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RESEARCH**

APPLICATION NUMBER:

219132Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 134369

MEETING MINUTES

IntraBio Inc.
c/o Strategic Drug Development Services, LLC
Attention: Scott A. Oglesby, PhD
Executive Consultant
6518 Green Rise Road
Hillsborough, NC 27278

Dear Dr. Oglesby:

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

We also refer to the video conference between representatives of your firm and the FDA on September 21, 2023. The purpose of the meeting was to discuss your proposed data package to support a marketing application for N-acetyl-L-leucine.

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

If you have any questions, contact Jenny Doan, Regulatory Project Manager, at Jenny.Doan@fda.hhs.gov or (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Janet W Maynard, MD, MHS
Director
Office of Rare Diseases, Pediatrics, Urologic and
Reproductive Medicine
Office of New Drug
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes



MEMORADUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 21, 2023; 1:00 PM – 2:00 PM EDT
Meeting Location: Video Conference

Application Number: IND 134369
Product Name: N-acetyl-L-leucine
Indication: Treatment of Niemann-Pick disease type C

Sponsor Name: IntraBio Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

Janet Maynard, MD, Director
Christine Nguyen, MD, Deputy Director

Division of Rare Diseases and Medical Genetics (DRDMG)

Yuliya Yasinskaya, MD, Deputy Director
Jacqueline Karp, MD, Clinical Team Leader
Maura Ruzhnikov, MD, Clinical Reviewer

Division of Pediatrics and Maternal Health

Yao Lynn, MD, Director

Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

Mukesh Summan, PhD, Director
Shawna Weis, PhD, Pharmacologist, (Acting) Team Leader
Saryu Goel, PhD, Pharmacologist, Reviewer

Office of Regulatory Operation/Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

Pamela Lucarelli, Director, Project Management Staff
Michael White, PhD, Chief, Project Management Staff
CAPTAIN Jenny Doan, MSN, BSN, Regulatory Health Project Manager

Office of Clinical Pharmacology/Division of Translational and Precision Medicine

Jie (Jack) Wang, PhD, Clinical Pharmacology Team Leader
Sydney Stern, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics/ Division of Biometrics IV

Yan Wang, PhD, Statistical Team Leader

Therri Usher, PhD, Statistical Reviewer

Office of Biostatistics/ Division of Biometrics III/ Patient-Focused Statistical Scientists (PFSS)

Lili Garrard, PhD, Master Mathematical Statistician

Marian Strazzeri, MS, PFSS Reviewer

Office of Drug Evaluation Sciences (ODES), Division of Biomedical Informatics, Research, and Biomarker Development (DBIRBD)

Linda Jeng, MD, PhD, Associate Director for Biomedical Informatics

Division of Clinical Outcome Assessment (DCOA)

Naomi Knoble, PhD, Associate Director

Office of Pharmaceutical Quality

Sharon Kelly, PhD, CMC Reviewer

Office of Surveillance and Epidemiology, Office of Medication Error Prevention and Risk Management, Division of Risk Management

Karima Waziri, PharmD, Risk Management Analyst

Sali Mahmoud, PharmD, BCPS, Safety Evaluator, DMEPA

Su-Lin, PharmD, Safety Regulatory Project Manager

SPONSOR ATTENDEES

Dr. Marc Patterson, MD, Professor Neurology and Chair of the Division of Child and Adolescent Neurology at Mayo Clinic; Scientific Advisor, IntraBio Inc.

Dr. Michael Strupp, MD, FRCP, FANA, FEAN Professor at the University of Munich, Germany in the Department of Neurology and German Centre for Vertigo and Balance Disorders; Scientific Founder and Medical Expert, IntraBio Inc.

Professor Mallory Factor, Chairman, IntraBio Inc.

Jim Meyers, President & Chief Executive Officer, IntraBio Inc.

Taylor Fields, Chief Product Development Officer & Senior Vice-President, IntraBio Inc.

Dr. Ian Billington, PhD, Chief Information Officer, IntraBio Inc.

(b) (4)



(b) (4)

1.0 BACKGROUND

FDA Regulatory Background

The Sponsor, IntraBio Inc. (IntraBio), is developing N-acetyl-L-leucine, also referred by company code IB1001, for the treatment of Niemann-Pick disease type C (NPC).

IB1001 is formulated in 1000 mg granules (b) (4). IntraBio intends to submit a New Drug Application (NDA) for IB1001 via the 505(b)(1) regulatory pathway.

IntraBio received Fast Track designation on March 19, 2020. Orphan drug designation was granted for N-acetyl-L-leucine for the treatment of NPC on September 8, 2021.

Previous interactions between the FDA and IntraBio have been focused on the design of the clinical trials for IB1001, including a phase 2b study, IB1001-201, titled “Effects of N-Acetyl-L-Leucine on Niemann-Pick Disease Type C: A Multinational, Multicenter, Open-Label, Rater Blinded Phase II Study” and a phase 3 pivotal study, IB1001-301, titled “Effects of N-Acetyl-L-Leucine on Niemann-Pick Disease Type C (NPC): A Phase III, Randomized, Placebo-Controlled, Double-Blind, Crossover Study.”

For study IB1001-201, the FDA advised that the trial, as designed (single-arm, open-label), was unlikely to provide interpretable data to demonstrate substantial evidence of effectiveness to support a marketing application. The FDA’s position and guidance were communicated in multiple forums including during an informal teleconference on January 23, 2019, followed up with comments in the Study May Proceed letter issued on February 7, 2019; during an informal teleconference on February 25, 2020, which was also followed up with an advice letter on February 28, 2020; during a type C guidance meeting held on November 17, 2020 (meeting minutes issued December 2, 2020); and most recently, in an advice letter issued on January 9, 2023.

For study IB1001-301, during a type C guidance meeting on May 27, 2021, the FDA provided its recommendations on several key features of the trial design, including the primary endpoints, clinical outcome measurement instruments, and statistical approach. The meeting minutes were issued on June 14, 2021. Additional communications were provided in advice letters issued on December 20, 2021, and March 21, 2022, wherein the FDA reiterated its remaining concerns on the proposed trial design for IB1001-301.

The Sponsor submitted the current pre-NDA meeting request on July 21, 2023, to discuss their proposed data package for their marketing application for IB1001. The meeting, granted on July 25, 2023, was scheduled for September 21, 2023. A statistical

analysis plan for study IB1001-301 was received on August 7, 2023. The meeting briefing package was received on August 22, 2023. On September 18, 2023, the Sponsor submitted clinical study report for study IB1001-201. The bioanalytical method validation reports were also provided.

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The FDA sent Preliminary Comments on September 19, 2023. On the morning of September 21, 2023, IntraBio provided, via email, a slide presentation for the meeting discussion (see section 5.0 Attachments and Handouts). The meeting took place as scheduled on September 21, 2023.

(b) (4)

FDA Clinical Background

Under IND 134369, the Sponsor is developing IB1001 for the treatment of NPC. The IND was opened with submission of a protocol for study IB1001-201, a phase 2, open-label, rater-blinded study of patients with NPC using 4g/day of orally administered IB1011 for 6 weeks in patients older than 18 years of age. In the Study May Proceed letter issued on February 7, 2019, and a subsequent teleconference, the Division informed the Sponsor that study IB1001-201 by itself would not provide substantial evidence of effectiveness to support a marketing application, primarily due to its short treatment duration, open-label design, and subjective primary endpoint.

The Sponsor subsequently requested the type C meeting held on May 27, 2021, to discuss their preliminary study design and proposed endpoints for a newly planned phase 3 study that would serve as their pivotal trial. Study IB1001-301 was initially proposed as a phase 3, randomized, double-blind, placebo-controlled crossover study in patients 4 years of age and older. Each crossover period would be 12 weeks in duration, and the doses being studied were 4g/day for subjects 13 years of age and older, with weight-based dosing for 4-12 years of age. The Division agreed to the proposed study design in principle, but did not agree with their proposed primary endpoint

(b) (4)

or considering a modified version of the Scale for the Assessment and Rating of Ataxia (SARA) to better assess ataxia, a predominant symptom of NPC.

The full clinical protocol for IB1001-301 was submitted on November 5, 2021. The primary endpoint was changed to a modified SARA using 6 domains (gait, speech, finger chase, nose-finger test, fast alternative hand movements, and heel-shin slide). In

advice letters sent on December 20, 2021, and March 21, 2022, the Division stated that there were concerns regarding their measurement approach for the modified SARA as the primary endpoint. The Division was concerned that there was not adequate evidence to support that SARA items 5-8 (finger chase, nose-finger test, fast alternating hand movements, heel shin slide) measure clinically relevant and meaningful functions. The Sponsor declined to change their primary endpoint based on input they received from disease experts and the NPC patient community's feedback; however, they incorporated both the full SARA assessment as well as an additional measure of ataxia, the Spinocerebellar Ataxia Functional Index (SCAFI), as secondary endpoints.

The Sponsor requested this pre-NDA meeting to discuss the adequacy of their data package to submit a marketing application for IB1001. In their pre-NDA meeting briefing package, they report high-level results from their pivotal trial, study IB1001-301, as well as their open-label phase 2 study, IB1001-201. The Sponsor reports that IB1001-301 met its primary endpoint

(b) (4)

They also report statistically significant improvements on the secondary endpoints the SARA, SCAFI, modified Disability Rating Scale (mDRS), and Clinical Global Impression of Improvement (CGI-1). An exploratory modification of the SARA incorporating 4 domains (gait, stance, sitting, speech disturbance) also met statistical significance. The Sponsor reports that study IB1011-201 also showed statistical significance for the Clinical Impression of Change in Severity (CI-CS) primary endpoint as well as their secondary endpoints.

NPC is caused by bi-allelic pathogenic variants in the genes *NPC1* or *NPC2*. Functional loss of NPC1/2 causes a deficiency of intracellular lipid trafficking proteins and results in the accumulation of unesterified cholesterol and glycosphingolipids in late endosomes and lysosomes. NPC is always progressive, but the primary manifestations, severity, and rate of progression are age dependent. The hallmark of the infantile presentation of NPC is life-threatening cholestatic liver disease, the most common cause of death in this population. Children greater than one year of age often present with mild organomegaly, hypotonia, developmental delays, epilepsy, ataxia, and/or supranuclear gaze palsy. Older adolescents and adults can present with learning difficulty, psychosis, or dementia. Disease progression most commonly impacts ambulation, cognition, and swallowing across age groups outside of the infantile period. The reported median age of death is 13 years (range 0.1 to 69 years). In individuals with the non-infantile presentation of NPC, death is most frequently associated with aspiration and/or other respiratory complications. NPC is a rare disease with an estimated incidence of 1-89,000-120,000 live births. The current standard of care is supportive only. Miglustat is approved in the European Union (EU), Canada, and Japan for the treatment of NPC and is frequently used off-label in the United States (US) for the neurological manifestations of NPC. There are no approved therapies for NPC in the US.

IB1001 is a modified amino acid, N-acetyl-L-Leucine, which is the L-enantiomer of N-Acetyl-DL-Leucine. The racemate N-Acetyl-DL-Leucine has been available in France

since 1957 as a short-term oral treatment in tablet form primarily used for acute vertigo in adults. Based on the nonclinical data described below, the Sponsor hypothesizes that N-Acetyl-L-Leucine has the potential to improve the symptoms of NPC.

FDA Nonclinical Background

The Sponsor states that IB1001 (N-acetyl-L-leucine) mediates neuroprotective and disease modifying effects of NPC through a reduction in neuroinflammation in the cerebellum. The Sponsor believes that this leads to an improvement in energy metabolism and increased activity of antioxidant pathways in the brain, partial restoration in autophagic flux, and improvement in neuropathology and lipid storage in the cerebellum. The Sponsor states that treatment of fibroblasts derived from NPC patients with N-acetyl-L-leucine resulted in reduced lysosomal volume. In addition, the Sponsor states that *Npc1*^{-/-} mice (Niemann-Pick disease model) treated with N-acetyl-L-leucine showed a beneficial delay in body weight loss, improvements in ataxia, gait and mobility, improvements in motor function, and a small increase in lifespan. Furthermore, the Sponsor states that in a rotarod study performed to test the effect of acetyl-leucine enantiomers on motor function, *Npc1*^{-/-} mice treated with N-acetyl-L-leucine or the racemate remained on the rotarod for a longer amount of time than untreated *Npc1*^{-/-} mice. Based on this evidence, the Sponsor hypothesizes that N-acetyl-L-leucine has the potential to improve the symptoms of NPC.

In support of the safety evaluation of IB1001, the Sponsor has conducted a 26-week rat oral chronic toxicity study at doses up to 2500 mg/kg/day. In addition, the Sponsor conducted a 39-week dog oral chronic toxicity study at doses up to 600 mg/kg/day. Additionally, the Sponsor completed genetic toxicity studies demonstrating IB1001 was non-genotoxic. However, the nonclinical program lacks juvenile toxicity studies, developmental and reproductive toxicity studies (Segment 1, 2, and 3), and carcinogenicity studies.

2.0 DISCUSSION

FDA Introductory Comments

To support your proposed NDA submission, you will need to provide substantial evidence of effectiveness. Your development program includes Study IB1001-301, a double-blind, placebo-controlled, randomized, crossover trial, and Study IB1001-201, an uncontrolled, open-label study with a subjective primary endpoint. As was communicated to you in the February 7, 2019, Study May Proceed letter, Study IB1001-201 does not appear to be an adequate and well-controlled trial. In addition, Study IB1001-201 does not appear to provide data sufficient to serve as confirmatory evidence under the framework outlined in the FDA guidances for industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological*

Products^{1,2} and *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*.³ As previously communicated at the type C teleconference held on May 27, 2021, to meet the substantial evidence of effectiveness approval standard based on a single adequate and well-controlled clinical trial, additional confirmatory evidence of the treatment effect must also be provided in your NDA. The confirmatory evidence may include nonclinical and/or clinical evidence that further corroborates the findings of effectiveness observed in the single trial. See the aforementioned guidances^{2,3} for further information on this topic. You should clearly identify what will comprise your confirmatory evidence for the efficacy of IB1001 in treating patients with NPC. In the NDA, the integrated summary of efficacy (ISE) should include a thorough description of the sources of confirmatory evidence, such as the results from nonclinical or dose-response studies, establishing that the results from study IB1001-301 are reproducible in other experimental settings at clinically relevant doses and durations. Refer to section 3.0 Additional FDA Comments below for further advice on developing the confirmatory evidence necessary to support a successful application.

Additionally, there appears to be inadequate pharmacology/toxicology and clinical pharmacology information to support an NDA submission. Results from additional nonclinical and clinical pharmacology studies will be needed to support your submission. Refer to our responses to Questions 1, 2, and 3, and section 3.0 Additional FDA Comments. Note that an incomplete clinical pharmacology or pharmacology/toxicology package may result in the Agency refusing to file your NDA. See meeting minutes dated December 2, 2020.

Finally, based on the summary level data provided in your meeting package, it appears that the efficacy data from Study IB1001-301 may demonstrate a treatment benefit (b) (4)

(b) (4) However, (b) (4) whether your NDA supports a (b) (4) labeled indication (b) (4) will be a review issue. In your submission, include clinical and any mechanistic nonclinical data that you believe will support your proposed indication.

Meeting Discussion:

The meeting started with a slide presentation from IntraBio highlighting their proposed timeline for submission of the non-clinical study reports to support their marketing application for IB1001 (see section 5.0 Attachments and Handouts). The FDA acknowledged the unmet medical need for patients with

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

² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products>

³ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-based-one-adequate-and-well-controlled-clinical>

NPC and the need for safe and effective medicines for children and adults with this disease.

The FDA stated that, for a drug primarily intended for lifetime administration in children, a complete package of repeat-dose toxicology studies, reports of carcinogenicity, reproductive toxicology (including embryofetal development), and juvenile animal studies, are expected at the time of NDA submission. FDA reminded IntraBio that the Agency has requested these studies since 2018. The FDA stated that these studies are part of the overall risk/benefit framework that will be applied in weighing the application for approvability, but that some flexibility may be afforded in certain circumstances. The FDA highlighted the absence of data from a juvenile animal study, carcinogenicity study(ies), and reproductive toxicology studies with IB1001 and outlined circumstances under which flexibility might be afforded with the use of dose-ranging data and post-marketing requirements to deliver final reports in an expeditious timeframe.

(b) (4)



The FDA agreed that, provided that the reports of the dose-ranging embryofetal studies were provided in the NDA submission, the definitive studies could be ongoing during the NDA review period and submitted for review as a post-marketing requirement. The FDA stated that the final protocols of the definitive studies should be submitted in the NDA along with the timeline for completion of the studies.

IntraBio stated that they were conducting the dose-ranging study for the transgenic mouse carcinogenicity study and that they would request a carcinogenicity special protocol assessment as soon as possible. The FDA also stated that IntraBio should provide the carcinogenicity weight of evidence evaluation to the FDA as soon as possible to determine the need for and/or timing of the 2-year rat carcinogenicity study.

In response to IntraBio's position about the current safety data available for IB1001, the FDA stated that there is a gap in safety information for N-acetyl-L-leucine. The FDA stated that it is not possible to extrapolate the pharmacologic and pharmacokinetic-absorption, distribution, metabolism, and excretion (PK-ADME) data from racemic N-acetyl-leucine (N-acetyl-DL-leucine) due to large differences in the PK-ADME profiles of the individual enantiomers, and by the potential interference of pharmacodynamic activity and biodistribution of the L-enantiomer by the D-enantiomer. The FDA stated that N-acetyl-D-leucine, N-

acetyl-L-leucine, and L-leucine are transported across membranes by different transporters such that nonclinical studies performed with racemate or L-leucine may not inform the safety risks of the L enantiomer.

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FDA informed IntraBio that the nonclinical studies with N-acetyl-L-leucine are needed to justify the safety of IB1001 in pediatric or adult patients.

The FDA reminded IntraBio that they will need to demonstrate substantial evidence of effectiveness to support their NDA submission. The FDA advised IntraBio to request a type C meeting to discuss what they plan to submit for confirmatory evidence in their NDA submission.

The FDA also clarified (b) (4)

IntraBio acknowledged this advice and stated that they would submit a plan to the FDA.

As follow-up, IntraBio stated that they will submit their plan for the non-clinical study reports submission, outlining what non-clinical data will be available for IB1001 and their proposed timeline for completion of these studies.

Post-Meeting Comment:

The FDA reminds IntraBio that nonclinical studies intended to support clinical trials and marketing application (NDA) should be conducted using the same route of administration as the intended route of administration in humans as outlined in ICH M3(R2).⁴ If there is a large data gap due to the conduct of studies by a route of administration (i.e. intravenous) other than the intended route of administration in humans (i.e. oral route), the Sponsor should conduct appropriate bridging studies (e.g. ADME, safety pharmacology) by the oral route to support their NDA.

We acknowledge receipt of your submission dated September 29, 2023, containing follow-up information on your nonclinical study timelines, (b) (4) and confirmatory evidence of efficacy. We continue to recommend that you request a type C meeting to discuss your

⁴ See the FDA guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* available at <https://www.fda.gov/media/71542/download>
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plans for confirmatory evidence (adequacy of non-clinical and clinical data) to support a single adequate and well controlled trial.

Question 1: Does the Agency agree that the NDA can be submitted with less than 12 months stability data from registration batches, given the availability of 36 months of supportive stability data generated from 3 clinical batches which can be considered representative for the commercial drug product?

FDA Response to Question 1:

If all the following conditions are met, we can accept less than 12 months of stability data from three registration batches of drug product at the time of submission of your new drug application:

- The drug substance manufactured at (b) (4) is proven to be closely comparable to drug substance manufactured at (b) (4)
- The drug products manufactured using the drug substance from both manufacturers are proven to be closely comparable.
- The registration batches of drug product are manufactured at the same site, using the same process, and with the same class of manufacturing equipment as the clinical batches of the drug product intended to represent the commercial product.

Meeting Discussion:

No further discussion occurred.

Question 2: Based on the data generated to date for IB1001, the Sponsor plans to submit an NDA application / allow for NDA review before the following non-clinical studies are finally reported:

- 2a. Juvenile toxicity study
- 2b. DART (Segment 1, 2, and 3) studies
- 2c. Carcinogenicity study in rasH2 mice (dose range-finding and pivotal study)

Does the Agency agree, based on the available data and safety profile of IB1001, that this is an acceptable strategy?

FDA Response to Question 2a:

No. We do not agree with your plan to submit an NDA before the completion of a juvenile toxicity study. As stated (b) (4) you will need to submit a juvenile animal study in the rat, with dosing initiated on PND7. Because IB1001 is planned for use in pediatric patients, it is important to determine the potential toxicity of IB1001 in juvenile animals. We have also previously requested a study in juvenile animals in meeting minutes dated July 26, 2018; December 2, 2020; and June 14, 2021. The report of your juvenile animal study

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will inform labeling for a product intended for use in pediatric patients. Submit the juvenile toxicity study report at the time of your NDA submission.

Alternatively, if sufficient information exists in the published literature to support the safety of N-acetyl-L-leucine in juvenile animals or in children, you can use a literature-based assessment in lieu of conducting a study in animals. For the literature-based assessment to be adequate, provide information that supports effects of the N-acetyl-L-leucine on the core juvenile toxicology endpoints that are measured in these studies (motor function, neurocognitive endpoints, and effects on growth and development). The ages of the animals used in the published studies should be sufficient to support the developmental ages of the children for which the labeled product will be used. If you intend to provide published information in lieu of data from a dedicated juvenile animal study to support safe use in children, you should submit this as soon as possible to ensure that the rationale is adequate to support your proposed marketing application.

Please also see our response to Question 3.

Meeting Discussion:

See meeting discussion under FDA Introductory Comments.

FDA Response to Question 2b:

No. The Division does not agree with your plan to submit your NDA without data to support labeling for embryofetal risk and data to inform patients about the risk to fertility. The Division has previously requested (meeting minutes dated July 26, 2018; December 2, 2020; and June 14, 2021) that developmental and reproductive toxicity (DART) studies be submitted to support development of IB1001. Information about the potential for DART (fertility, embryofetal development, and pre- and post-natal development) is a safety assessment that will inform safe use of the product. Therefore, submit the study reports of your DART studies at the time of NDA submission. Please also see our response to Question 3.

Meeting Discussion:

See meeting discussion under FDA Introductory Comments.

FDA Response to Question 2c:

As discussed at our meeting which took place on July 17, 2018, the report of your 6-month carcinogenicity study in transgenic mice should be included in your NDA. The meeting minutes dated July 26, 2018, reflect this agreement. The data from the 6-month mouse carcinogenicity study are important to inform the benefit/risk considerations for your product. Provide your expected timeline for the completion of your 6-month mouse carcinogenicity study and submission of its final report. We recommend submitting the final report for the 6-month mouse carcinogenicity study as soon as feasible or no later than your NDA submission.

If the study report for the 6-month mouse carcinogenicity study is not submitted in your original NDA submission, we may be unable to evaluate the results of the study during the initial NDA review cycle. The lack of the study report for the six-month carcinogenicity study could impact our ability to review and complete the labeling of your product. Therefore, we emphasize the importance of completing and submitting the study report for the six-month mouse carcinogenicity study as soon as possible.

To ensure that the study is appropriately designed to evaluate the carcinogenicity potential of N-acetyl-L-leucine, we recommend that you request a special protocol assessment (SPA) for your proposed carcinogenicity study.⁵ To support a SPA for your Tg.rasH2 mouse carcinogenicity study, provide your proposed study protocol and the report of your dose range-finding study in mice (including TK evaluations).

If you propose to provide a weight of evidence assessment in lieu of conducting a 2-year carcinogenicity study in the rat, you should formally submit your weight-of-evidence justification for FDA concurrence and recommendations. To support a weight-of-evidence assessment for carcinogenicity labeling, provide a thorough weight-of-evidence analysis for carcinogenic risk as outlined in the ICH S1B(R1) guideline⁶ and addendum to ICH S1B(R1).⁷ If you have concluded that the carcinogenicity studies are unnecessary based on a presumed absence of human carcinogenic risk, provide data showing that chronic administration in animals was not associated with the formation of neoplastic or preneoplastic lesions in chronic toxicity studies and that there was an absence of genotoxicity, an absence of immunosuppressive effects, and an absence of hormonal modulation. If you have concluded that the carcinogenicity studies are unnecessary based on a presumption of likely human carcinogenic risk, provide data demonstrating the carcinogenic hazard to humans. In your assessment, include a discussion of the safety multiples achieved in nonclinical studies compared with those observed clinically at the recommended human dose.

Please also see our response to Question 3.

Meeting Discussion:

See meeting discussion under FDA Introductory Comments.

Question 3: Does the Agency agree that the completed, ongoing, and planned nonclinical studies will provide a proper basis to inform the non-clinical safety evaluation to support a future NDA filing with IB1001 and that no additional nonclinical studies are expected to be needed?

FDA Response to Question 3:

⁵ See the FDA guidance for industry *Carcinogenicity Study Protocol Submissions* available at: <https://www.fda.gov/files/drugs/published/Carcinogenicity-Study-Protocol-Submissions.pdf>

⁶ See the guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals* available at: <https://www.fda.gov/media/71935/download>

⁷ See the guidance for industry *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals* available at <https://www.fda.gov/media/152777/download>

No, we do not agree.

The Division recognizes that clinical trials have been completed in pediatric patients. However, the trials conducted in children do not address endpoints (such as multisystem histopathological evaluations) that are measured in animals to assess safety risks in patients. Therefore, clinical trials do not substitute for comprehensive safety assessments in nonclinical studies. In the meeting minutes dated December 2, 2020, the Agency previously informed you that if your proposed marketing application does not, on its face, contain adequate pharmacology and toxicology information required under section 505(b) or 505(j) of the FD&C Act and 21 CFR 314.50; this may result in the Agency refusing to file the application (21 CFR 314.101(d)(3)). Please see also, our responses to Question 2.

Meeting Discussion:

See meeting discussion under FDA Introductory Comments.

Question 4: Does the Agency agree that the Clinical Trial No. IB1001-301, which is further supported by the Phase 2b IB1001-201 study in NPC (IND 134,369) provides adequate efficacy data to support an NDA filing, in view of the seriousness of NPC and the high unmet medical need?

FDA Response to Question 4:

Upon review of your summarized high-level results, it appears that study IB1001-301 may be adequate to support an NDA submission; however, the final determination of the fileability of your NDA can only be made after the NDA has been submitted to the Agency (refer to FDA Introductory Comments). To optimize your future NDA submission, we have the following comments:

1. We reiterate concerns previously conveyed in advice letters issued on December 20, 2021, and March 21, 2022, regarding the primary efficacy endpoint in Study IB1001-301. Provide evidence to support your claims that your selected subtests from the SARA are associated with functional, clinically meaningful activities, and that they can be administered validly and reliably in an intellectually impaired patient population, leading to interpretable results that correspond to other established meaningful outcomes.
2. To support your submission and the review of your clinical outcome assessment (COA) evidence for Study IB1001-301, you should include copies of the COAs, study manuals, and other key documents in your submission. We refer you to the evidence and documents listed in the Appendix of the FDA guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, "Appendix: Information on a PRO Instrument Reviewed by the FDA."⁸ While this guidance is specific to patient-reported outcomes, the

⁸ <https://www.fda.gov/media/77832/download>

structure and evidence needed can be applied to other types of COAs, such as clinician-reported outcomes.

3. Regarding your exit interview surveys with patients and/or caregivers, submit your collated results summary and include:
 - a. Sample demographics, including participants who declined interviews;
 - b. All raw data (i.e., verbatim survey questions and responses); and
 - c. All interview study materials (e.g., study coordinator training materials, qualitative analysis codebooks, qualitative analyses).
4. For Study IB1001-301, submit all datasets (and corresponding reviewer's guides, define files, and annotated Case Report Forms [aCRFs]), including responses to individual SARA items and scoring algorithms, and all computer program code used to:
 - a. Compute COA scores (e.g., the SARA, mSARA, and Axial SARA);
 - b. Construct endpoint scores from COA data;
 - c. Quantitatively analyze COA data (e.g., quantitatively evaluate measurement properties of COA scores); and
 - d. Evaluate meaningful treatment benefit in all primary and multiplicity-controlled secondary efficacy endpoints.
5. Although the meeting briefing package received on August 22, 2023, contains several references to "clinically meaningful" efficacy results in Study IB1001-301 (e.g., pages 3-4, 16, 33, 34, 35, and 39/125), neither protocol Version 1.2 nor SAP Version 1.0 describe how meaningful treatment benefit was evaluated in Study IB1001-301. In your NDA submission, clarify how meaningful treatment benefit was evaluated in Study IB1001-301, including a detailed description of how the exit interview data (discussed in protocol Section 6.1.7) were used to evaluate meaningful treatment benefit, and submit the results of these analyses.

Meeting Discussion:

No further discussion occurred.

Question 5: Does the Agency agree that an ISE is not needed?

FDA Response to Question 5:

No, we do not agree. The ISE is required as a part of the NDA submission. If you believe that your Summary of Clinical Efficacy (Section 2.7.3) would be sufficiently detailed to serve as the text portion of the ISE, then, size permitting, you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in section 5.3.5.3. An explanation and electronic links should be placed in both Module 2 and Module 5. Refer to the FDA guidance for

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www.fda.gov

industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*.⁹

Meeting Discussion:

No further discussion occurred.

Question 6: Does the Agency agree to the proposed plan for the ISS?

FDA Response to Question 6:

While we agree that safety data (b) (4) in the ISS for the general review of adverse events. (b) (4)

Plan to provide an integrated summary of safety in Module 5.3.5.3 per 21 CFR 314.50(d)(5)(vi). However, if you believe that your Summary of Clinical Safety (Section 2.7.4) would be sufficiently detailed to serve as the text portion of the ISS, you may provide an explanation and electronic links in both Module 2 and Module 5 (see FDA Response to Question 5).

Meeting Discussion:

No further discussion occurred.

Question 7: Does the Agency agree that the totality of the data forms a proper scientific basis to inform the risk/benefit of IB1001 for the treatment of NPC to support an NDA filing?

FDA Response to Question 7:

It is premature to comment on the totality of data to inform the risk/benefit of IB1001 for the treatment of NPC. The evaluation of the risk/benefit of IB1001 can only be made after a full review of the data and evidence submitted in the NDA. Refer to FDA Introductory Comments, our comments in the previous question responses, and section 3.0 Additional FDA Comments for the data and evidence required to support your NDA.

Meeting Discussion:

No further discussion occurred.

Question 8: Does the Agency agree that no sponsor-proposed Risk Evaluation and Mitigation Strategies (REMS) is required at the time of the initial NDA submission?

FDA Response to Question 8:

A REMS is not required at the time of NDA submission. At this time, there is insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is

⁹ <https://www.fda.gov/media/75783/download>

necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion:

No further discussion occurred.

3.0 ADDITIONAL FDA COMMENTS

Confirmatory Evidence

As stated in the FDA Introductory Comments, if you are seeking approval based on a single adequate and well-controlled trial, confirmatory evidence will be needed to support an approval. Confirmatory evidence can be derived from multiple sources, including clinical, clinical pharmacology, or nonclinical data. You should request our input about the confirmatory evidence package that you intend to use to ensure that the data are adequate to support your submission.

The pharmacology data provided in *Npc1*^{-/-} mice treated with Tanganil, while potentially informative, are not sufficient to provide confirmatory evidence of efficacy of IB1001. If you intend to provide nonclinical confirmatory evidence data to support approval of IB1001 with a single adequate and well-controlled trial, you should use a pathogenically-relevant animal model and evaluate effects on an objective outcome that you are also measuring in patients. Effects on other objective outcomes (e.g., survival) could also be meaningful. We strongly recommend that you correlate effects on your proposed clinical outcomes measured in animals with drug-related effects (i.e., using PK/PD modeling) on a pathogenically-relevant biomarker that can support the mechanism of action of the drug. Ensure that the bioanalytical method for your biomarker is validated and establish the correlation between drug exposure, effects on the biomarker, and effects on the clinically meaningful endpoint that you select. The choice of biomarkers should be justified based on the disease pathogenesis. Although the animal studies do not need to be GLP-compliant, the bioanalytical method that you choose to employ for your biomarker should be validated, as should the bioanalytical method that you use to measure drug levels in your animal models. For additional information about the nonclinical considerations for demonstrating substantial evidence of effectiveness and bioanalytical method validation, see the FDA's guidances for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*,¹⁰ *Demonstrating Substantial Evidence of Effectiveness Based on*

¹⁰ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products>

One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence,¹¹ and *Bioanalytical Method Validation*.¹²

Meeting Discussion:

No further discussion occurred.

Clinical Pharmacology

We remind you that your NDA will need to address the clinical pharmacology comments and recommendations that were conveyed in the type C meeting held on November 17, 2020 (meeting minutes issued December 2, 2020). Based on the limited information provided in the meeting briefing package, we have the following comments and recommendations regarding the information you will need to address in your NDA:

1. You state that a waiver for a thorough QT/QTc study is requested. Submit a formal TQT study waiver request with scientific justification to the IND for review prior to the NDA submission.
2. You state that no food effect study is planned. We recommend that you evaluate the food effect on PK of your product with the to-be-marketed formulation and include such information in your NDA. Refer to the following FDA guidance for industry for more information:
 - *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations*¹³
3. You should use validated bioanalytical assays to determine the drug and pharmacodynamic (PD) biomarker concentrations in all PK and PD samples from your clinical studies. The assays should be demonstrated to be specific, sensitive, and reproducible. Refer to the following guidances for industry for more information:
 - *Bioanalytical Method Validation*¹⁴
 - *M10 Bioanalytical Method Validation and Study Sample Analysis*¹⁵

Submit in the NDA bioanalytical method performance summary tables for all the bioanalytical methods used for the PK and PD assessment in your clinical studies. Use the format of summary tables as in FDA guidance for industry

¹¹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-based-one-adequate-and-well-controlled-clinical>

¹² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioanalytical-method-validation-guidance-industry>

¹³ <https://www.fda.gov/media/121313/download>

¹⁴ <https://www.fda.gov/media/70858/download>

¹⁵ <https://www.fda.gov/media/162903/download>

Bioanalytical Methods Templates.¹⁶ Include the method performance summary for each of the supported clinical studies. Do not delete any rows from the tables. State “not applicable” if certain rows or columns are not applicable. Include any other additional bioanalytical information in a separate table that might be relevant for your NDA review.

4. We acknowledge that you have planned to conduct population PK analysis of N-acetyl-L-leucine. We recommend that you also submit a study report describing exposure-response relationships for pharmacodynamic biomarkers (if any), efficacy, and safety in the target patient population. Submit all the datasets, codes, and define files that are associated with your population PK and exposure-response (E-R) analyses. Refer to the FDA guidances for industry for additional information related to population PK¹⁷ and E-R analyses.¹⁸

Meeting Discussion:

No further discussion occurred.

Labeling

As we are aiming for consistency in our labeling across the division, we recommend that you review the Prescribing Information (PI) for recently approved enzyme replacement therapies to treat inborn errors of metabolisms as a reference on how information in the PI should be written and presented. Refer to section 4.0 Other Important Information “Prescribing Information” for additional guidance for developing the PI.

Meeting Discussion:

No further discussion occurred.

4.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

¹⁶ <https://www.fda.gov/media/131425/download>

¹⁷ See the FDA guidance for industry *Population Pharmacokinetics* available at: <https://www.fda.gov/media/128793/download>

¹⁸ See the FDA guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* available at: <https://www.fda.gov/media/71277/download>

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information¹⁹ and Pregnancy and Lactation Labeling Final Rule²⁰ websites, which include:

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

¹⁹ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

²⁰ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

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

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.²¹

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.²²

MANUFACTURING FACILITIES

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

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

²¹ <http://www.fda.gov/ectd>

²² <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

time of submission.

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h²³ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*²⁴. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments,

²³ <https://www.fda.gov/media/84223/download>

²⁴ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.²⁵

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to identify uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products*.²⁶ For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

5.0 ATTACHMENTS AND HANDOUTS

On September 21, 2023, the Sponsor provided slides, via email, to present during the meeting discussion.

²⁵ <https://www.fda.gov/media/85061/download>

²⁶ <https://www.fda.gov/media/124795/download>

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

/s/

JANET W MAYNARD
10/11/2023 08:04:50 AM