              | 0                   |
| Increased glucose                   | 1.2                              | 0                   |
| <b>Hematology</b>                   |                                  |                     |
| Decreased neutrophils               | 9                                | 8                   |
| Decreased hemoglobin                | 4.7                              | 2.4*                |

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|                             |     |   |
|-----------------------------|-----|---|
| Decreased white blood cells | 2.4 | 0 |
| Decreased platelets         | 1.2 | 0 |

<sup>a</sup> The table presents laboratory parameters reported as adverse events according to CTCAE Version 4.03.

<sup>b</sup> Grade 1 adverse events were not comprehensively collected in Study 3b.

<sup>c</sup> No Grade 5 events were reported.

\* Events of Grade 3 only (no Grade 4 occurred).

## Vital Signs

### Data:

Vital signs including temperature, heart rate, resting blood pressure, and weight were collected in both Study 3b and Study 14. No clinically meaningful changes were generally observed in vital signs across both studies (1500 mg/m<sup>2</sup>) pooled. Mean BSA, height, and weight consistently increased compared to baseline over the study period (ISS Table 14.3.2.1.1), consistent with growth and development that would be expected in this pediatric population over the 2-year DFMO treatment period. HR generally decreased compared to baseline during the 2-year DFMO treatment period (ISS Table 14.3.2.1.1) across both studies pooled. The magnitude of the decrease in HR tended to increase over the study period in a manner that was generally consistent with decreases in HR that would be expected in growing children.

### The Applicant's Position:

Vital signs assessments indicated a good safety profile in patients treated with DFMO for 24 months at the indicated dose level of 1500 mg/m<sup>2</sup>.

### The FDA's Assessment:

FDA agrees that no clinically meaningful changes were observed in vital signs across Study 3(b) and Study 14.

In the **pooled safety population (N=360)**, the median weight at baseline was 16.7 kilograms (range 7.7 to 74.3). The median body surface area (BSA) at baseline was 0.75 mg/m<sup>2</sup> (range 0.39 to 2.1). Considering all observed measurements across the studies, the median heart rate was 104 beats per minute (range 51 to 206); there were only 7 instances of heart rate values greater than 160 beats per minute. The median temperature was 36.6 degrees Celsius; there were 6 instances

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of temperature values > 38 degrees Celsius. The median systolic blood pressure was 100 mmHg (range 55 to 147), and the median diastolic blood pressure was 60 mmHg (range 15 to 98).

## **Electrocardiograms (ECGs) and QT**

### Data:

No dedicated QT studies were conducted for DFMO.

The cardiac effects of DFMO were studied by analysis of ECG parameters in patients who participated in Study 14. ECGs were not required per the Study 3b protocol. ECG parameters included ventricular rate, PR interval, and QT, and QRS. In Study 14 All Strata except 1b, the mean PR interval increased compared to baseline over the course of the study. The mean change from baseline in the PR interval also increased over the course of the study from 2.85 on Treatment Day 1 to 3.77 msec at Month 3 and 4.86 msec at Month 6 (Module 2.7.4 Table 28). There was no change in any of the other ECG parameters at the time points assessed. Less than 1% of patients experienced QTcF interval >450 msec to ≤480 msec at each post-baseline time point, and no patients experienced a QTcF >480 msec at any post-baseline time point.

### The Applicant's Position:

ECG assessments indicated a good safety profile in patients treated with DFMO for 24 months at the indicated dose level of 1500 mg/m<sup>2</sup>.

### The FDA's Assessment:

Study NMTRC014 was used to evaluate the potential for QT prolongation as this study included ECG/PK measurements at screening and at 3 h (T<sub>max</sub> ~ 3.5 h) on days 1, 91, and 181. Notably, digital ECGs were not available for this study. This study included 5 strata: 1, 1b, 2, 3, and 4. The dosing in strata 1, 2, 3, and 4 was the proposed labeled dose corresponding to 750 mg/m<sup>2</sup> (±250 mg/m<sup>2</sup>). In strata 1b, the dose was also adjusted by BSA, but the target dose was 2500 mg/m<sup>2</sup>. Reported C<sub>max,ss</sub> for patients receiving 750 mg/m<sup>2</sup> (500 to 1000 mg/m<sup>2</sup>) was 21 µg/mL (CP table) compared to 49.5 µg/mL for stratum 1b (120-day safety report; Table 12).

Based on FDA's review of the QT assessment from Study NMTRC014, the following labeling language was recommended for the Cardiac Electrophysiology subheading under Pharmacodynamics subsection (Section 12.2):

### *Cardiac Electrophysiology*

IWILFIN does not cause a mean increase in the QTc interval ≥ 20 milliseconds at the approved recommended dose.

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Refer to the Interdisciplinary Review Team for Cardiac Safety Studies consult documentation for further details.

### **Immunogenicity**

#### **The Applicant's Position:**

Not applicable.

#### **The FDA's Assessment:**

Not applicable.

### **8.2.4. Analysis of Submission-Specific Safety Issues**

#### **Adverse Events of Special Interest (AESI)**

##### **The Applicant's Position:**

AESIs included renal impairment, hepatic impairment, hearing loss, and gastrointestinal abnormalities. Search strategies used to assess AEs potentially related to events of special interest consisted of standard MedDRA Queries (SMQs) for the following: hearing and vestibular disorders, acute renal failure, hepatic disorders, and gastrointestinal nonspecific inflammation and dysfunctional conditions (5.3.5.3 ISS SAP v1.0).

Across both studies (1500 mg/m<sup>2</sup>) pooled, there were no trends in AESIs of renal impairment or gastrointestinal abnormalities. The AESIs related to hepatic disorders that occurred in more than one patient were ALT increased and AST increased, which occurred in 37 (11.9%) and 21 (6.8%) patients, respectively.

#### **Hearing Loss**

##### **Data:**

Hearing loss, although a common long-term effect in pediatric cancer patients as a result of extensive anticancer therapy, has previously been reported in other studies assessing DFMO for the treatment of HRNB and other cancers ([Saulnier Sholler 2018](#), [Croghan 1991](#), [Croghan 1988](#), [Meyskens 1986](#)). Therefore, hearing changes were assessed by audiograms at Screening, after 6 months of treatment, after 12 months of treatment, at end of DFMO maintenance therapy, and as otherwise clinically indicated for both Study 3b and Study 14. The results of protocol-required audiograms were assessed by local audiologists and reported by the site PI.



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Per FDA's request, narratives are provided for all subjects with an AESI of new or worsening hearing loss (Module 5.3.5.3 All Narratives). Across both studies (1500 mg/m<sup>2</sup>) pooled, thirty-seven (11.9%) experienced an AESI of hypoacusis, indicating new or worsening hearing loss during the study (ISS Table 14.3.1.12.1). Two of the 37 patients from Study 14 reported treatment emergent hearing loss Grade 3 events starting on Study Day 1 and are not considered among patients with an AESI of hearing loss. Among the other 35 patients with an AESI of hearing loss, the AESIs were reported recovered/resolved in 31% of patients (Module 2.7.4 Figure 7). The AESI of hearing loss was reported as recovered or resolved in 75% of patients whose dosing was temporarily interrupted and then resumed at a lower dose and in 50% of the patients whose DFMO dosing was temporarily interrupted and then resumed at the original dose. These findings are generally consistent with results from other studies assessing orally administered DFMO that reported improvement in new or worsening hearing loss upon discontinuation of DFMO in some but not all subjects (range 30% improved in [Meyskens 2008](#) to 87% in [Chow 2022](#)).

#### The Applicant's Position:

The contribution of individual agents (e.g., DFMO) to hearing loss can be difficult to determine in cancer patients 1) due to the approach to treatment, which often consists of multiple agents being administered either concomitantly or very close in time to each other (i.e., within months), and 2) because of the potential delay in onset of hearing loss related to platinum chemotherapies, which may not present until months or even years after treatment has completed (reference). Further, the study-level interpretation of hearing changes over the course of these studies is inherently difficult due to different methodologies used to assess hearing and the variability and subjectivity of certain methodologies when assessing hearing loss in young children (i.e., conditioned play audiometry), differences in hearing loss present in study patients at baseline, and concurrent clinical events that can acutely impact hearing (e.g., otitis media). The open-label, single-arm designs of Studies 3b and Study 14 further confounds determination of the relatedness of hearing loss events that occurred during or after DFMO administration in those studies. Despite these challenges, the available data suggest that new and/or worsening hearing loss may occur during DFMO treatment at the indicated dose in the intended patient population. New or worsening hearing loss that occurs during DFMO treatment may be reversible with dose modifications, including temporary drug interruption and/or dose reductions.

#### The FDA's Assessment:

FDA agrees with the Applicant's identification of AESIs hepatic impairment and hearing loss. FDA considered the additional information below in the review of safety.

The proposed warnings and precautions for product labeling included myelosuppression,

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hepatotoxicity, and hearing loss.

### **Myelosuppression**

In the pooled safety population (N=360), Grade 3 or 4 neutropenia occurred in 4.2% of patients. Febrile neutropenia occurred in 0.6% of patients. Grade 3 or 4 thrombocytopenia occurred in 1.4% of patients. Grade 3 anemia occurred in 3.3% of patients. The clinical studies included monitoring for blood counts including neutrophil count, platelet count, and hemoglobin level prior to administration of eflornithine and periodically during treatment.

One patient had a Grade 4 treatment-emergent adverse event of bone marrow failure. Patient ID (b) (6) was a 3-year-old White female with Stage 4 neuroblastoma enrolled on Study 14, Stratum 3 (relapsed/refractory disease) with baseline CBC within normal limits. She developed reported Grade 4 bone marrow failure on Study Day 71. Eflornithine was withdrawn and work-up did not reveal an alternative etiology for this serious adverse event. The event was attributed as possibly related and reported as “recovering/resolving” 2.5 months after onset. The patient died due to disease progression on Study Day 289.

### **Hepatotoxicity**

In the pooled safety population (N=360), Grade 3 or 4 events of increased alanine aminotransferase (ALT) occurred in 11% of patients. Grade 3 or 4 events of increased aspartate aminotransferase (AST) occurred in 6% of patients. Grade 3 or 4 events of increased bilirubin occurred in 0.3% of patients. Increased ALT/AST leading to dose interruption or reduction occurred in 2.5% of patients. Eflornithine was discontinued due to increased ALT/AST in 0.6% of patients. The clinical studies included monitoring of liver function tests (ALT, AST, and total bilirubin) prior to administration of eflornithine and periodically during treatment.

There were no events of liver failure or drug-induced liver injury reported in Study 3(b) or Study 14.

### **Hearing Loss**

Hearing loss was an adverse event of special interest due to the known risk with eflornithine in non-oncology populations and chemoprevention trials. Studies 3(b) and 14 included an audiogram prior to initiation of therapy, at 6-month intervals, and as clinically indicated. Most patients had an abnormal audiogram at baseline, likely due to platinum-based therapy received during up-front treatment. It is challenging to isolate the independent effect of DFMO from the ongoing toxicity of platinum therapy in this population.

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In the pooled safety population (N=360), 81% of patients had an abnormal audiogram at baseline. New or worsening hearing loss occurred in 13%; hearing loss worsened from baseline to Grade 3 or 4 in 12% of patients. Tinnitus occurred in 1 patient. Hearing loss leading to dose interruption or reduction occurred in 7% of patients. Eflornithine was discontinued due to hearing loss in 1.4% of patients. Of 47 patients with hearing loss worsened from baseline, it resolved in 4 patients (9%). The clinical studies included monitoring with audiograms prior to initiation of therapy, at 6-month intervals, and as clinically indicated.

At FDA's request, the Applicant performed an in-depth analysis of audiograms conducted per protocol in Study 3(b) and Study 14. Raw data from the audiograms were not entered into the database for either Study 3(b) or 14; results were recorded as Normal, Abnormal (change in grade), or No Significant Change (stable or no change in grade). In addition, pre-induction (pre-platinum chemotherapy) audiograms were not available. During the review period, an independent audiologist reviewed audiograms for patients with abnormal post-baseline audiograms and assigned grades per CTCAE criteria (Table 65; compared decibel shifts by frequency compared to 5 dB at all frequencies). Of the 47 patients with events of hearing loss worsened by at least 1 grade from baseline, 11 were normal or missing at baseline and became abnormal during DFMO treatment, and 36 were abnormal at baseline and worsened during DFMO treatment. Some patients had worsening hearing loss within a grade (i.e., started at Grade 3 with some evidence of worsening within Grade 3, but without progressing to Grade 4).

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**Table 65: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, Hearing Loss**

| Ear and labyrinth disorders                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                     |   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|
| Adverse Event                                                                                                                                           | Grade                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                     |   |
|                                                                                                                                                         | 1                                                                                                                                                                                                                                                                                                                                                                                                                                  | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 4                                                                                                                                                                                                                                                                   | 5 |
| Hearing impaired                                                                                                                                        | <p>Adults enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear.</p> <p>Adults not enrolled in Monitoring Program: subjective change in hearing in the absence of documented hearing loss.</p> <p>Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift &gt;20 dB at 8 kHz in at least one ear.</p> | <p>Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of &gt;25 dB averaged at 2 contiguous test frequencies in at least one ear.</p> <p>Adults not enrolled in Monitoring Program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL.</p> <p>Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift &gt;20 dB at 4 kHz and above in at least one ear.</p> | <p>Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of &gt;25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated.</p> <p>Adults not enrolled in Monitoring Program: hearing loss with hearing aid or intervention indicated; limiting self care ADL.</p> <p>Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift &gt;20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.</p> | <p>Adults: Decrease in hearing to profound bilateral loss (absolute threshold &gt;80 dB HL at 2 kHz and above); non-servicable hearing.</p> <p>Pediatric: Audiologic indication for cochlear implant and additional speech-language related services indicated.</p> | - |
| Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures. |                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                     |   |

Source: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, Available at: [https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

Most reported treatment-emergent adverse events (TEAE) of hearing loss were Grade 3. Four patients had a Grade 2 TEAE of hearing loss (however, in Study 14, no Grade 1 or 2 events were recorded, and in Study 3(b), no Grade 1 events were recorded). One patient had a Grade 4 TEAE of hearing loss, with details as follows: Patient ID (b) (6) was a 7-year-old White male enrolled on Study 14 Stratum 1 with abnormal hearing at baseline requiring hearing aids (Grade 3). He had worsening hearing loss to Grade 4 on Study Day 734 (end of therapy audiogram). Repeat audiogram on Study Day 825 demonstrated a return to Grade 3 hearing loss. The event was attributed as possibly related to DFMO.

Two clinical SGE's considered the potential for new or worsening hearing loss due to DFMO to be a concern during their review of the summarized data provided by FDA. They stated that hearing loss should be considered in the benefit:risk assessment given that these patients would otherwise not be receiving any treatment in the maintenance setting and that many patients with HRNB are at the age of language acquisition when hearing loss may have more profound effects on development.

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As previously stated, hearing loss has been observed with DFMO in other studies in non-oncology populations and in chemoprevention studies. The product labeling for eflornithine (Ornidyl), the reference listed drug intended to support the current 505(b)2 application, states that hearing loss occurred in ~5% of patients. The reduction in hearing acuity was judged as severe in 2 of 14 patients and prompted cessation of therapy in 4 instances. Recovery was reported for 7 of 14 (50%) of the patients.

The effect of DFMO on hearing was evaluated in a study of 66 patients previously treated for bladder, prostate, or colon cancer with no current evidence of neoplastic disease, or healthy individuals at increased risk for colon cancer, all without need of hearing amplification at baseline (Pasic et al, 1997). Patients were randomized to receive eflornithine (doses ranged from 500 mg to 3g per m<sup>2</sup>) vs. placebo for 6 to 12 months. As the daily dose of eflornithine increased, the magnitude and incidence of threshold shift increased, and the time to onset of threshold shift decreased. Threshold changes were greater in the lower frequencies than in the higher frequencies. Subjects' sex, age, and renal function had no effect on eflornithine associated threshold shifts. Threshold shifts were reversible after eflornithine treatment was discontinued.

#### **8.2.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability Data:**

No COA analyses informing safety/tolerability were performed.

#### **The Applicant's Position:**

No COA analyses informing safety/tolerability were performed.

#### **The FDA's Assessment:**

FDA agrees no COA analyses were performed.

#### **8.2.6. Safety Analyses by Demographic Subgroups**

##### **The Applicant's Position:**

The integrated safety analysis included analysis of safety data by disease history (i.e., Remission After Initial Upfront Treatment or Remission After Relapse or Refractory Disease) to assess whether the greater exposure to toxic oncolytic treatments experienced by patients achieving remission after relapse or refractory disease may have contributed to higher incidence of safety events in that group.

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Severe TEAE, incidence of AEs, SAEs, and AESIs, PCS Chloride and QTcB >450 msec to ≤ 480 msec (30.2% vs. 19.5%) or QTcB CFB >30 to ≤ 60 (16.5% vs. 11.7%) were higher in the remission after initial upfront treatment group (ISS Table 14.3.1.1.2 and 14.3.1.4.2 and 14.3.3.2.2)

Generally, no notable differences were identified between the disease history groups.

#### The FDA's Assessment:

FDA agrees no notable differences in safety were identified by sex, age group (< 6 years vs. ≥ 6 years), or disease status (newly diagnosed vs. relapsed/refractory). There were no between-group differences >10% in these subpopulations (Table 66).

**Table 66: Key Safety Findings for Subgroups of the Pooled Safety Population by Sex, Age Group, and Disease Status**

|                    | All Patients                              | Sex             |                   | Age Group            |                      | Disease status             |                               |
|--------------------|-------------------------------------------|-----------------|-------------------|----------------------|----------------------|----------------------------|-------------------------------|
|                    | Total Pooled Safety Population (n=360), % | Male (n=203), % | Female (n=157), % | < 6 years (n=234), % | ≥ 6 years (n=126), % | Newly Diagnosed (n=267), % | Relapsed/Refractory (n=93), % |
| Any Grade TEAEs    | 55                                        | 51              | 59                | 56                   | 53                   | 57                         | 49                            |
| Grade 3 or 4 TEAEs | 42                                        | 39              | 46                | 43                   | 40                   | 44                         | 35                            |
| SAEs               | 16                                        | 13              | 20                | 15                   | 18                   | 16                         | 14                            |
| Dose modifications | 9                                         | 8               | 10                | 9                    | 9                    | 9                          | 11                            |

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|                                    |    |    |    |    |    |    |    |
|------------------------------------|----|----|----|----|----|----|----|
| <b>(interruption or reduction)</b> |    |    |    |    |    |    |    |
| <b>Discontinuations</b>            | 7  | 5  | 9  | 8  | 4  | 6  | 8  |
| <b>Hearing Loss TEAEs</b>          | 11 | 12 | 10 | 11 | 10 | 11 | 10 |

**8.2.7. Specific Safety Studies/Clinical Trials**The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable

**8.2.8. Additional Safety Explorations****Human Carcinogenicity or Tumor Development**The Applicant's Position:

Human carcinogenicity studies have not been conducted.

The FDA's Assessment:

Not applicable

**Human Reproduction and Pregnancy**The Applicant's Position:

Pregnancy and lactation are unexpected in the intended pediatric patient population. Pregnant or lactating women were excluded from all studies. There were no reports of pregnancy in the integrated safety database.

The FDA's Assessment:

FDA agrees that there were no reports of pregnancy in the datasets submitted in the application. Pregnancy tests were required per the Study 3(b) protocol at baseline and prior to the start cycle. The inclusion criteria required a negative pregnancy test and agreement from both male and

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female post-pubertal patients to use one or more effective birth control methods during treatment and for 6 months after completion of treatment.

Refer to Section 5 for additional details regarding the nonclinical studies evaluating the risk of embryo-fetal toxicity.

There are no data on the presence of eflornithine in human milk, the effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in breastfed children, the proposed product labeling includes a recommendation to advise women not to breastfeed during treatment with eflornithine and for 1 week after the last dose.

### **Pediatrics and Assessment of Effects on Growth**

#### **The Applicant's Position:**

DFMO is intended for use in pediatric patients. The safety and effectiveness of DFMO have been assessed in clinical trials in pediatric patients who achieved remission following upfront or relapse therapy for HRNB.

#### **The FDA's Assessment:**

There were no nonclinical or clinical data to suggest that eflornithine has an adverse effect on the growth of pediatric patients. Patient height and weight were measured per protocol at baseline and at the start of each cycle. While growth charts for each patient were not recorded in the datasets, the median height and weight of patients increased from the baseline evaluation (median height 102 cm [range: 76, 184]; median weight 16.3 kg [range: 9.4, 68.9]) to the end of DFMO treatment (median height 106 cm [range: 89, 184]; median weight 20.3 kg [range: 12.5, 84.1]).

### **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

#### **The Applicant's Position:**

There were no reports of overdose in Study 3b or Study 14. There were no reports of overdose in the literature. The drug would typically be administered by the parent or guardian which limits the risk of overdose.

#### **The FDA's Assessment:**

FDA agrees with the Applicant's assessment.



## 8.2.9. Safety in the Postmarket Setting

### Safety Concerns Identified Through Postmarket Experience

#### The Applicant's Position:

No oral formulations of DFMO have been approved in any market for any indication. DFMO is not currently approved for use in the treatment of neuroblastoma in any market.

DFMO has previously been approved by FDA in an intravenously administered (IV) injectable formulation (ORNIDYL 1990) for the treatment of *Trypanosoma brucei gambiense* infection (also known as West African trypanosomiasis or West African sleeping sickness) and in a topical cream formulation for the treatment of unwanted facial hair in women (ORNIDYL 1990, VANIQA 2018).

Use of Ornidyl, an IV formulation of eflornithine hydrochloride, at high doses (400 mg/kg/day or approximately 24 g/day) for the treatment of *Trypanosoma brucei gambiense* infection (West African sleeping sickness) has been associated with AEs and laboratory abnormalities. AEs in this setting have included hair loss, facial swelling, seizures, hearing impairment, stomach upset, loss of appetite, headache, weakness and dizziness. A variety of hematological toxicities, including anemia, thrombocytopenia and leukopenia have also been observed, but these were usually reversible upon discontinuation of treatment (ORNIDYL 1990).

The majority of adverse reactions during topical use of Vaniqa cream, 13.9%, for reduction of unwanted facial hair in women, were skin-related. Notable adverse reactions occurring at >1% in both controlled and open-label studies were temporary redness, stinging, burning, tingling or rash on areas of the skin where it is applied. Folliculitis (hair bumps) also occurred. Treatment-related skin AEs that occurred in less than 1% of the patients treated with Vaniqa were: bleeding skin, cheilitis, contact dermatitis, swelling of lips, herpes simplex, numbness, and rosacea. AEs were primarily mild in intensity and generally resolved without medical treatment or discontinuation of Vaniqa. Only 2% of patients discontinued studies due to an AE related to use of Vaniqa. No laboratory test abnormalities have been consistently found to be associated with Vaniqa. In an open-label study, some patients showed an increase in their transaminases; however, the clinical significance of these findings is not known (VANIQA 2018).

#### The FDA's Assessment:

FDA agrees with the Applicant that the safety data from clinical studies of ORNIDYL and VANIQA are generally similar to the safety findings observed in the neuroblastoma patient populations. The FDA's assessment of safety for this application primarily relied upon data from Study 3(b) and Study 14 in patients with high-risk neuroblastoma.

### Expectations on Safety in the Postmarket Setting

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The Applicant's Position:

Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor the safety of DFMO in HRNB patients who have achieved remission after upfront or relapse therapy.

The FDA's Assessment:

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

**8.2.10. Integrated Assessment of Safety**

Data:

DFMO has been investigated in numerous pre-clinical and clinical studies and has a well-characterized and favorable safety profile. Consistent with those findings, data from Studies 3b and 14, DFMO demonstrated a very favorable safety profile. Across both studies pooled, 19.9% of patients receiving the proposed dose (1500 mg/m<sup>2</sup>) experienced an adverse event related to the study medication, with 6.8% of study patients discontinuing because of these events. The most frequently reported TEAEs regardless of causality among patients who received the proposed dose level were alanine aminotransferase increased (11.9%) and hypoacusis (11.9%). Treatment emergent SAEs regardless of causality reported were reported in 16.4% of patients across both studies pooled, with 1.9% of those patients having serious events assessed by the study investigators to be treatment related. There were no TEAEs leading to death in either study.

Hearing loss is a well characterized and common long-term side effect of chemotherapies used to treated pediatric cancers. Reports from other studies assessing the safety of DFMO have also identified hearing loss as a DFMO-related adverse drug effect. Hearing assessments conducted for Study 3b and Study 14 found that 82.7% of patients had abnormal hearing assessments before starting treatment with DFMO. Among patients with normal hearing at study initiation, about 5% developed a new abnormal hearing determination and about 10% of patients classified as having abnormal hearing at baseline were determined to have hearing changes that represented worsening of hearing compared to baseline. Among patients whose DFMO dosing was temporarily interrupted and then resumed (either at a lower dose or the original dose), the AESIs were reported recovered/resolved in 67% of patients.

The Applicant's Position:

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Patients' prior treatment with platinum-based chemotherapies likely contributes to the hearing loss reported during DFMO treatment in Study 3b and Study 14. Chemotherapy-related ototoxicity presents clinically as hearing loss that may begin during treatment or develop after treatment has completed and can worsen over time, and is often permanent ([Bertolini 2004](#), [Knight 2005](#), [Friedman 2018](#)). Thus, it is possible that new and/or worsening hearing loss that occurred during DFMO treatment, and particularly cases of non-reversible hearing changes, could be related to late-onset hearing loss caused by prior platinum treatment.

The Applicant concludes that DFMO has a strongly favorable benefit -risk profile. DFMO improves treatment outcomes in HRNB patients following the completion of multiagent, multimodality high risk neuroblastoma therapy, during the highest risk period for a patient to relapse, with a manageable side effect profile that permits chronic dosing without causing further long-term damage. This undoubtedly addresses an unmet medical need for which no therapies currently exist.

#### The FDA's Assessment:

The pooled safety population includes 360 pediatric patients with newly diagnosed or relapsed/refractory high-risk neuroblastoma who received eflornithine as a single agent taken orally twice daily based on body surface area, until disease progression or unacceptable toxicity for a maximum of 2 years, in Study 3b (n=101) and Study 14 (n=259).

The primary safety population includes a subset of 85 patients who received eflornithine at the proposed dose of eflornithine in Study 3(b) Stratum 1 (in which the population was reflective of the proposed indication) for whom safety data was available.

Given the collected safety data were limited in both clinical studies, the incidence of the observed adverse events may be higher in a larger population. Study 3(b) collected Grade 2 or higher AEs and no laboratory data. Study 14 collected Grade 3 or higher AEs. However, all high-grade and serious adverse events were captured in both studies; thus, the proposed warnings of myelosuppression, hepatotoxicity, hearing loss, and embryo-fetal toxicity are appropriate.

Hearing loss was described in the proposed labeling as a Warning, consistent with the findings in this study and findings with eflornithine in other populations. Notably, the population of patients with HRNB who have completed initial multimodality therapy are at risk for hearing loss due to receipt of platinum chemotherapy; this hearing loss may continue to emerge or worsen in the years following treatment. Therefore, the contribution of platinum chemotherapy to the observed treatment-emergent hearing loss observed in Study 3b is not clear. However, based on the review

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of available data, new or worsening hearing loss appears to be a risk associated with eflornithine in patients with HRNB. Clinical SGEs consulted during review of the application were concerned about this population being exposed to an additional risk factor for hearing loss, particularly given the timing with respect to key language and social development in young children.

The demographics and disease characteristics of the safety populations are generally similar to the intended use population. In the primary safety population (n=85), the median age of patients was 4 years (range: 1 to 17); 59% male; 85% White, 7% Black, 1% Asian; 8% Hispanic or Latino; 87% had International Neuroblastoma Staging System Stage 4 disease; 47% had neuroblastoma with known *MYCN*-amplification.

There were no Grade 5 treatment-emergent adverse events in Study 3(b) or Study 14. Serious adverse reactions occurred in 12% of patients who received eflornithine. Serious adverse reactions in > 1 patient included skin infection (3 patients).

Permanent discontinuation of eflornithine due to an adverse reaction occurred in 11% of patients. Adverse reactions which resulted in permanent discontinuation of eflornithine in > 1 patient included hearing loss. Dose reductions of eflornithine due to an adverse reaction occurred in 8% of patients. Adverse reactions which required dose reductions in > 1 patient included hearing loss.

The most common ( $\geq 5\%$ ) adverse reactions, including laboratory abnormalities, were otitis media, diarrhea, cough, sinusitis, pneumonia, upper respiratory tract infection, conjunctivitis, vomiting, pyrexia, allergic rhinitis, decreased neutrophils, increased ALT, increased AST, hearing loss, skin infection, and urinary tract infection.

Clinically relevant adverse reactions in <5% of patients who received eflornithine included rash, extremity pain, and alopecia.

There were no notable differences in safety by sex, age group (< 6 years vs.  $\geq 6$  years), or disease status (newly diagnosed vs. relapsed/refractory).

The 120-day safety update included an additional 12 months of safety data for the 62 patients in Study 14 who were ongoing in treatment at the time of the NDA data cutoff (June 30, 2021) and data from 40 patients enrolled after the NDA data cutoff. Of the 40 new patients, 28 received

eflornithine at a higher dose than the proposed dose (2500 mg/m<sup>2</sup> BID) in Study 14 Stratum 1b. No additional data from Study 3(b) was collected after the original NDA data cutoff because all patients had completed treatment and safety data were not collected in the long-term follow-up phase of the study. While patients who received the higher dose of eflornithine experienced more high-grade adverse events and required more dose modifications compared to patients who received the proposed dose of eflornithine, there were no new safety signals identified in the updated safety population.

The review team considers the identified risks of eflornithine to be acceptable in the context of a life-threatening disease. Further, it is anticipated that eflornithine will be prescribed by pediatric oncologists who routinely monitor and manage toxicities including those described in the product labeling.

## SUMMARY AND CONCLUSIONS

### 8.3. Statistical Issues

#### The FDA's Assessment:

The statistical review of this application was based on the single ECT, derived from two previously conducted trials contributing to the investigation and control arms. As described in greater detail in Sections 8.1.3 and 8.1.4, the control arm was derived from the experimental arm of a previously completed randomized trial, Study ANBL0032, a multi-center, randomized, open-label trial in pediatric patients with newly diagnosed high-risk neuroblastoma (HRNB) who had previously received induction and consolidation therapy, achieving at least a partial response prior to autologous stem cell transplant treatment. Patients were enrolled between November 2004 and July 2015 at 197 sites including 172 in the United States, as well as sites in Australia, New Zealand, and Canada. The investigational arm was derived from Study 3(b), a prospectively defined, multi-center, non-randomized, multi-cohort, open-label, phase 2 trial of eflornithine (DFMO, IWILFIN) monotherapy administered as extended maintenance for up to 2 years in pediatric patients who completed standard of care up-front therapy including immunotherapy. Most patients on Study 3(b) were previously treated on ANBL0032, and the trial enrolled patients from June 2012 to February 2016 across 22 sites in the United States. The comparative analyses of the ECT were performed in a set of patients determined by a common set of eligibility criteria (Figure 23, Figure 24), and per the Applicant's proposed primary analyses

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were further matched based on propensity scores derived from a model that included 10 key clinical covariates as well as a direct match on *MYCN* status. The primary efficacy outcome was investigator assessed event-free survival (EFS), with overall survival (OS) as a secondary endpoint without a formal hypothesis testing plan.

There were numerous complex statistical issues to address in the review of this application, due to the reliance on an ECT to establish effectiveness of eflornithine. Study 3(b) was originally developed as and considered to be an exploratory study, and FDA's early advice on the development program noted that a randomized control trial would be required to demonstrate evidence of efficacy in this therapeutic context. However, after the Applicant's review of the Study 3(b) results, an external control comparator was proposed in a preliminary Breakthrough Therapy Designation (BTD) discussion in 2018, in which the Applicant compared the results of Study 3(b) to a historical control rate derived from ANBL0032. FDA recommended that the Applicant compare patient-level data from the studies intended to support the request. Further discussion between the Applicant and FDA regarding the formal development of a statistical analysis plan of an externally controlled trial were conducted over the course of several IND meetings and related interactions after FDA's agreement to consider an ECT to provide primary evidence of efficacy for eflornithine.

Discussions of the statistical analysis plan for the ECT were primarily focused on the selection of comparable patient populations across studies, analytical methodology required for appropriate comparison, and the need for sensitivity and supportive analyses to adequately characterize the data and treatment effect.

One major limitation of the ECT is that the statistical analysis plan was specified with knowledge of the results of the investigational arm from Study 3(b) and after completion of ANBL0032. However, given that the FDA did not have access to the patient-level data and provided extensive advice to the Applicant during the development of the statistical analysis plan, particularly on the selection of the populations for comparison, the potential for bias due to unblinded development of the analysis plan is lessened. Additionally, FDA indicated that while flexibility could be exercised with respect to the use of an external control, no single analysis would serve as the primary evidence of efficacy; rather, the collective results of all sensitivity and supportive analyses would be considered to build a characterization of efficacy of eflornithine in this therapeutic context.

Critically, due to the post-hoc development of the statistical analysis plan and the stated

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approach to characterization of efficacy, FDA did not consider there to be an overall pre-specified Type I error rate for the Applicant's proposed primary analysis or a plan to control Type I error for the multiple sensitivity and supportive analyses. There is increased risk inherent in this approach, for both the Applicant and the FDA, because if the fit-for-purpose or comparability of the source of data is determined to be insufficient, statistical inference can be challenging without appropriate Type I or Type II error control. However, accepting this level of risk was considered appropriate for this application given the need for regulatory flexibility in this disease setting.

Upon examination of the submitted patient-level external control data derived from ANBL0032, FDA determined that the data were largely complete providing sufficient ability to evaluate measured clinical and demographic characteristics between populations. Although some clinical variables were not measured in both populations, the review team deemed there to be sufficient information of appropriate reliability and relevance to classify the external control data as a fit-for-use comparator to Study 3(b). The external data source and Applicant procurement of the data was inspected and determined to be of acceptable quality and appropriate procurement. Additionally, the patient populations were considered to be sufficiently similar to enable formal comparisons. Specifically, since most patients on Study 3(b) had previously been enrolled in ANBL0032, there was evidence that the underlying patient populations were similar or the same. Further, comparisons of measured patient characteristics among the two populations were similar prior to any analytical adjustments (e.g., matching).

In selecting the primary analysis population, eligibility criteria were applied to the complete case population, to ensure that adjusted analyses would not be subject to missing data concerns. While this approach is reasonable, a complete case analysis assumes that the missing data are missing completely at random (MCAR), which is a very strong assumption regarding missing data. The patients with missing data were compared to those without missing data to examine patterns of missingness and to determine whether these populations appeared to be different with respect to distributions of observed covariates. Based on these comparisons, there were no major concerns that systematic missingness led to bias in the control patient sample. Additionally, the Applicant conducted analyses of the EFS according to their proposed primary analysis plan, but with missing covariate data imputed to test the sensitivity of the observed results to the inclusion of those patients excluded in the complete case analysis. The results of the imputed analyses were consistent with Applicant's proposed primary analysis.

The Applicant proposed propensity score-based matching to address population selection bias

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and confounding. Although propensity score-based approaches are not a substitute for randomization as all sources of confounding cannot be removed, results of the matching appear to create balance across arms of the analysis population and provide adjustment for known and measured confounders. It is noteworthy that this method depends on several key assumptions for causal inference including exchangeability (comparative groups are sampled from the same underlying distribution) or conditional exchangeability (exchangeability after adjustment for confounders) and no unmeasured confounders (all important baseline characteristics that may be related to treatment assignment or outcome are available and measured with the granularity and precision required). If these assumptions are not met, propensity score-based methods cannot be fully relied upon to adjust for population selection bias and confounding by the factors included in the model. Additionally, if bias due to unmeasured confounding is suspected, even if the propensity score-based matching improves the balance across arms for the distributions of measured characteristics, the balance of unmeasured characteristics cannot be examined.

These assumptions are difficult to fully verify; however, sensitivity analyses of the data can indicate whether the assumptions are reasonable in the context of the study. As previously described, given that most patients on Study 3(b) were previously enrolled on ANBL0032, this is supportive of the general assumption of exchangeability. Further, when examining post-matching covariate distributions in each arm or the post-matching standardized mean differences of each covariate, it is apparent that conditional exchangeability is achieved, at least for those measured covariates.

The second assumption of no unmeasured confounding is somewhat more difficult to justify, as it is possible that variables related to both treatment and outcome that are unmeasured exist. However, it is notable that in order for a confounding variable, measured or unmeasured, to be a concern for bias on the treatment effect there must either be a differential association with the outcome by treatment arm or have differential prevalence by treatment arm. This limits the scope of concern for potential unmeasured confounders to only those which meet these criteria. Discussions with clinical SGEs indicate that there are likely a few potential sources of unmeasured confounding meeting the criterion of differential association of outcome or prevalence by arm (e.g., social determinants of health).

To explore this concern, FDA conducted several sensitivity analyses exploring the potential for bias due to unmeasured confounding that would render the observed treatment effect null using two methods, the E-value and a method proposed by Lin et al (1998). Each of these methods has its advantages and disadvantages. In particular, the E-value makes few assumptions, is easily



interpretable, and does not require a parametric or other underlying structure of the association of the unmeasured confounder with respect to its association with outcome or treatment; however, the E-value may be overly simplistic and may not reflect real world scenarios. The method proposed by Lin et al. allows for the consideration of survival outcomes in the assessment of unmeasured confounding but requires the association between unmeasured confounder and the outcome to be the same across treatment arms and that the distributions for unmeasured and measured confounders are approximately independent within treatment arms (among other assumptions). Although the potential for bias due to unmeasured confounding cannot be eradicated, the results of both of these analyses were consistent and indicated that it is unlikely that there is the presence of a bias due to an unmeasured confounder that would be fully attributable for the observed treatment effect of eflornithine on EFS.

Apart from the assumptions required, consequences of the matching process is another statistical review consideration with regards to the use of propensity score matching as the primary analytic methods to provide balance in the analysis population. While matching using propensity scores is attractive as it creates a population that most closely resembles a randomized study, criticisms of the approach include: 1) Not all eligible patient data is used in the analysis; and 2) The matching algorithm could be subject to the ordering of the data set. To address the latter concern regarding data structure and ordering, analyses were conducted using repeated draws of the population, each with matching conducted with the population re-ordered using a random seed each time. This removed the sensitivity of the matched results to the ordering of the data itself, and the results were consistent with the primary analysis using only a single matched sample. To address the former concern of use of all available patient information, weighted analyses per inverse probability of treatment weighting (IPTW) were conducted. These analyses were conducted for both the same causal estimand as the primary analyses per matching (average treatment effect, or ATE) and in an alternative causal estimand which focuses on the average treatment effect among a population that would reflect the treated population (average treatment effect on the treated, or ATT). IPTW analyses were conducted in the overall eligible population as well as in populations that had restrictions or adjustment to reflect the various sensitivity analyses conducted to address other potential sources of bias. Results of all weighted analyses, however, were consistent the Applicant's proposed primary analysis results.

Given the non-randomized nature of the comparative trial, there were several additional challenges in the design of the study as well as several known sources of potential bias that could threaten the internal validity of the study. A robust statistical analysis plan with several sensitivity and supportive analyses to explore the impact of study design choices, analytical

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assumptions, or potential sources of bias on the observed results was developed. Analyses were planned to address identification of appropriate index date, the potential presence of immortal time, differential follow-up/ availability of imaging data, treatment era of each study arm, missing covariate information, and the potential for selection bias and confounding (measured, residual, and unmeasured). The Applicant and the FDA performed multiple sensitivity and supportive analyses including use of alternative analysis populations or alternative statistical methods to characterize the treatment effect on the efficacy outcomes in the presence of these design factors.

In particular, FDA's approach to the sensitivity and supportive analyses included a multi-step and multi-layer approach to statistical adjustment. This scientifically rigorous approach is more comprehensive in addressing or accounting for the several known sources of bias than considering the effect of each source of bias in isolation. The simultaneous employment of these statistical methods helped increase confidence that comparisons of the ECT were not confounded by other differences in the population and was more likely to have a valid estimation of the treatment effect of eflornithine. Overall, the results of these analyses indicate that the observed treatment effect estimate of eflornithine on EFS is generally robust to the design choices, analytical assumptions, and impact of potential bias. While we may never completely dismiss the potential for some bias in the observed treatment effect estimate, it is reasonable to conclude that it is unlikely that the observed effect is fully attributable to bias rather than the treatment effect of eflornithine.

The statistical review of this application supports the determination that the ECT is adequate and well controlled. The comparison to an external control is considered appropriate in this therapeutic context given the high and predictable mortality after relapse, and the external control data are fit-for-use in for a valid comparison for various reasons including the similarities in the defining underlying distributions of the patient populations. Despite the post-hoc nature of the development of the ECT, the statistical analysis plan was developed through discussions with FDA and included a thorough plan for characterizing the observed treatment effect using primary, sensitivity and supportive analysis. Potential sources of bias were minimized through detailed eligibility criteria and in the analytical plan, and there were objective and reliable measurement of EFS for up to 5 years in follow-up as well as key baseline covariates. Given these factors supporting the assessment that the ECT was adequate and well controlled, and that the numerous statistical analyses conducted to characterize treatment effect indicated a consistent treatment benefit of eflornithine on EFS that is unlikely to be attributable to sources of bias (measured or unmeasured), the conclusion of the statistical review team is that the ECT provides

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consistent evidence of efficacy of eflornithine in the maintenance setting of pediatric patients with high risk neuroblastoma in remission after completion of multiagent, multimodality upfront therapy. Whether this primary evidence of efficacy meets the standard for substantial evidence of efficacy to support a regulatory approval relies on the assessment of the available confirmatory evidence of efficacy in the context of a single adequate and well controlled trial.

## 8.4. Conclusions and Recommendations

### The FDA's Assessment:

The FDA review team recommends traditional approval of eflornithine to reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy. The statutory requirement for demonstration of substantial evidence of effectiveness is met based on the efficacy results from one adequate and well-controlled clinical investigation, as defined in 21 CFR 314.126, and confirmatory evidence, to establish the effectiveness of eflornithine for the proposed indication.

In 1962, as described in the Food, Drug, and Cosmetic Act, Congress determined that a drug's effectiveness must be established by substantial evidence. Substantial evidence consists of "adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have" (FD&C Act section 505(d) [21 U.S.C. § 355(d)]). This standard refers to both the quality and quantity of evidence. Effectiveness may be supported by two adequate and well-controlled investigations, or, under certain circumstances, by one adequate and well-controlled investigation with confirmatory evidence. Approval based on a single adequate and well-controlled investigation with confirmatory evidence may be acceptable depending upon the persuasiveness of the trial, robustness of the confirmatory evidence, seriousness of the disease and unmet medical need, and whether it is ethical and practicable to conduct more than one adequate and well-controlled investigation.

The Applicant submitted results of a single externally controlled trial (ECT) and supportive data to provide evidence of effectiveness for eflornithine to reduce the risk of relapse in pediatric patients with HRNB who have completed multiagent, multimodality therapy. The ECT was designed to compare data from Study 3(b), a multi-center, open-label, single arm trial of eflornithine monotherapy for up to 2 years in pediatric patients with HRNB in remission after immunotherapy, to an external control arm constructed from patients with HRNB enrolled on

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Study ANBL0032, a multi-center, open-label, randomized trial of immunotherapy plus standard up-front therapy vs. up-front therapy alone.

The population for the Applicant’s primary analysis of efficacy included 90 eflornithine-treated patients and 270 control patients from Study ANBL0032 who met the criteria for the comparison, had complete data for specified clinical covariates, and were matched (1:3) using propensity scores. The primary endpoint was event-free survival (EFS), defined as the time from the end of immunotherapy until the first occurrence of disease progression, relapse, secondary cancer, or death due to any cause. Overall survival (OS), defined as death due to any cause, was a secondary endpoint.

The Applicant’s primary analysis resulted in a hazard ratio (HR) for EFS of 0.48 (95% Confidence Interval [CI]: 0.27, 0.85) and 0.32 (95% CI: 0.15, 0.70) for OS, favoring the DFMO arm. FDA conducted multiple sensitivity and supportive analyses to evaluate potential threats to study validity. The estimation of the treatment effect from these analyses generally appeared to be robust to potential sources of bias.

Randomized trials are generally required to assess the effect of a drug on a time-to-event endpoint (e.g., event-free survival, overall survival) because randomization controls for both known and unknown prognostic factors. In some cases where there is an appropriate justification, an externally controlled trial may be considered to support a demonstration of effectiveness of a drug. Such an investigation must still be considered adequate and well-controlled, and provide a valid analysis of the treatment effect based on, among other things, “comparable patients or populations” (21 CFR 314.126).

As discussed in the 2023 FDA Draft Guidance for Industry: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products, ECTs differ in several important ways from randomized trials. Most notably, randomization is not a feature of external control designs and is the most powerful design feature to facilitate balance in known and unknown confounding influences. As a result, there may be differences in baseline patient characteristics or concomitant treatments in the trial population compared to the external control population that may lead to differences in outcomes that are independent of the investigational treatment. The 2019 FDA Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products also states that the level of support for effectiveness provided by an externally controlled trial is strengthened if the following conditions are present:

- the natural history of a disease is well defined,

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- the external control population is very similar to that of the treatment group,
- concomitant treatments that affect the primary endpoint are not substantially different between the external control population and the trial population, and
- the results provide compelling evidence of a change in the established progression of disease (such as partial or complete response in a disease where spontaneous regression is not observed).

HRNB is a rare and life-threatening disease with a high unmet need. Prognosis after relapse is poor and there are no available therapies in the proposed disease setting. Despite inherent uncertainties given the lack of a randomized design to interpret the effect on a time-to-event endpoint, and the uncertainty in the exact magnitude of the treatment effect in the design of a non-randomized trial, the external control data in this application was of high quality due to its provenance and the large set of individual patient-level trial data, and the results of sensitivity analyses were generally consistent with the Applicant's primary analysis.

Considering these factors and given the design and estimated treatment effect observed, the FDA review team determined that the use of the submitted ECT was acceptable to support this marketing application. Based on review of the study design, study conduct, and submitted data, the FDA concluded that the ECT was adequate and well-controlled with a clear statement of objectives, an appropriately constructed external control design with appropriate patient selection, reliable clinical assessments to evaluate the effect of the drug, and adequate analysis of the results of the study to assess the effect of the drug.

In addition to the results of the single ECT, the Applicant submitted supportive evidence including nonclinical data and data from exploratory clinical studies and an expanded access program of DFMO in related populations. A determination of whether the available supportive evidence is sufficiently strong to be considered confirmatory evidence depends both on the strength and persuasiveness of the single adequate and well-controlled trial serving as primary evidence, and the strength of the supportive evidence itself.

In many oncology applications, the evidentiary package is supported by dose-dependent tumor response data in early-stage studies with or without additional clinical data showing early activity or efficacy in other cancer indications. Given the suggested cytostatic mechanism of action of DFMO as a single agent in this application, response rate data are not expected in this clinical setting. Therefore, FDA considered whether the submitted non-clinical data could serve as confirmatory evidence to provide substantial evidence of effectiveness.

The 2019 Substantial Evidence draft guidance states that “compelling mechanistic evidence in

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the setting of well-understood disease pathophysiology, may be sufficient to provide substantial evidence of effectiveness of a new drug or a new indication.” Such mechanistic evidence would generally be obtained from clinical testing using a relevant and well understood pharmacodynamic endpoint; however, the guidance states it could also be collected from other sources such as animal studies.

The underlying pathophysiology of the *ODC* and *MYCN* pathways in neuroblastoma is well understood, creating a setting in which it is appropriate to consider the possibility of leveraging mechanistic data as confirmatory evidence. The review team carefully reviewed data submitted by the Applicant and identified in an independent FDA literature search and found it to provide strong mechanistic support, as the drug directly targets these underlying critical oncogenic pathways in this disease. In particular, the review team finds the mechanistic evidence provided by two well-established, relevant animal models of neuroblastoma which showed that eflornithine prevents or delays tumor formation in mice who have no initial evidence of disease to be compelling and appropriate as confirmatory evidence of eflornithine’s effectiveness. While LIN28 overexpression is observed in multiple tumor types, and there have been negative trials of eflornithine in adults with cancer, the *ODC1* and *MYCN* genes are largely not considered major drivers of tumors in which studies of eflornithine were negative, summarized further in Section 8.1.5 and Table 54. In contrast, these genes are particularly relevant in neuroblastoma and aberrations of *ODC* and *MYCN* are correlated with poor prognosis in this disease. In addition, pediatric solid tumors have largely different ontogeny and biology from adult tumors, with the latter being more likely to have substantially higher mutational burdens and multiple driver mutations. Thus, the lack of activity in other adult tumor types does not necessarily imply a lack of activity in neuroblastoma.

Based on the nonclinical data provided in the application and on the FDA’s independent literature review, the FDA nonclinical review team concluded that strong nonclinical mechanistic support and data from relevant animal models of neuroblastoma provide sufficient confirmatory evidence to substantiate the results of the single externally controlled trial in the setting of this rare disease with established pathophysiology.

The finding of substantial evidence of effectiveness is necessary but not sufficient for FDA approval. The approval decision also requires a determination that the drug is safe for the intended use, that is, whether the benefits of the drug outweigh its risks under the conditions of use defined in labeling.

The pooled safety population included 360 patients with newly diagnosed or relapsed/refractory high-risk neuroblastoma in Study 3(b) (N=101; NCT02679144) and Study 14 (N=259;

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NCT02679144) who received eflornithine orally twice daily for a maximum of 2 years. Safety data collection was limited as these studies were investigator-initiated. In this pooled safety population, the most common ( $\geq 5\%$ ) adverse reactions, were hearing loss (11%), otitis media (10%), pyrexia (7%), pneumonia (5%) and diarrhea (5%). The most common ( $\geq 2\%$ ) Grade 3 or 4 laboratory abnormalities were increased ALT (11%), increased AST (6%), decreased neutrophils (4.2%), and decreased hemoglobin (3.3%). Proposed warnings for product labeling included myelosuppression, hepatotoxicity, and hearing loss. Although DFMO can cause serious adverse reactions, these safety concerns are adequately addressed by product labeling, and DFMO will be prescribed by oncologists who know how to monitor, identify, and manage the toxicities described in product labeling. When considering the safety profile of eflornithine in the context of the toxicity of the therapies utilized for upfront HRNB treatment, and for the treatment of pediatric cancer in general, and the benefits in potentially extending EFS and OS in children with HRNB, the risks of eflornithine are considered acceptable from a regulatory perspective. In addition, commentary by parents of children with HRNB who received eflornithine during the Open Public Hearing portion of the Oncology Drugs Advisory Committee (ODAC) Meeting, and in the public comments docket established as part of the ODAC, consistently advised that the safety risks of treatment with eflornithine are considered acceptable by the patient community.

As described, an ODAC meeting was held on October 4, 2023. In response to the voting question, “Has the Applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?”, 14 members voted “yes,” and 6 members voted “no.” The discussion was robust, highlighting both strengths and limitations of the application.

While there are limitations of non-randomized trials as previously described, FDA may exert regulatory flexibility where appropriate and rely on study designs that produce less certainty in some circumstances when a better design is not feasible. The 2019 FDA guidance on Demonstrating Substantial Evidence of Effectiveness states that “in certain settings, a somewhat greater risk (compared to placebo-controlled or other randomized superiority trials) of false positive conclusions – and therefore less certainty about effectiveness – may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy...for an unmet medical need. The data supporting effectiveness could, despite the greater risk of error, support a conclusion that there is substantial evidence of effectiveness.”

The strength of the scientific evidence provided by the ECT and confirmatory evidence was considered in the context of the unmet medical need in this pediatric patient population with a life-threatening disease and feasibility of conducting a randomized trial. Although a randomized

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controlled trial in this disease setting could potentially have been conducted prior to the publication of Study 3(b) results, the review team considers it unlikely that a randomized controlled trial could be completed at this time., The review team determined that application contains substantial evidence of effectiveness to conclude that eflornithine reduces the risk of relapse in patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.

The factors leading to this determination have been meticulously described throughout this review and in FDA’s presentations at the ODAC meeting. These factors are highly specific to this application, which involves a treatment for a rare pediatric population with a life-threatening condition for which there are no available therapies to prevent the risk of relapse, and where an ECT design was deemed appropriate based on the individual development plan. The ECT was derived from clinical trial patient-level data providing a uniquely comparable, high quality external control data source where results of primary and sensitivity analyses were robust in the evaluation of potential sources of bias, along with strong nonclinical supportive evidence based on a relevant animal model of the disease. These elements, when considered in totality, are highly unlikely to be easily replicated in future marketing applications. Furthermore, the benefit-risk assessment for the proposed indication is favorable.

Therefore, the FDA review team recommends traditional approval of eflornithine for the following indication:

“to reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.”

X

X

Primary Statistical Reviewer

Statistical Team Leader

Arup Sinha, PhD

Pallavi Mishra-Kalyani, PhD



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X

X

Primary Clinical Reviewer

Clinical Team Leader

Elizabeth Duke, MD

Diana Bradford, MD

## **9. ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS**

### **The FDA's Assessment:**

During the initial review period, FDA consulted with four Special Government Employees (SGE). All discussions were held with only one SGE at a time. The application was also presented to experts at the FDA CDER Medical Policy and Program Review Committee (MPPRC) on March 29, 2023.

Subsequently, the Application was discussed at an ODAC meeting on October 4, 2023.

The primary discussion points for each of these external and internal consultations are summarized below.

### **SGE Discussion Summaries**

Overall, the independent experts noted there were strengths and limitations of the data submitted in the application. There were concerns expressed by some experts on reasons patients elected to enroll in an additional clinical trial, as well as the uncertainty in the magnitude of effect, alongside notation by other experts that the estimates appear consistent and stable in demonstrating an effect. Areas of residual uncertainty included the evaluation of specific variables contributing to the comparability of populations, such as contemporaneity and social determinants of health, and the measurement of the magnitude of treatment effect observed in the externally controlled trial. FDA explored these areas of uncertainty with sensitivity and supportive analyses as summarized in Section 8. The individual discussions with four SGEs are summarized below:

#### **SGE #1:**

On March 21, 2023, the review team met via teleconference with Dr. Steven DuBois, Pediatric Oncologist and Director of Experimental Therapeutics at Dana-Farber/Boston Children's Hospital and Associate Professor of Pediatrics at Harvard Medical School.

The review team asked Dr. DuBois his opinion regarding comparability of the study populations in the investigational arm (Study 3(b)) and control arm (patients from ANBL0032). Dr. DuBois expressed concerns regarding differences in contemporaneity and index date. He expressed agreement with the sensitivity analyses conducted to address these potential differences. He also

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noted there were likely unmeasured differences in patients who opted to go onto Study 3(b) vs. not go onto Study 3(b) at the same sites. He stated that he was somewhat reassured that Study 3(b) was multi-center and included small-medium sized programs across the U.S. (rather than solely the largest children's hospitals).

Regarding the feasibility of conducting a randomized controlled trial in this disease setting, he stated that with the current available treatments, investigators would likely participate in randomized trial of DFMO vs. no DFMO post-immunotherapy, but he was less certain about the acceptance of the patient community. He suggested that the Children's Oncology Group (COG) could theoretically conduct such a trial, but noted the long lead-time required to design and open trials and noted that ongoing trials (including NMTRC012 and COG ANBL1821) may read-out in the interim and change the treatment landscape. He conveyed that, in hindsight, this would have been a "perfect example for a hybrid control", potentially leveraging the large external database with a subset of contemporaneously randomized patients. He commented that the DFMO dose in the proposed application is lower than other studies, which gave him some pause in interpreting the results of Study 3(b), and wondered about the feasibility of a dose randomization trial in this population rather than a placebo-controlled trial.

Regarding the magnitude of effect, he stated that he did not "see convincing evidence in the context of an externally controlled trial". In his benefit:risk assessment, he described a "relatively modest effect" and was concerned about the risk of hearing loss over and above that related to platinum therapy in first-line treatment. The risk of hearing loss, along with the continuation of 2 years of oral therapy after patients had recently completed 18 months of intensive up-front therapy, were considered in his assessment of the benefit:risk ratio. He stated that these patients would have recently completed 1.5 years of therapy, and he "would want to make sure there was true benefit if extending therapy by 2 years (even if oral medication at home) which would keep them as patients and not get back to being kids again". He stated that if DFMO was approved, it would become the "de facto standard of care", but he would have "lingering concerns about the benefit:risk [ratio]" and "feel ambivalent about recommending it to his patients".

## **SGE #2:**

On March 10, 2023, the review team met via teleconference with Dr. Rochelle Bagatell, Pediatric Oncologist and Solid Tumor Section Chief, Division of Oncology at The Children's

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Hospital of Philadelphia, and Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania.

Regarding the use of an externally controlled trial in this disease setting, she noted that the study design appeared reasonable given the challenges of trial design in this rare disease.

Regarding comparability of the study populations, she expressed concern regarding the contemporaneity of the investigational arm vs. the external control arm. She noted that there is “unmeasurable evolution in supportive care” from the early 2000’s to the 2010’s, and “we get better as we go.” She stated that there are some factors that are likely not “missing at random,” such as histology and completeness of surgery, and these factors may impact patient outcome. For example, patients with missing histology results may not have had their tumor sampled, which may reflect different patterns of care at different sites (i.e., larger centers were more likely to have tumors biopsied).

Regarding potential missing clinical characteristics, she noted that social determinants of health are likely to impact clinical outcomes and are generally not accounted for in clinical trial design. She cited a recent publication which concluded that poverty is independently associated with increased risk of relapse and death among neuroblastoma patients treated with targeted immunotherapy (Bona K et al. Poverty and Targeted Immunotherapy: Survival in Children's Oncology Group Clinical Trials for High-Risk Neuroblastoma. J Natl Cancer Inst. 2021 Mar 1;113(3):282-291). She expressed concern that the patients who went onto Study 3(b) after recently completing ANBL0032, are likely “a different population” with regard to geographic location, parent education, resources, and motivation to continue on therapy after up-front treatment.

She also noted that the response criteria for neuroblastoma have evolved over time, with improvements in diagnostic imaging (e.g., MIBG) and bone marrow disease assessment. While the 1993 INRC criteria were used for both studies, she noted that investigator interpretation of the response criteria may have evolved over time and may differ by treatment center.

She noted that the efficacy of DFMO in this disease setting is an “important question” and one that should be “answered well”. She expressed she is “nervous to draw conclusions [from these data] about something this important for the field”.

Due to lack of time to review the pre-determined questions, the review team met again via

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teleconference with Dr. Ro Bagatell on March 28, 2023.

In this meeting, Dr. Bagatell expressed concern that Study ANBL0032 was not originally designed to be compared to Study 3(b), and “retrofitting the data” to compare the two populations is challenging.

Regarding the feasibility of a randomized controlled trial, she stated that investigators would likely be willing to participate in a randomized trial of DFMO vs. no DFMO in this disease setting and she thought patients might be willing to enroll.

Regarding the magnitude of effect and benefit:risk assessment, she stated that she was unable to make a determination due to the perceived lack of comparability of the patient populations in the externally controlled trial. She considered the risks of treatment to be relatively low given the side effect profile of the drug; although the presented hazard ratio suggested an effect, given the concerns with the study design, she questioned the interpretability of the results.

### **SGE #3:**

On March 13, 2023, the review team met via teleconference with Dr. Michele Jonsson-Funk, Associate Professor in the Department of Epidemiology at UNC Chapel Hill, and Director of the Center for Pharmacoepidemiology at UNC Chapel Hill.

Regarding the methodologic approaches utilized, she stated that propensity score matching is a method used to control for confounding and is generally a good approach for adjusting for potentially important covariates. She stated one can also consider analytic methods that include adjustment for propensity score model error in the outcome model (e.g., doubly-robust methods, G-computation). Regarding the Sponsor’s choice to conduct a propensity-score matched vs. weighted analysis, she stated that different methods may be applied in different settings depending on the estimand of interest and other factors. She preliminarily recommended also evaluating weighted analyses using the ATT estimand (average treatment effect on the treated), and stated that this could be accomplished using inverse probability of treatment weighting (IPTW) or standardized mortality ratio weighting (SMRW). She asked several questions regarding censoring and covariate balance after matching (e.g., the standardized mean differences); additional documents were provided for her review.

Due to lack of time to review the questions the review team sent in advance of the March 13,

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2023 meeting, the review team met again via teleconference with Dr. Michele Jonsson-Funk on March 22, 2023.

In this meeting, she noted that her main concerns were related to index date and censoring. She reflected that index date is a general source of concern in externally controlled trials because of immortal time in individuals who go on to start the treatment of interest. She agreed with the sensitivity analyses performed and suggested using the time from the end of immunotherapy to the start of DFMO as a matching criterion to further interrogate this potential issue.

Regarding censoring, she noted that there could be potentially different drop-out between the two arms. She recommended using baseline characteristics to create a censoring weight, and to use this weight to evaluate the impact of censoring on the hazard ratios. She stated it would be reassuring if censoring was not strongly related to the outcome.

She stated that the comparability of populations was generally good, particularly after matching. Regarding the sensitivity analyses, she observed that the results “potentially moved the most” with the contemporaneous population analysis. She recommended considering additional analyses with cut-offs at different points in time to further evaluate this difference.

Overall, she stated that she did not see strong evidence of differences before matching based on the measured variables. She noted “stability in the overall survival result” and that there appeared to be a “big effect based on the hazard ratio.” She stated that the hazard ratios and Kaplan Meier curves were more indicative of the whole picture compared to the difference in 3-year rates which are a “moment in time” and “depending where you are on the timeline, you may be seeing different pieces of that difference.”

Furthermore, in a meeting on May 9<sup>th</sup>, she mentioned the importance of evaluating the ATT and ATE, as fundamentally they are estimating different constructs and the nature of ATT provides gains in precision. Overall, she mentioned that the use of externally controlled trial is dependent on setting and that it would be justifiable in this setting; however, the strength of the evidence as the single clinical study is based on the available alternatives and how robust the ECT is to all potential biases.

#### **SGE #4:**

On March 27, 2023, the review team met via teleconference with Dr. Yun Li, Associate

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Professor of Biostatistics in the Department of Biostatistics, Epidemiology and Informatics at the Perelman School of Medicine at the University of Pennsylvania, and Associate Professor in the Department of Pediatrics at The Children's Hospital of Philadelphia.

Regarding the statistical methods utilized, she stated that overall, many analyses have already been conducted and based on her assessment, the treatment “looks very effective” and “consistent.” She noted that the wide confidence intervals around the hazard ratio are related to power and that ultimately the clinical meaningfulness of the absolute differences need to be evaluated in the context of the disease.

She noted that her main potential concerns were related to index date, immortal time bias, and unmeasured confounding. She reflected on the variability in the end of immunotherapy date in both arms and suggested that this variable could be added to the final model to adjust for residual imbalance.

She stated that matching “looks good,” but there are potential residual unmeasured confounders, including treatment site, which need to be considered cumulatively. She noted that the unmeasured confounding would have to be “enormous” to overturn the observed treatment effect, but this could potentially be observed if, for example, the control arm was all enrolled ex-U.S. and compared to the investigational arm treated in the U.S.

Regarding additional types of sensitivity analyses she would recommend with respect to testing assumptions required for the design or analysis of this externally controlled trial, she recommended consideration of a Cox model stratified by propensity score matches as well as a covariate-adjusted Cox model for potential confounders related to outcome. She noted that 3:1 matching is more robust given the large number of control patients and ability to use the additional data to better understand the treatment effect.

### **ODAC Summary:**

Please refer to the publicly available briefing documents from the Applicant and the FDA, as well as the final agenda, committee roster, slide presentations, transcripts, and a recording of the virtual meeting. The committee engaged in a robust discussion regarding results of the ECT and in particular the impact of potential unmeasured confounding factors, the feasibility and considerations regarding the need for a randomized trial, and the strengths and limitations of the

nonclinical evidence. In response to questions from the committee, FDA expressed their opinion regarding the truly unique nature of this ECT, and expectations that availability of an appropriate, fit-for-purpose control arm would seriously limit the replicability of this approach.

The committee was asked to discuss two questions, and vote on one question. The discussion and vote are briefly summarized below.

1. **DISCUSSION:** Discuss the strengths and limitations of the externally controlled trial results to support the use of DFMO in pediatric patients with high-risk neuroblastoma.

**Committee Discussion:** Committee members appreciated the thorough analyses that had been performed by FDA and the Applicant to assess the impact of potential biases on the results of the externally controlled trial. However, there was not a unanimous consensus regarding the certainty or reliability of the results of the externally controlled trial. Many committee members had concerns about setting precedent regarding utilization of an external control. Several committee members questioned whether a randomized controlled trial could be performed in this setting, while others stated that such a trial would be infeasible. Some committee members were concerned about the impact of such an approval on other trials in pediatric oncology. Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION:** Discuss the strengths and limitations of the additional nonclinical and clinical data to support the use of DFMO in pediatric patients with high-risk neuroblastoma.

**Committee Discussion:** Some committee members noted that the nonclinical data appeared to use a relevant model and provided supportive evidence of the effect of DFMO in this setting. However, as for limitations, some committee members commented that nonclinical data does not always translate into an effect in clinical studies. Please see the transcript for details of the Committee's discussion.

3. **VOTE:** Has the Applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?



**Vote Result:      Yes: 14                      No: 6                      Abstain: 0**

**Committee Discussion:** The majority of the committee members agreed that the Applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma; however, there were questions for clarity around if this was intended to mean substantial evidence and deferred to FDA on that aspect. Committee members who voted “Yes” noted the totality of data appeared to support the assertion that DFMO improves event- free survival given the robustness and uniqueness of the external control. There was also trust in the nonclinical data. Those who voted “No” questioned whether this type design could be used to demonstrate efficacy given the concerns regarding confounding and bias that are inherent with use of external control arms. There were some differences of opinions among Committee members as to whether a randomized controlled trial of this drug in the proposed indication could be feasible, and, if so, whether such a trial could be completed in a timely fashion. Please see the transcript for details of the Committee’s discussion.

## 10. PEDIATRICS

### The Applicant's Position:

Neuroblastoma is a pediatric cancer that primarily affects young children. Accordingly, patients enrolled into Studies 3b and 14 were pediatric patients <18 years of age with few exceptions. Additionally, DFMO for neuroblastoma was granted orphan drug status; therefore, DFMO is exempt from PREA requirements.

### The FDA's Assessment:

FDA agrees with the Applicant's position. The application does not trigger the requirements under the amended provisions of the Pediatric Research Equity Act (FDARA 2017) to conduct a molecularly targeted pediatric cancer investigation.

## 11. LABELING RECOMMENDATIONS

### The Applicant's Position:

The Applicant has no changes to proposed labeling provided in 1.14.1 of the NDA.

### The FDA's Assessment:

| Summary of Significant Labeling Changes (High level changes and not direct quotations) |                                                                                                                                                          |                                                                                                                                                                                                                                      |
|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section                                                                                | Applicant's Proposed Labeling                                                                                                                            | FDA's proposed Labeling                                                                                                                                                                                                              |
| Section 1, Indications and Usage                                                       | Indication: to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma (HRNB) who have completed multiagent, multimodality therapy | FDA refined the indication to include adult and pediatric patients with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy |
| Section 2, Dosage and Administration                                                   | (b) (4)                                                                                                                                                  | FDA included dosage modifications for adverse reactions, and included more details instructions for administration, crushed preparation, and missed doses                                                                            |
| Section 5, Warnings and Precautions                                                    |                                                                                                                                                          | FDA recommended addition of warnings for observed adverse events for which specific laboratory/clinical monitoring is indicated; warnings added for                                                                                  |

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

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|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                        |                                                                                                                                                  | myelosuppression, hepatotoxicity, and hearing loss                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Section 6, Adverse Reactions           | Proposed safety population included 311 patients who received eflornithine in Study 3(b) and Study 14 at the proposed dose                       | <p>FDA revised the pooled safety population to include 360 patients, including 49 additional “transfer patients” in Study 3(b) had partial safety data collected as a result of transition from NMTRC003 to NMTRC003b. FDA considered the available safety data derived from these patients to be informative, particularly given that there are no other approved indications for this formulation of eflornithine to help inform the assessment of safety.</p> <p>The primary safety population included 85 patients from Study 3(b) who were representative of the primary efficacy population.</p> |
| Section 7, Drug Interactions           | None                                                                                                                                             | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Section 8, Use in Specific Populations | Proposed Sections 8.1 to 8.4; stated in Sections 8.5 and 8.6 that eflornithine has not been studied in patients with renal or hepatic impairment | <p>Expanded information under Animal Data in Section 8.1.</p> <p>Removed Sections 8.5 and 8.6 since eflornithine has not been studied in these populations; see details on PMR for patients with renal impairment</p>                                                                                                                                                                                                                                                                                                                                                                                  |
| Section 10, Overdosage                 | N/A                                                                                                                                              | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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|                                            |                                                                                                                                             |                                                                                                                                                                                                                                                            |
|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section 12, Clinical Pharmacology          | Included Absorption, Distribution, and Elimination information                                                                              | Minor edits to provide more details in this section                                                                                                                                                                                                        |
| Section 13, Nonclinical Toxicology         | Included Section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility                                                                 | Expanded data in Section 13.1 and added Section 13.2, Animal Toxicology                                                                                                                                                                                    |
| Section 14                                 | Described Study 3(b), the External Control comparison, and Study 14. Proposed ECT results (b) (4) included EFS and OS hazard ratios (b) (4) | Revised to provide additional details of Study 3(b), ANBL0032 design, and the externally controlled trial. Results included the protocol-specified primary analysis and KM plot for EFS, as well as discussion of supplementary analyses conducted by FDA. |
| Section 17, Patient Counseling Information | (b) (4)                                                                                                                                     | Revised to include specific counseling for the warnings and precautions included in Section 5.                                                                                                                                                             |

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

## **12. RISK EVALUATION AND MITIGATION STRATEGIES (REMS)**

### **The FDA's Assessment:**

FDA determined that a REMS was not needed to ensure safe and effective use of eflornithine in the indicated patient population. Eflornithine will be prescribed by pediatric oncologists who are skilled in monitoring, diagnosing, and managing serious toxicities.

### 13. POSTMARKETING REQUIREMENTS AND COMMITMENT

#### The FDA's Assessment:

USWM has agreed to the following postmarketing requirements and commitments which will be included in the approval letter. Please refer to the approval letter for PMR/PMC milestones.

#### **Clinical PMR:**

Conduct an integrated safety analysis of clinical trial data to assess the serious risk of ototoxicity and to further characterize the serious risks of severe adverse reactions including myelosuppression and hepatotoxicity and their sequelae in a sufficient number of patients exposed to IWILFIN; and to identify risk factors for development of these adverse reactions. Safety assessments will include audiograms prior to and at regular intervals during treatment. The study should include appropriate monitoring and risk mitigation strategies.

Draft Protocol Submission (Analysis Plan): 06/2024

Final Protocol Submission (Analysis Plan): 03/2025

Study Completion: 06/2027

Final Report Submission: 12/2027

#### **Clinical Pharmacology PMR:**

Conduct a clinical pharmacokinetic trial to determine an appropriate dosage of DFMO to minimize a potential serious risk of increased drug toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled [“Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing.”](#)

Draft Protocol Submission: 03/2024

Final Protocol Submission: 06/2024

Trial Completion: 09/2025

Final Report Submission: 03/2026

**14. DIVISION DIRECTOR (DHOT) (NME ONLY)**

X



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**15. DIVISION DIRECTOR (OCP)**

X

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**16. DIVISION DIRECTOR (OB)**

**X**

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**17. DIVISION DIRECTOR (CLINICAL)**

X

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**18. OFFICE DIRECTOR (OR DESIGNATED SIGNATORY  
AUTHORITY)**

*This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.*

X

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## 19. APPENDICES

### 19.1. References

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## 19.2. Financial Disclosure

### The Applicant's Position:

All investigators have been researched for conflicts of financial interests/arrangements. No investigator had disclosable financial interests/ arrangements with the Applicant. Supporting documentation including a list for financial disclosure of all investigators was submitted in Module 1.3.4.

### The FDA's Assessment:

Financial disclosure information was collected for the investigators and sub-investigators participating in Study 3(b) and Study 14. There were no investigators who were Sponsor employees or who had disclosable financial interests/arrangements.

### **Covered Clinical Study (Name and/or Number):\* NMTRC003B (Study 3(b))**

|                                                |                                                        |                                                           |
|------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> (Module 1.3.4) | No <input type="checkbox"/> (Request list from Applicant) |
|------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------|

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



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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------------------------------------------|
| Total number of investigators identified: <u>282</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                              |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                              |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):<br><u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                              |                                                                  |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in study: _____</p> <p>Sponsor of covered study: _____</p> |                              |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                              |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

\*The table above should be filled by the applicant, and confirmed/edited by the FDA.

**Covered Clinical Study (Name and/or Number):\* NMTRC014 (Study 14)**

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

{Eflornithine [DFMO]}

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                           |                                                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Yes <input checked="" type="checkbox"/><br>(Module 1.3.4) | No <input type="checkbox"/> (Request list from Applicant)        |
| Total number of investigators identified: <u>406</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                           |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                           |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                           |                                                                  |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in study: _____</p> <p>Sponsor of covered study: _____</p> |                                                           |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Yes <input type="checkbox"/>                              | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Yes <input type="checkbox"/>                              | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                           |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Yes <input type="checkbox"/>                              | No <input type="checkbox"/> (Request explanation from Applicant) |

\*The table above should be filled by the applicant, and confirmed/edited by the FDA.

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

### 19.3. Nonclinical Pharmacology/Toxicology

#### The Applicant's Position:

All relevant nonclinical data from the eflornithine program is summarized in Section 5.

#### The FDA's Assessment:

The FDA agrees that there is no additional information to add here. See Section 5 for the FDA Nonclinical review.

### 19.4. Additional Analyses Conducted by FDA

#### The FDA's Assessment:

**Figure 50: FDA Kaplan-Meier Plots of Event-free survival and Overall Survival for the Eligible Control Patients (n=852) by Missing Covariate Status for the Propensity Score Model**

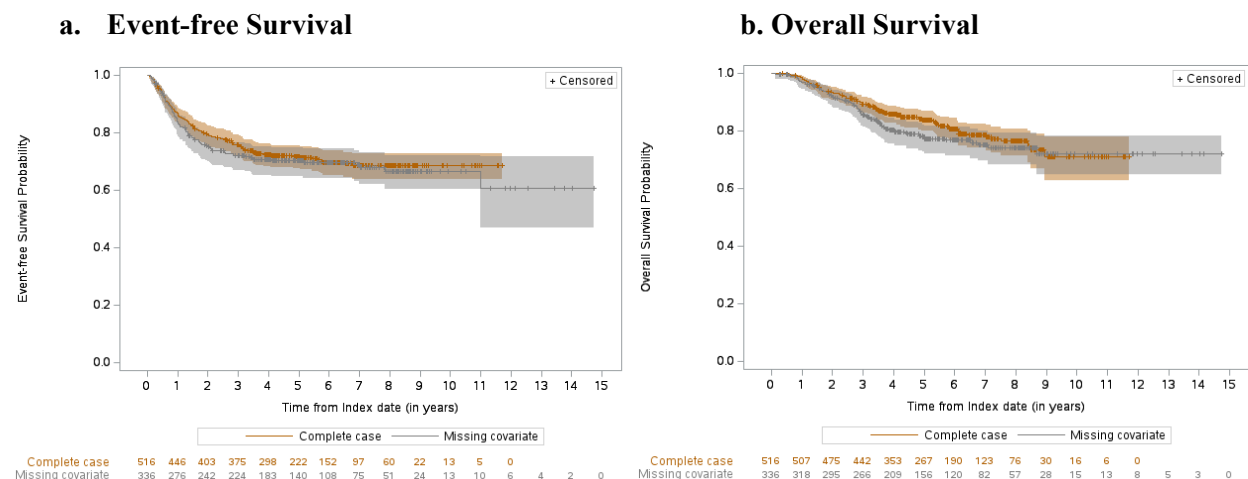


Figure 50 shows an analysis of EFS and OS for eligible patients in the control arm (n=852) who had complete information for all variables included in the propensity score and matching (n=516,

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{Eflornithine [DFMO]}

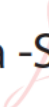
“complete case, in orange) and those who had one or more missing covariates (n=336). Outcomes appeared similar between these groups.

## Signatures

| DISCIPLINE                                        | REVIEWER                                                                                                        | OFFICE/DIVISION    | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED                                                                                                 |
|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------|
| Clinical Pharmacology Reviewer                    | Hairat Sabit, PhD                                                                                               | CDER/OTS/OCP/DCPII | Sections: 6                 | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                                   | <b>Signature:</b><br>Hairat Sabit -S Digitally signed by Hairat Sabit -S<br>Date: 2023.12.13 08:09:18 -05'00'   |                    |                             |                                                                                                                    |
| Clinical Pharmacology Team Leader                 | Hong Zhao, PhD                                                                                                  | CDER/OTS/OCP/DCPII | Sections: 6                 | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                                   | <b>Signature:</b><br>Hong Zhao -S Digitally signed by Hong Zhao -S<br>Date: 2023.12.13 11:01:50 -05'00'         |                    |                             |                                                                                                                    |
| Clinical Pharmacology Pharmacometrics Team Leader | Jiang Liu, PhD                                                                                                  | CDER/OTS/OCP/DPM   | Sections: 6                 | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                                   | <b>Signature:</b><br>Jiang Liu -S Digitally signed by Jiang Liu -S<br>Date: 2023.12.13 11:11:30 -05'00'         |                    |                             |                                                                                                                    |
| Clinical Pharmacology Pharmacometrics Reviewer    | Yangbing Li, PhD                                                                                                | CDER/OTS/OCP/DPM   | Sections: 6                 | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                                   | <b>Signature:</b><br>Jiang Liu -S Digitally signed by Jiang Liu -S<br>Date: 2023.12.13 11:12:08 -05'00'         |                    |                             |                                                                                                                    |
| Clinical Pharmacology/ Division Director          | Nam Atiqur Rahman, PhD                                                                                          | CDER/OTS/OCP/DCPII | Sections: 6                 | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                                   | <b>Signature:</b><br>Nam A. Rahman -S Digitally signed by Nam A. Rahman -S<br>Date: 2023.12.13 11:39:12 -05'00' |                    |                             |                                                                                                                    |

| DISCIPLINE                            | REVIEWER                                                                                                                           | OFFICE/DIVISION    | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED                                                                                          |
|---------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------------------|-------------------------------------------------------------------------------------------------------------|
| Clinical Reviewer                     | Elizabeth Duke, MD                                                                                                                 | CDER/ OND/OOD/DOII | Sections: 1-4, 7-13         | Select one:<br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                       | Signature: Elizabeth Duke -S<br><small>Digitally signed by Elizabeth Duke -S<br/>Date: 2023.12.13 07:58:10 -05'00'</small>         |                    |                             |                                                                                                             |
| Clinical Team Leader                  | Diana Bradford, MD                                                                                                                 | CDER/OND/OOD/DOII  | Sections: All               | Select one:<br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                       | Signature: See Signature in DARRTS.                                                                                                |                    |                             |                                                                                                             |
| Cross-Disciplinary Team Leader (CDTL) | Diana Bradford, MD                                                                                                                 | CDER/OND/OOD/DOII  | Sections: All               | Select one:<br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                       | Signature: See Signature in DARRTS.                                                                                                |                    |                             |                                                                                                             |
| Deputy Division Director (Clinical)   | Nicole Drezner, MD                                                                                                                 | CDER/OND/OOD/DOII  | Sections: All               | Select one:<br><input checked="" type="checkbox"/> Approved                                                 |
|                                       | Signature: See Signature in DARRTS.                                                                                                |                    |                             |                                                                                                             |
| Associate Director for Labeling       | Barbara Scepura, MSN                                                                                                               | CDER/OND/OOD/DOII  | Sections: All               | Select one:<br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                       | Signature: Barbara A. Scepura -S<br><small>Digitally signed by Barbara A. Scepura -S<br/>Date: 2023.12.13 10:40:19 -05'00'</small> |                    |                             |                                                                                                             |

| DISCIPLINE                                 | REVIEWER                                                                                                                                         | OFFICE/DIVISION   | SECTIONS AUTHORED/<br>APPROVED | AUTHORED/<br>APPROVED                                                                                       |
|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------------------------------|-------------------------------------------------------------------------------------------------------------|
| Statistical<br>Reviewer                    | Arup Sinha, PhD                                                                                                                                  | CDER/OTS/OB/DBV   | Sections: 1, 8, 9              | Select one:<br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                            | Signature: Arup K. Sinha -S<br><small>Digitally signed by Arup K. Sinha -S<br/>Date: 2023.12.13 10:55:10 -05'00'</small>                         |                   |                                |                                                                                                             |
| Statistical<br>Deputy Division<br>Director | Pallavi<br>Mishra-Kalyani, PhD                                                                                                                   | CDER/OTS/OB/DBV   | Sections: 1, 2, 8, 9           | Select one:<br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                            | Signature: Pallavi S. Mishra-kalyani -S<br><small>Digitally signed by Pallavi S. Mishra-kalyani -S<br/>Date: 2023.12.13 08:48:59 -05'00'</small> |                   |                                |                                                                                                             |
| Statistical<br>Division Director           | Shenghui Tang, PhD                                                                                                                               | CDER/OTS/OB/DBV   | Sections: 1, 8, 9              | Select one:<br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                            | Signature: Shenghui Tang -S<br><small>Digitally signed by Shenghui Tang -S<br/>Date: 2023.12.13 08:34:17 -05'00'</small>                         |                   |                                |                                                                                                             |
| Nonclinical<br>Reviewer                    | Emily Wearne, PhD                                                                                                                                | CDER/OND/OOD/DHOT | Sections: 1.2, 5, 8.4, 19.3    | Select one:<br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                            | Signature: Emily F. Wearne -S<br><small>Digitally signed by Emily F. Wearne -S<br/>Date: 2023.12.13 08:04:12 -05'00'</small>                     |                   |                                |                                                                                                             |
| Nonclinical<br>Team Leader                 | Claudia Miller, PhD                                                                                                                              | CDER/OND/OOD/DHOT | Sections: 1.2, 5, 8.4, 19.3    | Select one:<br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                            | Signature: Claudia Miller -S<br><small>Digitally signed by Claudia Miller -S<br/>Date: 2023.12.13 08:28:45 -05'00'</small>                       |                   |                                |                                                                                                             |
| Nonclinical<br>Director                    | John Leighton, PhD                                                                                                                               | CDER/OND/OOD/DHOT | Sections: 1.2, 5, 8.4, 19.3    | Select one:<br><input checked="" type="checkbox"/> Approved                                                 |
|                                            | Signature: John K. Leighton -S<br><small>Digitally signed by John K. Leighton -S<br/>Date: 2023.12.13 09:08:16 -05'00'</small>                   |                   |                                |                                                                                                             |

| DISCIPLINE                                                       | REVIEWER                                                                                                                                                                                                   | OFFICE/DIVISION | SECTIONS AUTHORED/<br>APPROVED | AUTHORED/<br>APPROVED                                                                                       |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|--------------------------------|-------------------------------------------------------------------------------------------------------------|
| Epidemiology<br>Reviewer                                         | Catherine Lerro,<br>PhD, MPH                                                                                                                                                                               | OCE             | Sections: 1, 8, 9              | Select one:<br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                                                  | Signature: <b>Catherine C. Lerro -S</b>  Digitally signed by Catherine C. Lerro -S<br>Date: 2023.12.13 08:42:00 -05'00' |                 |                                |                                                                                                             |
| Epidemiology<br>Associate Director for<br>Pharmacoepidemiology   | Donna Rivera,<br>PharmD., MSc.                                                                                                                                                                             | OCE             | Sections: 1, 8, 9              | Select one:<br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                                                  | Signature: <b>Donna R. Rivera -S</b>  Digitally signed by Donna R.<br>Rivera -S<br>Date: 2023.12.13 08:54:33 -05'00'      |                 |                                |                                                                                                             |
| Associate Director for<br>Pediatric Oncology and<br>Rare Cancers | Martha<br>Donoghue, MD                                                                                                                                                                                     | OCE             | Sections: 1, 8.1.7, 8.3, 8.4   | Select one:<br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                                                  | Signature: <b>Martha Donoghue -S</b>  Digitally signed by Martha<br>Donoghue -S<br>Date: 2023.12.13 10:34:53 -05'00'     |                 |                                |                                                                                                             |



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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.**  
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/s/  
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ASHLEY R LANE  
12/13/2023 03:17:46 PM

DIANA L BRADFORD  
12/13/2023 03:19:47 PM

NICOLE L DREZNER  
12/13/2023 03:20:30 PM