

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**219132Orig1s000**

**INTEGRATED REVIEW**

## Integrated Review

**Table 1. Application Information**

|                                                                     |                                                                                                                                                                                                                                                                                                                                                                  |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------|----------------|--------------|--------------|-----|---------|-----|--------------|-----|-----|-----|---------------|-----|-----|-----|
| Table 1: Application information                                    |                                                                                                                                                                                                                                                                                                                                                                  |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Application type                                                    | NDA                                                                                                                                                                                                                                                                                                                                                              |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Application number(s)                                               | 219132                                                                                                                                                                                                                                                                                                                                                           |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Priority or standard                                                | Priority                                                                                                                                                                                                                                                                                                                                                         |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Submit date(s)                                                      | 1/24/2024                                                                                                                                                                                                                                                                                                                                                        |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Received date(s)                                                    | 1/24/2024                                                                                                                                                                                                                                                                                                                                                        |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| PDUFA goal date                                                     | 9/24/2024                                                                                                                                                                                                                                                                                                                                                        |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Division/office                                                     | Division of Rare Diseases and Medical Genetics (DRDMG)                                                                                                                                                                                                                                                                                                           |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Review completion date                                              | 9/24/2024                                                                                                                                                                                                                                                                                                                                                        |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Established/proper name                                             | Levacetylleucine                                                                                                                                                                                                                                                                                                                                                 |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| (Proposed) proprietary name                                         | Aqneursa                                                                                                                                                                                                                                                                                                                                                         |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Pharmacologic class                                                 | None                                                                                                                                                                                                                                                                                                                                                             |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Other product name(s)                                               | IB 1001; N-Acetyl-L-Leucine                                                                                                                                                                                                                                                                                                                                      |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Applicant                                                           | IntraBio Ltd.                                                                                                                                                                                                                                                                                                                                                    |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Dosage form(s)/formulation(s)                                       | For oral suspension: 1 gram levacetylleucine in a unit-dose packet                                                                                                                                                                                                                                                                                               |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Dosing regimen                                                      | (b) (4)                                                                                                                                                                                                                                                                                                                                                          |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Applicant-proposed indication(s)/population(s)                      |                                                                                                                                                                                                                                                                                                                                                                  |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| SNOMED CT code for proposed indication disease term(s) <sup>1</sup> |                                                                                                                                                                                                                                                                                                                                                                  |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Regulatory action                                                   | Approval                                                                                                                                                                                                                                                                                                                                                         |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Approved dosage (if applicable)                                     | Approved dosing (orally): <table><tr><td>Patient Body Weight</td><td>Morning Dose</td><td>Afternoon Dose</td><td>Evening Dose</td></tr><tr><td>15 to &lt;25 kg</td><td>1 g</td><td>No dose</td><td>1 g</td></tr><tr><td>25 to &lt;35 kg</td><td>1 g</td><td>1 g</td><td>1 g</td></tr><tr><td>35 kg or more</td><td>2 g</td><td>1 g</td><td>1 g</td></tr></table> | Patient Body Weight | Morning Dose | Afternoon Dose | Evening Dose | 15 to <25 kg | 1 g | No dose | 1 g | 25 to <35 kg | 1 g | 1 g | 1 g | 35 kg or more | 2 g | 1 g | 1 g |
| Patient Body Weight                                                 | Morning Dose                                                                                                                                                                                                                                                                                                                                                     | Afternoon Dose      | Evening Dose |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| 15 to <25 kg                                                        | 1 g                                                                                                                                                                                                                                                                                                                                                              | No dose             | 1 g          |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| 25 to <35 kg                                                        | 1 g                                                                                                                                                                                                                                                                                                                                                              | 1 g                 | 1 g          |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| 35 kg or more                                                       | 2 g                                                                                                                                                                                                                                                                                                                                                              | 1 g                 | 1 g          |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| Approved indication(s)/population(s) (if applicable)                | Treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing at least 15 kg                                                                                                                                                                                                                           |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |
| SNOMED CT code for approved indication disease term(s) <sup>1</sup> | 66751000 Niemann-Pick disease type C                                                                                                                                                                                                                                                                                                                             |                     |              |                |              |              |     |         |     |              |     |     |     |               |     |     |     |

<sup>1</sup> For internal tracking purposes only.

Abbreviations: PDUFA = prescription drug user fee act; SNOMED CT = systematized nomenclature of medicine clinical terms

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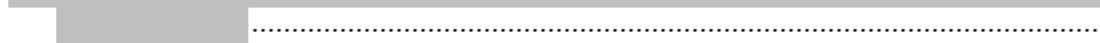
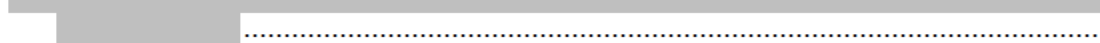
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## Glossary

|                  |                                                                                        |
|------------------|----------------------------------------------------------------------------------------|
| 5DNPCCSS         | 5-domain Niemann-Pick disease type C clinical severity scale                           |
| 8MWT             | 8-meter walk test                                                                      |
| 9HPT-D           | 9-Hole Peg Test of the dominant hand                                                   |
| AE               | adverse event                                                                          |
| ALT              | alanine aminotransferase                                                               |
| AR               | adverse reaction                                                                       |
| AST              | aspartate aminotransferase                                                             |
| ATP              | adenosine triphosphate                                                                 |
| AUC              | area under the concentration-time curve                                                |
| BCRP             | breast cancer resistance protein                                                       |
| BID              | twice daily                                                                            |
| BSEP             | bile salt export pump                                                                  |
| CE               | confirmatory evidence                                                                  |
| CGI-I            | clinical global impression scale of improvement                                        |
| CGI-S            | clinical global impression scale of severity                                           |
| CHO              | Chinese hamster ovary                                                                  |
| CI               | confidence interval                                                                    |
| CI-CS            | clinical impression of change in severity                                              |
| CL               | clearance                                                                              |
| C <sub>max</sub> | maximum plasma concentration                                                           |
| COVID-19         | coronavirus disease of 2019                                                            |
| CS               | clinically significant                                                                 |
| CYP              | cytochrome P450                                                                        |
| DRF              | dose-range finding                                                                     |
| ECG              | electrocardiography                                                                    |
| EFD              | embryo-fetal development                                                               |
| EOT              | end of the treatment period                                                            |
| EOW              | end of the washout period                                                              |
| EP               | extension phase                                                                        |
| E-R              | exposure-response                                                                      |
| FDA              | Food and Drug Administration                                                           |
| FOCE ELS         | First Order Conditional Estimation-Extended Least Squares                              |
| fSARA            | functional scale for assessment and rating of ataxia                                   |
| FSH              | follicle-stimulating hormone                                                           |
| GD               | gestation day                                                                          |
| GLP              | good laboratory practice                                                               |
| GSL              | glycosphingolipid                                                                      |
| HEK293           | 293 human embryonic kidney                                                             |
| hERG             | human ether-a-go-go-related gene                                                       |
| IC <sub>50</sub> | half-maximal inhibitory concentration                                                  |
| I <sub>gut</sub> | intestinal luminal concentration of the interacting drug calculated as the dose/250 mL |
| IID              | Inactive Ingredients Database                                                          |

|         |                                                        |
|---------|--------------------------------------------------------|
| IMP     | investigational medicinal product                      |
| IND     | investigational new drug                               |
| ITT     | intent-to-treat                                        |
| IV      | intravenous                                            |
| LOCF    | last observation carried forward                       |
| MDCK    | Madin-Darby canine kidney                              |
| MDE     | maximum daily exposure                                 |
| mDRS    | modified disability rating scale                       |
| mITT    | modified intent-to-treat                               |
| MMRM    | mixed model for repeated measures                      |
| MOA     | mechanism of action                                    |
| MRHD    | maximum recommended human dose                         |
| mSARA   | modified scale for the assessment and rating of ataxia |
| NALL    | N-acetyl-L-leucine                                     |
| NDA     | new drug application                                   |
| NOAEL   | no-observed-adverse-effect level                       |
| NPC     | Niemann-Pick disease type C                            |
| NPC-CSS | Niemann-Pick disease type C clinical severity scale    |
| OAT     | organic anion transporter                              |
| OCT     | organic cation transporter                             |
| OLE     | open-label extension                                   |
| PD      | pharmacodynamic                                        |
| PEG     | percutaneous endoscopic gastrostomy                    |
| PI      | prescribing information                                |
| PIND    | pre-investigational new drug application               |
| P-gp    | P-glycoprotein                                         |
| PK      | pharmacokinetic                                        |
| PMR     | postmarketing requirement                              |
| PND     | postnatal day                                          |
| PopPK   | population PK                                          |
| QD      | once daily                                             |
| SAE     | serious adverse event                                  |
| SAP     | statistical analysis plan                              |
| SARA    | scale for the assessment and rating of ataxia          |
| SCAFI   | spinocerebellar ataxia functional index                |
| SD      | standard deviation                                     |
| SEE     | substantial evidence of effectiveness                  |
| TEAE    | treatment-emergent adverse event                       |
| TID     | three times daily                                      |
| TK      | toxicokinetic                                          |
| ULN     | upper limit of normal                                  |
| US      | United States                                          |
| V       | volume of distribution                                 |

# I. Executive Summary

---

## 1. Overview

### 1.1. Summary of Regulatory Action

IntraBio Ltd. (Applicant) submitted this new drug application (NDA) for levacetylleucine, an N-acetyl-L-leucine drug product, also referred to by the company development code IB1001 (tradename Aqneursa), seeking approval of this small molecule as a treatment of Niemann-Pick disease type C (NPC).

Niemann-Pick disease type C is a rare and serious neurodegenerative lysosomal disorder caused by defective intracellular lipid trafficking and metabolism. As a result, patients with NPC have progressive accumulation of several lipid species in affected cells in the nervous system and several visceral organs. NPC is neurodegenerative, most commonly impacting ambulation, fine motor skills, speech, swallowing, and cognition in addition to visceral symptoms. After the aforementioned neurological symptoms, ataxia is one of the most common neurological symptoms reported. This NDA was reviewed by a multidisciplinary review team. Each discipline recommends approval of levacetylleucine for the treatment of the neurological manifestations of NPC in adults and pediatric patients weighing at least 15 kg. The signatory authority for this application concurs and recommends approval for this indication.

Substantial evidence of effectiveness of levacetylleucine for NPC was established using data from one adequate and well-controlled trial and confirmatory evidence (CE). For full details, refer to Section [1.2](#).

The available clinical safety data show that levacetylleucine is safe for its intended use. Common adverse reactions include dysphagia, upper respiratory tract infections, abdominal pain and vomiting. Aggravation of pre-existing rosacea was also reported as possibly related to treatment during the trial. These risks observed are deemed acceptable with appropriate product labeling and routine pharmacovigilance.

Data from dose-ranging nonclinical embryofetal development studies indicates that levacetylleucine is fetotoxic (decrease in fetal weight, increase in resorptions, and post-implantation loss) and causes external and skeletal malformation in both rodents and non-rodents. The embryo-fetal risks are adequately communicated through labeling. As described in Section [2.2](#), we conclude that the improvement in neurological function observed with use of levacetylleucine outweighs the risks when levacetylleucine is used as recommended in the approved labeling.

### 1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) of levacetylleucine for NPC was established using data from one adequate and well-controlled trial and confirmatory evidence. The adequate and

well-controlled trial, Trial IB1001-301, demonstrated a clinically meaningful improvement in neurological function that reached numerical statistical significance in children and adults with NPC aged 5 years and older. With a p-value of <0.005 and a clinically meaningful magnitude of improvement demonstrated for the primary endpoint in the treatment arm compared to placebo, the review team considered the results of this trial highly persuasive.

CE is comprised of both clinical data and nonclinical mechanistic data that support the results of Trial IB1001-301. The clinical data include the results of an open-label study of levacetylleucine in patients with NPC, Trial IB1001-201. Thirty-three patients with NPC were enrolled in the trial, which consisted of a 2-week baseline period, a 6-week treatment period, and a 6-week washout period. The rater-blinded primary endpoint, clinical impression of change in severity (CI-CS), measured each subject's change in performance on their primary anchor test (a timed subtest of the spinocerebellar ataxia functional index, either the 8-Meter Walk Test or the 9-Hole Peg Test of the dominant hand) between the beginning and end of the treatment and washout periods. Improvement in the CI-CS was observed in the treatment period and deterioration during the washout period. While Trial IB1001-201 was an open-label study, the methodology of blinding the CI-CS raters to time and treatment assignment increases the interpretability of the resulting scores by reducing the influence of knowledge of treatment assignment. The CI-CS results are supported by the timed spinocerebellar ataxia functional index subtests and indicate either improvement or stability in the treatment period, and either deterioration or stability in the washout period. Consequently, the Agency concludes that Trial IB1001-201 provided sufficient supportive evidence that the subjects' performance on the selected measures of gait and fine motor function is comparatively favorable in the treatment period.

The supportive nonclinical mechanistic data that contributed to CE include in vitro and in vivo data in (1) wildtype and NPC1-deficient Chinese hamster ovary (CHO) (*Npc1*<sup>-/-</sup> CHO) cells; (2) fibroblasts derived from patients with NPC; and (3) *Npc1*<sup>-/-</sup> mice, all of which support the potential for levacetylleucine treatment to slow disease progression in patients with NPC. Published data suggest that treatment of *Npc1*<sup>-/-</sup> CHO cells with levacetylleucine may modestly reduce accumulation of sphingosine, glycosphingolipids (GSLs), and cholesterol and may reduce lysosomal volume compared to untreated *Npc1*<sup>-/-</sup> CHO cells. Additionally, in vitro treatment of fibroblasts from patients with NPC with severe clinical presentation suggest that levacetylleucine may reduce lysosomal volume in these cells. Published data from studies in NPC1-null mice (*Npc1*<sup>-/-</sup> mice) treated with levacetylleucine reported a slight reduction in GSLs in brain and cerebellum; improvements in ataxia, gait, and mobility; reduction in neuroinflammation in the cerebellum and a small increase in lifespan compared to untreated *Npc1*<sup>-/-</sup> mice. These published nonclinical studies suggest that amelioration of biochemical (sphingosine, GSLs and cholesterol), cellular (lysosomal volume, neuroinflammation) and functional (ataxia, gait) changes in nonclinical NPC models (in vitro and in vivo) upon treatment with levacetylleucine may provide plausible mechanistic support for the effectiveness of levacetylleucine when administered to patients with NPC. The demonstration of improvement in neurological function (ataxia, gait, stance, sitting, and speech) in subjects with NPC in Trial IB1001-201, in combination with the supportive nonclinical mechanistic data derived from published literature, constitute the CE for this application. Refer to Section [6.3.3](#) for details.

## 2. Benefit-Risk Assessment

### 2.1. Benefit-Risk Framework

**Table 2. Benefit-Risk Framework**

| Dimension                 | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Analysis of condition     | <ul style="list-style-type: none"> <li>Niemann-Pick disease type C (NPC) is a rare, autosomal recessive neurodegenerative disorder caused by mutations in the genes <i>NPC1</i> or <i>NPC2</i>. Impaired NPC protein function results in impaired intracellular trafficking and metabolism, causing accumulation of unesterified cholesterol and glycosphingolipids.</li> <li>The primary manifestations and rate of disease progression is heterogenous. NPC can present with severe hepatic failure and/or respiratory failure in infancy up to the age of 2 years or with primarily progressive neurological degeneration including cognitive impairment, gross and fine motor delays, ataxia, psychiatric symptoms, vertical supranuclear palsy, dystonia, and epilepsy.</li> <li>Infants with systemic disease usually die in infancy. Across all types, the median age of death is 13 years (range 0.1 to 69 years). Death is most commonly due to respiratory failure in the setting of infection and/or aspiration. While patients who are diagnosed during adulthood may survive longer, they become fully dependent for supportive measures/ADLs</li> </ul> | NPC is a serious and life-limiting neurodegenerative disease that affects both children and adults and leads to premature death.                                                                                                                                                                                                                                                                   |
| Current treatment options | <ul style="list-style-type: none"> <li>Only very recently has one therapy been approved in the United States for the treatment of NPC. The current standard of care is primarily supportive management of individual disease manifestations. Zavesca (miglustat) is approved in the European Union, Canada, and Japan for the treatment of progressive neurological manifestations in adult and pediatric patients with NPC. In the United States, miglustat is approved for other indications including Gaucher disease. Off-label use is considered standard of care in adult and pediatric patients with NPC. Despite widespread use of miglustat, there is continued disease progression, thus there is an unmet need for approved therapies.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                          | <p>While there is one very recently approved drug to treat the neurological manifestations of NPC, there remains a need for additional therapeutic options for patients diagnosed with NPC, a devastating disease.</p> <p>Because concomitant miglustat use is common for patients with NPC, the impact of this concomitant exposure on efficacy and safety was considered during this review.</p> |

NDA 219132  
Aqneursa (levacetylleucine)

| Dimension | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Benefit   | <ul style="list-style-type: none"> <li>Aqneursa (levacetylleucine, IB1001) is a modified amino acid administered orally and intended for the treatment of the neurological symptoms of NPC.</li> <li>The efficacy of levacetylleucine was evaluated in an adequate and well-controlled trial (Trial IB1001-301) in children and adults with NPC. Changes in neurological symptoms as measured by a functional Scale for Assessment and Rating of Ataxia (fSARA) assessment of gait, stance, sitting, and speech were compared in subjects randomly assigned to treatment sequences to receive levacetylleucine followed by placebo or receive placebo followed by levacetylleucine. Most of the subjects (85%) in the trial used miglustat at baseline.</li> <li>The estimated mean fSARA score was 5.1 when subjects were treated with Aqneursa and 5.6 when subjects were treated with placebo. The estimated treatment difference in mean fSARA scores was -0.45 (95% confidence interval [CI]: -0.70, -0.19), favoring levacetylleucine and meeting numerical statistical significance (<math>p=0.0009</math>). This level of change on the fSARA is expected to affect how patients with NPC feel and function. The subgroup analyses showed a consistent treatment difference, including for the subgroup of subjects not on background miglustat.</li> <li>Confirmatory evidence (CE) of effectiveness is derived from the phase 2 open-label trial with a rater blinded primary endpoint, IB1001-201, which showed improvement in subject's performance on either 8MWT or 9HPT-D during the treatment period, and deterioration during the washout period (Hodges-Lehmann estimate:1.0, 90% CI: 0.25, 1.75).</li> <li>Additional supportive evidence is derived from published mechanistic studies showing that levacetylleucine may reduce accumulation of lipids (sphingosine, glycosphingolipids, cholesterol) and reduce lysosomal volume in <i>Npc1</i>-deficient Chinese hamster ovary (CHO) cells in vitro. In patient-derived cells, levacetylleucine was reported to reduce lysosomal volume. In <i>Npc1</i><sup>-/-</sup> mice, levacetylleucine was reported to slightly reduce GSLs in brain and cerebellum and to reduce ataxia, leading to improved gait and mobility. Levacetylleucine was also reported to reduce neuroinflammation in cerebellum and slightly improve lifespan. The published data described above are supportive of the potential for levacetylleucine to reduce aspects of NPC pathophysiology and is consistent with results from clinical trials.</li> </ul> | <p>The observed treatment difference is clinically meaningful to patients with NPC and/or their caregivers.</p> <p>The results of the adequate and well-controlled trial were highly persuasive. These results, in combination with the additional clinical and nonclinical data that both support CE, are adequate to support a treatment benefit. The data support the use of levacetylleucine alone or with background miglustat.</p> |

NDA 219132  
Aqneursa (levacetylleucine)

| Dimension                | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Conclusions and Reasons                                                                                                                                                                                                                                                                                     |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risk and risk management | <ul style="list-style-type: none"> <li>The high rate of concomitant miglustat use limits the interpretability of the safety data in determining the risk of use of levacetylleucine alone. There is clinical overlap of the adverse events identified during Trial IB1001-301 with those identified in miglustat labeling.</li> <li>The most noteworthy adverse reactions occurring in at least 5% of subjects in Trial IB1001-301 were abdominal pain, dysphagia, upper respiratory tract infections, and vomiting, and were more common in subjects treated with levacetylleucine than placebo.</li> <li>Subjects who are pregnant or lactating were not evaluated in the development program.</li> <li>Patient risk for adverse events with long-term exposure beyond two years is currently unknown.</li> <li>Safety concerns from nonclinical studies included embryo-fetal toxicities in rats and rabbits (decrease in fetal weight, increase in resorptions and post-implantation loss, and external and skeletal malformations).</li> <li>Juvenile toxicity, fertility and early embryonic development, pre- and postnatal development, and carcinogenicity studies have not been conducted pre-approval.</li> <li>Carcinogenicity studies have not been conducted.</li> </ul> | <p>Levacetylleucine's risks can be adequately mitigated with labeling and routine postmarketing surveillance.</p> <p>We are requiring juvenile toxicity, fertility, and early embryonic development, pre- and postnatal development, and carcinogenicity studies to be conducted postapproval.</p> <p>.</p> |

Abbreviations: 8MWT = 8-meter walk test; 9HPT-D = 9-Hole Peg Test of the dominant hand; ADL = activity of daily living; CE = confirmatory evidence; CI = confidence interval; CHO = Chinese hamster ovary; fSARA = functional Scale for Assessment and Rating of Ataxia; GSL = glycosphingolipid; NPC = Niemann-Pick disease type C

## 2.2. Conclusions Regarding Benefit-Risk

NPC is a rare and progressive neurovisceral disorder caused by mutations in the genes *NPC1* or *NPC2* ([Patterson 1993](#)). These mutations result in impaired intracellular trafficking and accumulation of unesterified cholesterol and GSLs within the late endosomes and lysosomes of affected cells in the brain and other tissues. NPC is always progressive, but the primary manifestations, severity, and rate of progression are variable. Individuals who develop the symptoms of NPC in early childhood (after the age of 2 years) have a primarily neurodegenerative course with progressive motor and cognitive impairment, supranuclear gaze palsy, dysphagia, dysarthria, ataxia, and epilepsy, ultimately progressing to respiratory failure and death.

There is currently only one very recently approved treatment for NPC. The current standard of care is primarily supportive, however the substrate reducing therapy Zavesca (miglustat) is approved in the European Union, Canada, and Japan for the treatment of NPC and off-label use is considered standard of care in the United States. Despite widespread use of miglustat, NPC continues to be progressive and life-limiting. Therefore, treatment and cure of NPC continue to represent unmet needs.

The benefit of levacetylleucine is based on comparison of functional Scale for Assessment and Rating of Ataxia scores in 60 subjects aged 5 to 67 years with NPC and at least one neurological symptom randomized either to levacetylleucine or placebo for 12 weeks. The estimated treatment difference in mean functional Scale for Assessment and Rating of Ataxia scores at the end of week 12 was -0.45 (95% confidence interval: -0.70, -0.19), favoring the levacetylleucine arm and meeting numerical statistical significance ( $p < 0.001$ ). CE of effectiveness is derived from a separate phase 2 rater blinded open-label trial (Trial IB1001-201) and nonclinical pharmacology studies (in vitro and in vivo) which are considered supportive of the overall package of CE.

While no subjects under 5 years old were enrolled, extrapolation of efficacy to children who are under 5 years old using pharmacokinetic data are supported by the similar disease pathophysiology and predominant clinical manifestations in children with NPC with disease onset after infancy. Similarly, a limited amount of extrapolation of clinical safety to children under 5 years old and weight at least 15 kg was reasonable given the favorable benefit/risk profile, the similar disease pathophysiology across the age spectrum, the ability to utilize pharmacokinetic data for dose selection, and the lack of anticipated differential safety risk.

While there is a limited amount of safety data in younger children, the available data support that levacetylleucine is safe for its intended use in adults and pediatric patients  $\geq 15$  kg and the overall benefit/risk is favorable. Common adverse reactions include dysphagia, abdominal pain, and vomiting. Aggravation of pre-existing rosacea was also reported as possibly related to treatment during the trial. These risks can be adequately mitigated via product labeling and further evaluated during routine pharmacovigilance.

Safety concerns from nonclinical studies include embryo-fetal toxicity. Uncertainties include the lack of juvenile toxicity studies, fertility studies, and embryofetal, prenatal and postnatal development studies, and carcinogenicity studies. These studies will be conducted as postmarketing requirements.

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Given that NPC is a serious and life-limiting rare disease with only one recently approved drug to treat the neurological manifestations of NPC and a remaining unmet need for additional therapeutic options, the review team has determined the benefit-risk of levacetylleucine to be favorable for the treatment of adults and pediatric patients weighing at least 15 kg.

## II. Interdisciplinary Assessment

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### 3. Introduction

Niemann-Pick disease type C (NPC) is an autosomal recessive lysosomal storage disorder caused by mutations in the genes *NPC1* (95%) or *NPC2* (5%) ([Patterson 1993](#)). NPC is a rare disease that has an estimated prevalence of one to three cases per million in the United States (US), although this is thought to be an underestimate given the heterogeneity of this disease and likelihood of missed diagnoses in patients with milder phenotypes. Estimated incidences in different populations around the world have ranged from 1:90,000 to 1:120,000 live births ([Wassif et al. 2016](#)) ([Labrecque et al. 2021](#)).

*NPC1* and *NPC2* are important for late endosomal and lysosomal lipid transport and homeostasis. Their loss of function impedes cellular lipid trafficking and causes the accumulation of unesterified cholesterol, glucosylceramide, and gangliosides in the late endosomes and lysosomes of affected cells ([Tang et al. 2010](#)). The accumulation of cholesterol and other lipid species in peripheral tissues (mainly the liver and spleen) and in neurons and other non-neuronal cells in the central nervous system is thought to ultimately lead to the devastating and progressive neurovisceral symptoms that are the hallmarks of NPC via downstream processes that are not fully understood.

NPC is always progressive, but the primary manifestations and prognosis are heterogenous, ranging from a rapidly progressive neonatal form to an adult-onset form that is characterized by a chronic neurodegenerative disease course. NPC is typically categorized into age-dependent phenotypes, recognizing that they likely represent a continuum rather than distinct phenotypes. The four phenotypes described are 1) early infantile, with perinatal onset to the age of 2 years, (2) late infantile, with onset between the ages of 2 and 6 years, (3) juvenile, with onset between the ages of 6 and 15 years, and (4) adolescent/adult, with onset after the age of 15 years. The early infantile presentation is predominantly visceral, with hepatosplenomegaly, jaundice, and pulmonary disease, although some also have neurological symptoms ([Seker Yilmaz et al. 2020](#)). Individuals with early infantile onset tend to have a rapidly progressive disease course, progressing to death in early childhood. The late infantile and juvenile presentations are predominantly neurological with progressive decline in previously attained cognitive, gross, and fine motor skills as well as progressive dysarthria and dysphagia. Additional neurological symptoms include ataxia, cataplexy, vertical supranuclear gaze palsy, and epilepsy. Adolescent and adult onset of disease can be more insidious, with cognitive and behavioral changes or other psychiatric manifestations at the onset, followed by chronic neurological decline ([Las Heras et al. 2023](#)).

Disease progression most commonly impacts ambulation, fine motor skills, speech, swallowing, and cognition, ultimately progressing to respiratory failure and death. Progressive neurological symptoms also include ataxia and other movement disorder symptoms and epilepsy. Ataxia is the most common movement disorder that occurs in NPC and can sometimes be a presenting symptom of the disease ([Devaraj et al. 2022](#)) ([Anheim et al. 2014](#)). While lifespan can vary from a few days (severe neonatal onset) to a few decades, the reported median age of death is 13 years (range: 0.1 to 69 years) ([Bianconi et al. 2019](#)).

An Externally Lead Patient-Focused Drug Development meeting was held on March 18, 2019 and was hosted by 8 patient advocacy organizations for NPC.<sup>1</sup> During the meeting, patients and caregivers shared their perspectives on disease symptoms, the impact of NPC on their daily lives, current experience with treatment, and expectations for future treatments. Eighty-three patients and caregivers responded to a survey prior to the meeting; the age of onset of neurological symptoms (developmental delays, ataxia, vertical gaze palsy, etc.) for most patients was after the age of 2 years (36.7% were 2 to 5 years old, 27.8% were 6 to 15 years old, and 12.7% were 16 to 29 years old). The six symptoms reported as having the greatest impact on patient and caregivers' daily lives were ambulation/walking difficulties and cognitive impairment, followed by swallowing difficulty, speech problems, seizures, and fine motor skills. Ambulation/walking and fine motor skills are often significantly impacted by ataxia in NPC; for example, one father of a 16-year-old male who had the onset of impaired coordination at 8 years old said "Less than one year after ataxia first appeared, his condition had deteriorated markedly. His gait became staggered, his handwriting reverted to kindergarten level, and the ataxia became more pronounced. Simple activities such as brushing teeth, or shampooing hair, became difficult tasks." The most meaningful targets for drug treatment were summarized as impacting neurological disease symptoms, including any slowing, halting, or improvement of disease symptoms.

In the United States, there is only one recently approved treatment for the neurological manifestations of NPC; additional therapeutic options for this devastating disease are needed. The current standard of care is primarily supportive and includes the treatment of epilepsy with anti-seizure medications as well as interventions to support feeding, mobility, communication, and behavior. Miglustat is an iminosugar that acts as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase, the initial enzyme in the synthesis of many glycosphingolipids (GSLs). Miglustat was approved in the United States in 2003 for patients with mild or moderate Gaucher disease when enzyme replacement therapy is not a therapeutic option. Miglustat was also approved for the treatment of the progressive neurological manifestations of NPC in pediatric and adult patients in many countries outside the United States. Miglustat is often prescribed "off-label" for patients with NPC in the United States and is considered standard of care for NPC amongst clinical experts.

Patients with NPC have a substantial and unmet treatment need. While miglustat has been reported in the medical literature to potentially slow disease progression in some patients, NPC remains progressive and life-limiting in all affected individuals. In the Voice of the Patient report for NPC (Externally Lead Patient-Focused Drug Development meeting) ([EL-PFDD 2019](#)), this unmet need was summarized as follows: "Patients and families most desire new treatments for neurological symptoms and improved quality of life even if they do not extend life span. Recognizing the heterogeneity of disease progression and symptoms, patients with NPC and their families emphasize the need for multiple therapeutic options so that treatment approaches can be tailored to meet individual patient needs."

N-acetyl-L-leucine (levacetylleucine) is a modified amino acid and is the L-enantiomer of N-acetyl-DL-leucine. The racemate N-acetyl-DL-leucine has been available in France since 1957

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<sup>1</sup> Externally Lead Patient-Focused Drug Development Meeting on March 18, 2019 was hosted by: Ara Parseghian Medical Research Fund at Notre Dame, Hide & Seek Foundation, Dana's Angels Research Trust, Hope for Marian, National Niemann-Pick Disease Foundation, Niemann-Pick Canada, Firefly Fund, and Johnathon's Dreams.

as a short-term oral treatment in tablet form primarily used for acute vertigo in adults. The Applicant states that levacetylleucine reduced unesterified cholesterol in fibroblasts derived from patients with NPC. In addition, the Applicant cited published data in which *Npc1*<sup>-/-</sup> mice treated with levacetylleucine showed a slight reduction in a subset of GSLs in the brain (GM2, GM1a) and a small reduction in GA1 and GA2 in the cerebellum ([Kaya et al. 2021](#)). The magnitudes of these effects were sufficiently small that it is unclear if they were physiologically meaningful; however, there was an apparent reduction in CD68 staining in *Npc1*<sup>-/-</sup> mice that were treated with levacetylleucine compared with that of untreated *Npc1*<sup>-/-</sup> mice. These changes were accompanied by histological evidence of reduced CD68 in the cerebellum in levacetylleucine-treated animals compared with untreated *Npc1*<sup>-/-</sup> mice. In addition, some markers of motor improvement were observed; however, the magnitude of the effect was relatively small. These effects were accompanied by a small (8-day) increase in median survival.

## 3.1. Review Issue List

The review team identified the key review issues listed in Sections [3.1.1](#) and [3.1.2](#) below relevant to the evaluation of benefit and risk, respectively. In-depth assessment of these benefit and risk issues can be found in Sections [6.3](#) and [7.7](#), respectively.

### 3.1.1. Key Efficacy Review Issues

- 3.1.1.1. Interpretability of the Primary Efficacy Endpoint
- 3.1.1.2. Establishment of Drug Effectiveness in Patients <10 Years Old
- 3.1.1.3. Adequacy of Confirmatory Evidence
- 3.1.1.4. Uncertainty Regarding Durability of Treatment Effect
- 3.1.1.5. Proposed Indication

### 3.1.2. Key Safety Review Issues

- 3.1.2.1. Embryofetal Development Toxicity in Rodents and Non-Rodents
- 3.1.2.2. Juvenile Toxicology Profile Unknown
- 3.1.2.3. Effects on Male and Female Fertility and Early Embryonic Development Unknown
- 3.1.2.4. Effects on Pre- and Postnatal Development Unknown
- 3.1.2.5. Carcinogenic Risk Unknown
- 3.1.2.6. Concomitant Miglustat Use
- 3.1.2.7. Assessment of Safety in Patients <10 Years Old (**≥15 kg**)

## 3.2. Approach to the Clinical Review

The Applicant submitted data from two trials that enrolled patients with NPC and one trial that enrolled patients with a different lysosomal storage disorder, GM2 gangliosidosis. The benefit-risk assessment is based on the single adequate and well-controlled trial in subjects with NPC (Trial IB1001-301) with supportive evidence from an open-label rater-blinded study (Trial IB1001-201) in subjects with NPC. The trial in GM2 gangliosidosis was reviewed for safety signals and trial withdrawals or deaths only and was not included in our efficacy assessment.

The clinical trials conducted to support the benefit-risk assessment of levacetylleucine for the treatment of the neurological manifestations of NPC are summarized in [Table 3](#).

### **Determination of Efficacy**

To evaluate the efficacy of levacetylleucine for treating the neurological symptoms of NPC, the results of the randomized, double-blinded period of phase 3 clinical trial IB1001-301 was considered the primary source of efficacy data. A total of 60 subjects who received both levacetylleucine and placebo in Trial IB1001-301 were evaluated. At the time of NDA submission on January 24, 2024, an open-label extension (OLE) phase was ongoing, and the efficacy data were not submitted. In addition to Trial IB1001-301, the open-label phase 2 clinical trial IB1001-201 provided confirmatory evidence (CE).

### **Determination of Safety**

The safety assessment was primarily based on data from Trial IB1001-301, the only source of randomized, placebo-controlled data in subjects with NPC. The safety data from the open-label study of levacetylleucine in subjects with NPC, Trial IB1001-201, as well as available data from the OLEs of both Trials IB1001-301 and IB1001-201 were also reviewed separately. The NPC safety population consisted of 84 subjects who received levacetylleucine, including 28 pediatric subjects and 56 adult subjects. Lastly, safety data from Trial IB1001-202, an open-label study of levacetylleucine in GM2 gangliosidosis, was also reviewed for potential safety signals.

The analysis of general safety assessment of adverse events (AEs), laboratory evaluations, vital signs, and electrocardiograms was based on descriptive summaries and review of source data. Case report forms and subject narratives were also reviewed for premature trial discontinuations or withdrawals. Clinical trial data were independently analyzed using JMP and Python software. All safety assessments and conclusions are those of the clinical review team unless otherwise specified.

### 3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1 to 3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):  
Treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing at least 15 kg
2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)
  - a. Adequate and well-controlled clinical investigation(s):
    - i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
    - ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations
  - OR**
  - b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence ([December 2019](#)) ([May 1998](#)) ([September 2023](#))
  - OR**
  - c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)<sup>2</sup>
3. Complete response, if applicable
  - a. ☐ SEE was established
  - b. ☐ SEE was not established (*if checked, omit item 2*)

**Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations<sup>1</sup> for Levacetylleucine**

| <b>Study/Trial Identifier (NCT#)</b> | <b>Study/Trial Population</b>                                 | <b>Study/Trial Design</b>                                                                                                                                                   | <b>Regimen (Number Treated), Duration</b>                                                                                                                                                                                                                                                                                                                             | <b>Primary and Key Secondary Endpoints</b>                                                                          | <b>Number of Subjects Planned; Actual Randomized<sup>2</sup></b> | <b>Number of Centers and Countries</b> |
|--------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|----------------------------------------|
| IB1001-301<br>(NCT05163288)          | Patients with a confirmed diagnosis of NPC aged 5 to 67 years | Control type: Placebo<br><br>Randomization: Randomized<br><br>Blinding: Double-blind<br><br>Innovative design features: Crossover design with two 12-week treatment periods | Drug: levacetylleucine<br><br>Dosage: Subjects ≥13 years: 4 g/day (2 g morning, 1 g afternoon, 1 g evening), 4-12 years (15 to <25 kg): 2 g/day (1 g morning, evening), 4-12 years (25 to <35 kg): 3 g/day (1 g morning, afternoon, evening), 4-12 years (≥35 kg): 4 g/day (same as ≥13 years).<br><br>Number treated: 60<br><br>Duration (quantity and units): 12 wk | Primary: Modified Scale for the Assessment and Rating of Ataxia (mSARA) at the end of each 12-week treatment period | Planned: 46<br>Randomized: 60                                    | 11 sites, 7 non-US countries           |

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| Study/Trial Identifier (NCT#)               | Study/Trial Population                                        | Study/Trial Design                                                                                                                                                                       | Regimen (Number Treated), Duration                                                                                                                                                                                                                                                                                                                                                                  | Primary and Key Secondary Endpoints        | Number of Subjects Planned; Actual Randomized <sup>2</sup> | Number of Centers and Countries |
|---------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|------------------------------------------------------------|---------------------------------|
| IB1001-201<br>(parent study)<br>NCT03759639 | Patients with a confirmed diagnosis of NPC aged 7 to 64 years | Control type: None<br><br>Randomization: Open-label<br><br>Blinding: Rater-blinded<br><br>Innovative design features: Central raters blinded for assessment of primary endpoint by video | Drug: levacetylleucine<br><br>Dosage: Subjects ≥13 years (Europe) or ≥18 years (US): 4 g/day (2 g morning, 1 g afternoon, 1 g evening); 6-12 years (15 to <25 kg): 2 g/day (1 g morning, 1 g evening); 6-12 years (25 to <35 kg): 3 g/day (1 g morning, afternoon, evening); 6-12 years (≥35 kg): 4 g/day (same as ≥13 years).<br><br>Number treated: 33<br><br>Duration (quantity and units): 6 wk | Primary: CI-CS, anchored with 8MWT or 9HPT | Planned: 30<br>Enrolled: 33                                |                                 |

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| Study/Trial Identifier (NCT#)                    | Study/Trial Population                                                                               | Study/Trial Design                                                        | Regimen (Number Treated), Duration                                                                                                                                                                                                                                                                                                                                                                    | Primary and Key Secondary Endpoints                                                                             | Number of Subjects Planned; Actual Randomized <sup>2</sup> | Number of Centers and Countries |
|--------------------------------------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|---------------------------------|
| IB1001-201 (open-label extension)<br>NCT03759639 | Patients with a confirmed diagnosis of NPC who completed IB1001-201 Parent Study, aged 7 to 64 years | Control type: None<br><br>Randomization: Open-label<br><br>Blinding: None | Drug: levacetylleucine<br><br>Dosage: Subjects ≥13 years (Europe) or ≥18 years (US): 4 g/day (2 g morning, 1 g afternoon, 1 g evening); 6-12 years (15 to <25 kg): 2 g/day (1 g morning, 1 g evening); 6-12 years (25 to <35 kg): 3 g/day (1 g morning, afternoon, evening); 6-12 years (≥35 kg): 4 g/day (same as ≥13 years).<br><br>Number treated: 19<br><br>Duration (quantity and units): 110 wk | Primary: Success rate in 5DNPCCSS from the extension phase baseline to the end of Extension Treatment Period I. | Planned: 20<br>Enrolled: 19                                |                                 |

| Study/Trial Identifier (NCT#)           | Study/Trial Population                                                       | Study/Trial Design                                                                                                                                                                       | Regimen (Number Treated), Duration                                                                                                                                                                                                                                                                                                                                                                                  | Primary and Key Secondary Endpoints          | Number of Subjects Planned; Actual Randomized <sup>2</sup> | Number of Centers and Countries |
|-----------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------------------|---------------------------------|
| IB1001-202/IB1001-202 OLE (NCT03759665) | Patients with a confirmed diagnosis of GM2 gangliosidosis aged 6 to 55 years | Control type: None<br><br>Randomization: Open-label<br><br>Blinding: Rater blinded<br><br>Innovative design features: Central raters blinded for assessment of primary endpoint by video | Drug: levacetylleucine<br><br>Dosage: Subjects ≥13 years (Europe) or ≥18 years (US): 4 g/day (2 g morning, 1 g afternoon, 1 g evening); 6-12 years (15 to <25 kg): 2 g/day (1 g morning, 1 g evening); 6-12 years (25 to <35 kg): 3 g/day (1 g morning, afternoon, evening); 6-12 years (≥35 kg): 4 g/day (same as ≥13 years).<br><br>Number treated: 30<br><br>Duration (quantity and units): 6 wk, 110 wk for OLE | Primary: CI-CS, anchored with 8MWT or 9HPT-D | Planned: 30<br>Enrolled: 30                                |                                 |

Source: IB1001-201, IB1001-202, IB1001-301 Clinical Study Reports

<sup>1</sup> Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

<sup>2</sup> If no randomization, then replace with "Actual Enrolled."

Abbreviations: 5DNPCSS = 5-domain Niemann-Pick disease type C clinical severity scale; 8MWT = 8-meter walk test; 9HPT-D = 9-Hole Peg Test of the dominant hand; CI-CS = clinical impression of change in severity; mSARA = modified Scale for the Assessment and Rating of Ataxia; NCT# = national clinical trial number; OLE = open-label extension; wk = week(s)

## 4. Patient Experience Data

**Table 4. Patient Experience Data Submitted or Considered**

| Data Submitted in the Application                                         |                                                                                                                              |                                        |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Check if Submitted                                                        | Type of Data                                                                                                                 | Section Where Discussed, if Applicable |
| <b>Clinical Outcome Assessment Data Submitted in the Application</b>      |                                                                                                                              |                                        |
| <input type="checkbox"/>                                                  | Patient-reported outcome                                                                                                     | Section <a href="#">6</a>              |
| <input type="checkbox"/>                                                  | Observer-reported outcome                                                                                                    |                                        |
| <input checked="" type="checkbox"/>                                       | Clinician-reported outcome                                                                                                   |                                        |
| <input type="checkbox"/>                                                  | Performance outcome                                                                                                          |                                        |
| <b>Other Patient Experience Data Submitted in the Application</b>         |                                                                                                                              |                                        |
| <input type="checkbox"/>                                                  | Patient-focused drug development meeting summary                                                                             | Section <a href="#">6</a>              |
| <input checked="" type="checkbox"/>                                       | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) |                                        |
| <input type="checkbox"/>                                                  | Observational survey studies                                                                                                 |                                        |
| <input type="checkbox"/>                                                  | Natural history studies                                                                                                      |                                        |
| <input type="checkbox"/>                                                  | Patient preference studies                                                                                                   |                                        |
| <input type="checkbox"/>                                                  | Other: (please specify)                                                                                                      |                                        |
| <input type="checkbox"/>                                                  | If no patient experience data were submitted by Applicant, indicate here.                                                    |                                        |
| <b>Data Considered in the Assessment (But Not Submitted by Applicant)</b> |                                                                                                                              |                                        |
| <input checked="" type="checkbox"/>                                       | Perspectives shared at patient stakeholder meeting                                                                           |                                        |
| <input checked="" type="checkbox"/>                                       | Patient-focused drug development meeting summary report                                                                      |                                        |
| <input checked="" type="checkbox"/>                                       | Other stakeholder meeting summary report                                                                                     |                                        |
| <input type="checkbox"/>                                                  | Observational survey studies                                                                                                 |                                        |
| <input type="checkbox"/>                                                  | Other: (please specify)                                                                                                      |                                        |

## 5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

### 5.1. Nonclinical Assessment of Potential Effectiveness

NPC is a lysosomal storage disease that is biochemically characterized by increased storage of multiple lipids including low-density lipoprotein -derived cholesterol, sphingoid bases (e.g., sphingosine and sphinganine), and other sphingolipids including GSLs and sphingomyelin. The combined biochemical and cellular defects in NPC lead to widespread pathology in the brain including neurodegeneration and neuroinflammation, and to the clinical signs of NPC. The pharmacological effects of levacetylleucine (also referred to as N-acetyl-L-leucine, NALL, or IB1001) in treating NPC are discussed here. It is concluded that the pharmacology parameters evaluated in nonclinical models are primarily proof-of-concept that suggest plausible mechanistic support for the overall package of CE of effectiveness for levacetylleucine in patients with NPC.

In their submission, the Applicant cited published data that describe potential modes of action whereby treatment with levacetylleucine slows the decline of biochemical and cellular defects present in nonclinical models of NPC, both in vitro and in vivo. These publications suggest that treatment with levacetylleucine may reduce accumulation of sphingosine, GSLs, and cholesterol, and that this treatment reduced lysosomal volume in NPC1-deficient Chinese hamster ovary cells in vitro. In vitro levacetylleucine treatment was also found to reduce lysosomal volume in cultured fibroblasts obtained from patients with NPC.

In vivo studies in *Npc1*<sup>-/-</sup> mice, a nonclinical model of NPC, were conducted in which animals were treated pre-symptomatically (i.e., from the age of 3 weeks). The authors reported a reduction in total GSL levels in the forebrain (GM1a and GM2) and cerebellum (GA2 and GA1). The authors also reported a reduction in ataxic symptoms in *Npc1*<sup>-/-</sup> mice treated pre-symptomatically at a later age (8 weeks old). When initiated at the age of 3 weeks, treatment with levacetylleucine was also associated with a modest increase in survival and a reduction in markers of neuroinflammation (CD68 staining) in the cerebellum.

These findings suggest that levacetylleucine may slow disease progression in mice by an undefined mechanism; however, these findings do not provide direct support for the primary efficacy endpoint measured in clinical trials (Trial IB1001-201, Trial IB1001-301, or both). As such, the nonclinical data can only suggest plausible mechanistic CE for levacetylleucine in treating patients with NPC and should only be considered as a contributing factor in conjunction with strong evidence of clinical efficacy in the phase 3 clinical trial, Trial IB1001-301, conducted in patients with NPC.

For additional details of cited publication see Section [13.2.2](#).

## 5.2. Clinical Pharmacology / Pharmacokinetics

The pharmacologic activity, pharmacokinetics (PK), and clinical pharmacology of levacetylleucine that are relevant to the interpretation of benefit and risk are summarized in [Table 5](#).

**Table 5. Summary of Clinical Pharmacology and Pharmacokinetics**

| Characteristic                                                                                                         | Drug Information                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                        | Pharmacologic Activity                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Mechanism of action                                                                                                    | The mechanism of action of levacetylleucine is unknown.                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Active moieties                                                                                                        | N-acetyl-L-leucine (NALL) is the active moiety. After being absorbed, NALL is metabolized into acetate and L-leucine by ubiquitously expressed enzymes. No other active metabolite of NALL has been identified.                                                                                                                                                                                                                                                               |
| QT prolongation                                                                                                        | The Applicant has not conducted a thorough QT/QTc study to assess the effect of NALL on QT interval prolongation. According to the applicant's evaluation, the nonclinical and clinical data demonstrated no potential for QT/QTc prolongation and no other cardiovascular related findings. The review team agreed with the applicant's evaluation and agreed with waiving a TQT study. See Cardiac IRT team review in DARRTS dated January 26, 2024 (Reference ID: 5317889) |
|                                                                                                                        | General Information                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Bioanalysis                                                                                                            | Levacetylleucine concentrations in human plasma were quantified using a validated LC-MS/MS assay. The sensitivity of the assay was 100 ng/mL.                                                                                                                                                                                                                                                                                                                                 |
| Healthy subjects versus patients                                                                                       | The pharmacokinetics (PK) of NALL has not been assessed in healthy subjects.                                                                                                                                                                                                                                                                                                                                                                                                  |
| Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug) | The full PK profile of NALL was assessed at steady state in 17 subjects with NPC after 365 days ( $\pm 14$ days) of dosing in the long-term extension phase of a phase 2 study. NALL maximum concentration ( $C_{max}$ ) and area under the curve from time 0 to 24 hours ( $AUC_{0-24h}$ ) were 8.3 (3.3) $\mu\text{g/mL}$ and 33.2 (12.5) $\text{h}\cdot\mu\text{g/mL}$ . No sex differences in PK parameters were observed.                                                |
| Range of effective dose(s) or exposure                                                                                 | The maximum proposed daily dose is 4 grams taken as 2 grams in the morning, 1 gram at noon, and 1 gram in the evening. This dose is the maximum daily dose tested in the clinical trials.                                                                                                                                                                                                                                                                                     |
| Maximally tolerated dose or exposure                                                                                   | A maximum tolerated dose has not been determined                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Dose proportionality                                                                                                   | Dose proportionality was not assessed in the submitted clinical trials.                                                                                                                                                                                                                                                                                                                                                                                                       |
| Accumulation                                                                                                           | No accumulation was observed after repeat administration                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Bridge between to-be-marketed and clinical trial formulations                                                          | The phase 3 trial used the to-be-marketed formulation; therefore, a PK bridging study between the to-be-marketed formulation and clinical trial formulation is not needed.                                                                                                                                                                                                                                                                                                    |

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| Characteristic                              | Drug Information                                                                                                                                                                                                                                                                                      |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                             | <b>Absorption</b>                                                                                                                                                                                                                                                                                     |
| Bioavailability                             | The absolute bioavailability of NALL following oral administration has not been determined.                                                                                                                                                                                                           |
| T <sub>max</sub>                            | After oral administration, NALL was absorbed with median (min, max) T <sub>max</sub> of 1 (0.5, 2.5) hour.                                                                                                                                                                                            |
|                                             | <b>Distribution</b>                                                                                                                                                                                                                                                                                   |
| Volume of distribution                      | The mean (SD) volume of distribution at steady state (V <sub>ss</sub> ) was 253 (125) L.                                                                                                                                                                                                              |
| Plasma protein binding                      | Plasma protein binding of NALL is very low with free drug about 100%.                                                                                                                                                                                                                                 |
|                                             | <b>Elimination</b>                                                                                                                                                                                                                                                                                    |
| Clearance                                   | The mean (SD) clearance is 139 (59) L/hour.                                                                                                                                                                                                                                                           |
| Half-life                                   | The estimated mean half-life is around 1 hour.                                                                                                                                                                                                                                                        |
| Metabolic pathway(s)                        | Levacetylleucine is metabolized into acetate and L-leucine by ubiquitously expressed enzymes, which are used endogenously in catabolic and metabolic pathways. Cytochrome P450 enzymes are not involved in the metabolism of levacetylleucine.                                                        |
| Primary excretion pathways (% dose)         | No mass balance study was conducted in humans. Following a single oral administration to rats, the metabolites are the amino acid L-leucine and acetic acid.                                                                                                                                          |
|                                             | <b>Intrinsic Factors and Specific Populations</b>                                                                                                                                                                                                                                                     |
| Body weight                                 | In the population PK analysis, body weight was identified as a significant covariate; apparent clearance (CL/F) and apparent volume of distribution (V/F) of NALL were lower in subjects with lower body weight. The recommended dosing regimen of NALL in patients with NPC is based on body weight. |
| Age                                         | Age was not identified as significant covariate affecting NALL PK in the population PK analyses.                                                                                                                                                                                                      |
| Renal impairment                            | The effect of renal impairment on the PK of IB1001 has not been evaluated. See Section <a href="#">8.1</a> .                                                                                                                                                                                          |
| Hepatic impairment                          | The effect of hepatic impairment on the PK of IB1001 has not been evaluated. See Section <a href="#">8.1</a> .                                                                                                                                                                                        |
|                                             | <b>Drug Interaction Liability (Drug as Perpetrator)</b>                                                                                                                                                                                                                                               |
| Inhibition/induction of metabolism          | No in vitro induction towards CYP enzymes was observed. No clinical drug-drug interaction studies have been conducted.                                                                                                                                                                                |
| Inhibition/induction of transporter systems | Inhibition of efflux transporters P-gp, BCRP, BSEP and OAT1/3 by NALL was observed in vitro.                                                                                                                                                                                                          |

Source: Summary of Clinical Pharmacology and Study reports

Abbreviations: AUC<sub>0-24h</sub> = area under the concentration-time curve from time 0 to 24 h; BCRP = breast cancer resistance protein; BSEP = bile salt export pump; CL/F = apparent clearance; C<sub>max</sub> = maximum plasma concentration; CYP = cytochrome P450; LC-MS/MS = liquid chromatography with tandem mass spectrometry; MDR1 = multidrug resistance mutation 1; NALL = N-acetyl-L-leucine; NPC = Niemann-Pick disease type C; OAT = organic anion transporter; PK = pharmacokinetics; QTc = corrected QT interval; SD = standard deviation; T<sub>max</sub> = time to maximum concentration; V/F = apparent volume of distribution; V<sub>ss</sub> = volume of distribution at steady-state

## 6. Efficacy (Evaluation of Benefit)

### 6.1. Assessment of Dose and Potential Effectiveness

#### 6.1.1. Proposed Levacetylleucine Dosage Regimen

**Proposed Dosage** (b) (4)

(b) (4)  
The Applicant's proposed dosage of levacetylleucine is based on patient's body weight in kilograms.

**Table 6. Proposed Levacetylleucine Dosages** (b) (4) (b) (4)

|         |  |
|---------|--|
| (b) (4) |  |
|---------|--|

**Table 7. Proposed Levacetylleucine Dose** (b) (4) (b) (4)

|         |  |
|---------|--|
| (b) (4) |  |
|---------|--|

#### 6.1.2. Dose Selection Rationale for Clinical Trials

The dose of levacetylleucine used in the clinical trials – approximately 0.1 g/kg/day – was chosen based on extrapolation from experience with the racemate N-acetyl-DL-leucine and in vivo studies in relevant animal models (including the NPC mouse model). The Applicant claimed that this dose was supported by the exposure safety margins demonstrated in nonclinical studies. The clinical dose selected was well-tolerated in the trials (i.e., a lower dose was not needed due to any toxicity concerns). The Applicant claimed that long-term clinical data from oral use of the racemate up to 8 g/day in subjects with NPC have shown the treatment to be safe and well-tolerated. Therefore, the Applicant chose the dose of up to 4 g/day.

Based on the similar dose selection rationale, the Applicant chose the 4 g/day dose of levacetylleucine for subjects aged 13 years and older, and approximately 0.1 g/kg/day of levacetylleucine for subjects aged 4 to under 13 years. Therefore, the selected dose for both the

phase 2 and phase 3 clinical trials was 4 g/day for subjects aged 13 years and over. Subjects under the age of 13 years were dosed based on body weight, as follows: children weighing 15 kg to under 25 kg received 2 g/day, children weighing 25 kg to under 35 kg received 3 g/day, and children weighing 35 kg and above received 4 g/day.

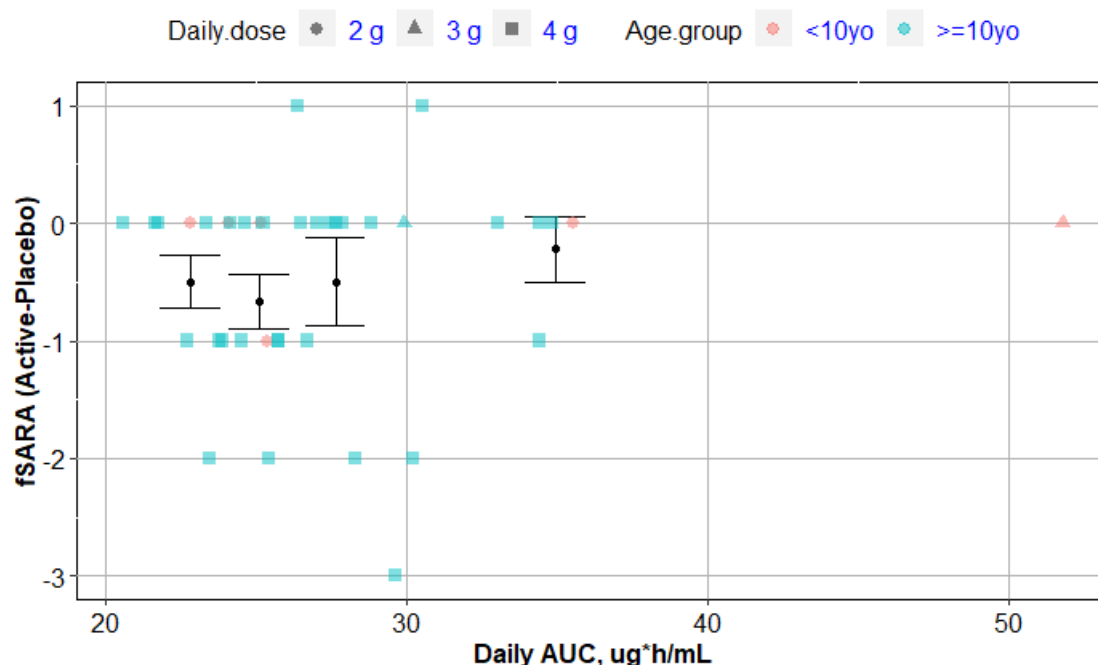
The efficacy of the clinical dose was consistent with the nonclinical pharmacology exposure range data and was clinically relevant when compared to placebo treatment. Exposure-response (E-R) analyses for efficacy did not reveal any apparent correlation between plasma exposures and drug effects.

Subjects weighing <15 kg were not enrolled in any of the Applicant's trials.

### 6.1.3. Exposure-Response Relationship for Efficacy

In the E-R analysis conducted based on the data from 38 subjects who had both efficacy and evaluable pharmacokinetic (PK) data in Trial IB1001-301, no E-R relationship was observed between the functional scale for assessment and rating of ataxia (fSARA) and the exposure metric, daily area under the concentration-time curve (AUC) at steady state at the proposed dosing regimen ([Figure 1](#)). However, due to the limited sample size, the E-R relationship for efficacy is inconclusive.

**Figure 1. Exposure-Response for fSARA**



#### 6.1.4. Exposure-Response Relationship for Safety

Due to the limited incident rate for each treatment-emergent adverse event (TEAE) (refer to Section 7.6.1.5), E-R analysis for safety was not performed.

### 6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

The Applicant's clinical trials to investigate levacetylleucine for the treatment of NPC consist of two studies: a multicenter, open-label, single arm study, Trial IB1001-201, and a pivotal placebo-controlled, randomized, crossover study, Trial IB1001-301. Trial IB1001-301 is considered a single adequate and well-controlled trial and will be the primary source to establish effectiveness.

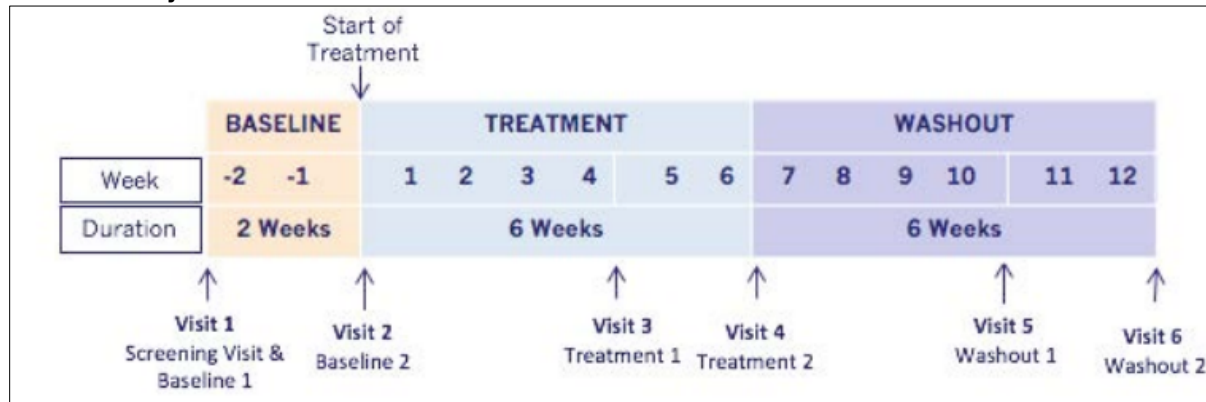
#### 6.2.1. Trial IB1001-201

##### 6.2.1.1. Design

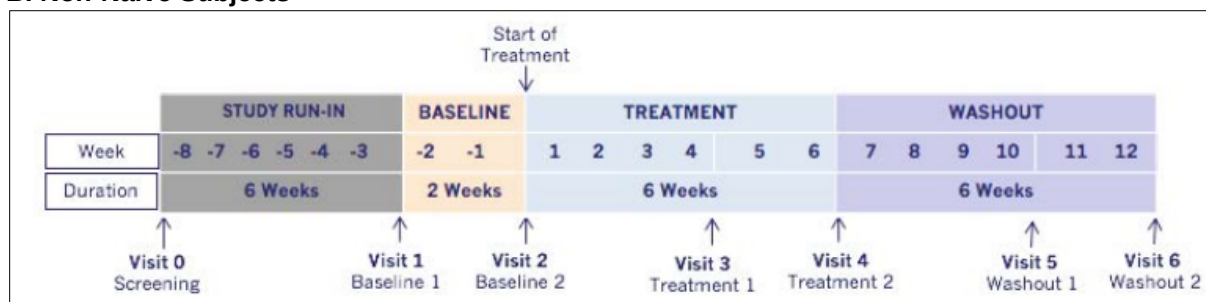
##### Parent Study

**Figure 2. Parent Study Design, Trial IB1001-201**

##### **A. Naïve Subjects**



##### **B. Non-Naïve Subjects**



Source: Trial IB1001-201 Clinical Study Report, page 3-4

Trial IB1001-201 was a multinational, multicenter, open-label, single-arm phase 2 study. A total of 34 participants were screened, of whom 33 (97.1%) were treated with levacetylleucine. One subject was considered a screen failure due to violation of inclusion/exclusion criteria. The parent study of Trial IB1001-201 consisted of a 2-week baseline period, a 6-week treatment period, and a 6-week washout period. Two visits were planned for each period. Due to coronavirus disease of 2019 (COVID-19) restrictions, Visit 3 and Visit 5 were classified as non-essential visits and were allowed to be skipped, while Visit 4 and Visit 6 remained essential visits.

At the initial screening visit, subjects were classified as either naïve or non-naïve based on the use of prohibited medication within the previous 42 days. For naïve subjects, the initial screening visit was treated as Baseline 1. For non-naïve subjects, the initial screening visit was treated as Visit 0 and the subjects underwent a minimum of 42 days of washout before Visit 1 (Baseline 1). During the treatment period, all subjects received 1000 mg powder for oral suspension in 60 mL glass bottles for approximately 42 days (+7 days).

The primary efficacy endpoint of the parent study was based on the blinded raters' clinical impression of change in severity (CI-CS) score comparing paired videos of the subject's performance on the predefined anchor test of either the 9-Hole Peg Test of the dominant hand (9HPT-D) or the 8-meter walk test (8MWT) at two visits. At Visit 1, the investigating physician selected a primary anchor test for each subject based on the predefined criteria. See Section [16.1](#) for the criteria.

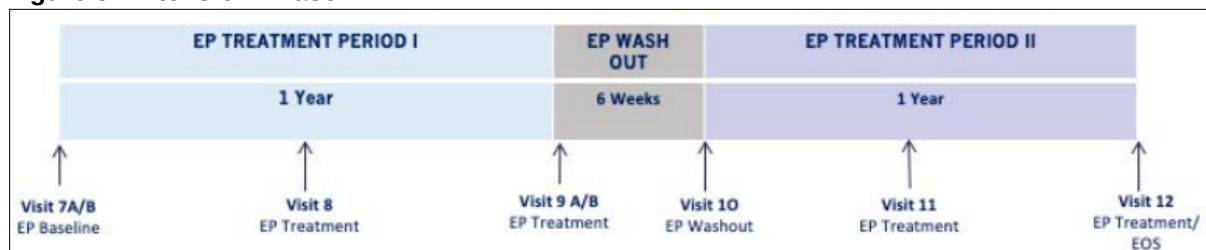
For the CI-CS assessment, two independent, primary raters were provided with 3 pairs of video recordings and asked to assess for each video pair: 'Compared to the first video, how has the severity of their performance on the 9HPT-D or 8MWT changed (improved or worsened) in 6-weeks as observed in the second video?' The video pairs that were made from videos at Visit 2, Visit 4, and Visit 6 were presented in random order, and the internal pairing of each video set was randomized. The raters were blinded to the timepoint of videos. The two primary raters' scores were averaged if there was a 1-point difference between the scores given by the two raters. If a difference was greater than 1 point, a third blinded rater reviewed the assessments and determined the most accurate assessment between the two scores.

The primary endpoint was the CI-CS comparing the end of treatment (Visit 4) with baseline (Visit 2) minus the CI-CS comparing the end of washout (Visit 6) with the end of treatment (Visit 4). Each CI-CS score is measured on a 7-point Likert scale (-3=significantly worse to +3=significantly improved).

While the evaluation of the primary endpoint CI-CS and a secondary endpoint Clinical Impression of Severity were performed by two blinded, independent neurologists based on videos of the anchor test, other secondary endpoints were assessed without blinding.

See Section [16](#) for the secondary and exploratory endpoints of the parent study.

**Figure 3. Extension Phase**



Source: Trial IB1001-201 Clinical Study Report, page 4  
Abbreviations: EOS = end of study; EP = extension phase

Upon completion of the parent study, eligible subjects were offered to participate in the extension phase (EP) that allows subjects to continue treatment with levacetylleucine for approximately 2 years. The EP comprises 6 visits over a 116-week period. The first visit of the EP (Visit 7) was conducted 1 day after Visit 6 at the end of the parent study. All subjects were planned to receive levacetylleucine for 365 days of EP Treatment Period I, followed by 42 days of a washout period. After the washout period, subjects were to receive levacetylleucine for 365 days of EP Treatment Period II.

All endpoints in the EP were considered secondary to those in the parent study. The primary endpoint in this EP was based on the 5-domain Niemann-Pick disease type C clinical severity scale (5DNPCCSS) from the EP baseline (Visit 7) to the end of treatment in the EP (Visit 9). The 5-domain NPCCSS is comprised of 5 major domains (ambulation, speech, swallow, fine motor skills, cognition), which add up to a composite value.

#### 6.2.1.2. Eligibility Criteria

##### **Parent Study**

##### **Inclusion Criteria**

Individuals who met all the following criteria were eligible to participate in Trial IB1001-201:

1. Written informed consent signed by the patient and/or their legal representative/parent/impartial witness.
2. Male or female aged  $\geq 6$  years in Europe **OR**  $\geq 18$  years in the United States with a confirmed diagnosis of NPC at the time of signing informed consent. For individuals in Europe confirmed diagnosis included:
  - a. Clinical features and positive biomarker screen and/or filipin test without genetic test results (had not been performed).
  - b. Clinical features and positive genetic test.
  - c. Clinical features and positive biomarker screen and/or filipin test but only one NPC mutation identified on genetic test.
  - d. Clinical features with positive biomarker screen and/or filipin test and positive genetic test.
3. Females of childbearing potential, defined as a premenopausal female capable of becoming pregnant, were included if they were either sexually inactive (sexually abstinent for 14 days prior to the first dose and confirmed to continue through 28 days after the last dose) or using

one of the following highly effective contraceptives (i.e., resulting in <1% failure rate when used consistently and correctly) 14 days prior to the first dose continuing through 28 days after the last dose:

- a. Intrauterine device
  - b. Surgical sterilization of the partner (vasectomy for 6 months minimum)
  - c. Combined (estrogen or progestogen containing) hormonal contraception associated with the inhibition of ovulation (either oral, intravaginal, or transdermal)
  - d. Progestogen only hormonal contraception associated with the inhibition of ovulation (either oral, injectable, or implantable)
  - e. Intrauterine hormone releasing system
  - f. Bilateral tubal occlusion
4. Females of non-childbearing potential had to have undergone one of the following sterilization procedures at least 6 months prior to the first dose:
- a. Hysteroscopic sterilization
  - b. Bilateral tubal ligation or bilateral salpingectomy
  - c. Hysterectomy
  - d. Bilateral oophorectomy

**OR** be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status. FSH analysis for postmenopausal women was done at screening. FSH levels should have been in the postmenopausal range as determined by the central laboratory.

5. Non-vasectomized male patients agreed to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days beyond the last dose of study medication and the female partner agreed to comply with inclusion criteria 3 or 4. For a vasectomized male who had his vasectomy 6 months or more prior to study start, it was required that they use a condom during sexual intercourse. A male who had been vasectomized less than 6 months prior to study start had to follow the same restrictions as a non-vasectomized male.
6. If male, patient agreed not to donate sperm from the first dose until 90 days after their last dose.
7. Patients had to fall within:
- a. A scale for the assessment and rating of ataxia (SARA) score of  $5 \leq X \leq 33$  points (out of 40).
- AND**
- b. Either:
    - i. Within the 2 to 7 range (0 to 8 range) of the Gait subtest of the SARA scale.
- OR**
- ii. Were able to perform the 9HPT-D (spinocerebellar ataxia functional index [SCAFI] subtest) in  $20 \leq X \leq 150$  seconds.
8. Weight  $\geq 15$  kg at screening.

9. Patients were willing to disclose their existing medications/therapies for (the symptoms) of NPC, including those on the prohibited medication list. Non-prohibited medications/therapies (e.g., miglustat, concomitant speech therapy, and physiotherapy) were permitted provided:
  - a. The Investigator did not believe the medication/therapy would interfere with the trial protocol/results.
  - b. Patients had been on a stable dose/duration and type of therapy for at least 42 days before Visit 1 (Baseline 1).
  - c. Patients were willing to maintain a stable dose/would not change their therapy throughout the duration of the study.
10. Had an understanding of the implications of study participation, provided in the written patient information and informed consent by patients or their legal representative/parent, and demonstrated a willingness to comply with instructions and attend required study visits (for children this criterion would also be assessed in parents or appointed guardians).

### **Exclusion Criteria**

Individuals who met any of the following criteria were not eligible to participate in Trial IB1001-201:

1. Asymptomatic patients.
2. Patient had clinical features of NPC and a positive biomarker screen and/or filipin test, but a completely negative result on a previous genetic test for NPC.
3. Patients who had any of the following:
  - a. Chronic diarrhea
  - b. Unexplained visual loss
  - c. Malignancies
  - d. Insulin-dependent diabetes mellitus
  - e. Known history of hypersensitivity to the Acetyl-Leucine (DL-, L-, D-) or derivatives
  - f. History of known hypersensitivity to excipients of Ora-Blend® (namely (b) (4) sorbitol, cellulose, carboxymethylcellulose, xanthan gum, carrageenan, dimethicone, methylparaben, and potassium sorbate)
4. Simultaneous participation in another clinical trial or participation in any clinical trial involving administration of an investigational medicinal product ([IMP]; 'study drug') within 6 weeks prior to Visit 1.
5. Patients with a physical or psychiatric condition which, at the Investigator's discretion, could put the patient at risk, confound the study results, or interfere with the patient's participation in the clinical trial.
6. Known clinically significant (CS) (at the discretion of the Investigator) laboratory findings in hematology, coagulation, clinical chemistry, or urinalysis, including, but not limited to:
  - a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5x upper limit of normal (ULN).
  - b. Total bilirubin >1.5x ULN, unless Gilbert's syndrome is present in which case total bilirubin >2x ULN.
7. Known or persistent use, misuse, or dependency of medication, drugs, or alcohol.
8. Current or planned pregnancy or women who were breastfeeding.

9. Patients with severe vision or hearing impairment (that is not corrected by glasses or hearing aids) that, at the Investigator's discretion, interfered with their ability to perform trial assessments.
10. Patients who had been diagnosed with arthritis or other musculoskeletal disorders affecting joints, muscles, ligaments, and/or nerves that by themselves affect patient's mobility and, at the Investigator's discretion, interfered with their ability to perform trial assessments.
11. Patients unwilling and/or who were not able to undergo a 42-day washout period from any of the following prohibited medication prior to Visit 1 (Baseline 1) and remain without prohibited medication through Visit 6:
  - a. Aminopyridines (including sustained-release form)
  - b. N-acetyl-DL-leucine (e.g., Tanganil®)
  - c. N-acetyl-L-leucine (prohibited if not provided as IMP)
  - d. Riluzole
  - e. Gabapentin
  - f. Varenicline
  - g. Chlorzoxazone
  - h. Sulfasalazine
  - i. Rosuvastatin

### **Extension Phase**

#### **Inclusion Criteria**

1. Completed Visit 6 of the IB1001-201 parent study.
2. The prescribing information determined further treatment with levacetylleucine to be in patient's best interest.
3. Written informed consent signed by the patient and/or their legal representative/parent/impartial witness for participation in the EP.
4. Patients were willing to continue to remain without the following prohibited medication from Visit 6 throughout the duration the EP:
  - a. Aminopyridines (including sustained-release form)
  - b. N-acetyl-DL-leucine (e.g., Tanganil)
  - c. N-acetyl-L-leucine (prohibited if not provided as IMP)
  - d. Riluzole
  - e. Gabapentin
  - f. Varenicline
  - g. Chlorzoxazone
  - h. Sulfasalazine
  - i. Rosuvastatin

#### **6.2.1.3. Statistical Analysis Plan**

The statistical analysis plan (SAP) was finalized on January 26, 2023 (Version 4.0) before database lock on April 5, 2023. The data cut-off date for efficacy analyses of the parent study was June 22, 2022. For the parent study, analyses were planned in the SAP Version 2.0 dated

May 20, 2020 and its COVID-19 addendum Version 1.0 dated September 16, 2020. For the EP, analyses were planned in SAP Version 4.0.

According to the SAP, the intent-to-treat (ITT) population consists of all subjects who receive at least one dose of levacetylleucine and have a video recording at either Visit 1 or Visit 2, or both. The modified intent-to-treat (mITT) population is defined as all subjects in the ITT population with one video recording at either Visit 3 or Visit 4, or both. The Per Protocol Set consists of all subjects with at least one video recording at baseline (Visit 1 or Visit 2), end of treatment (Visit 3 or Visit 4), and end of washout (Visit 5 or Visit 6), and without any major protocol deviation that could have influenced the validity of the data for the primary efficacy variable.

The primary analysis population for the primary and all secondary efficacy endpoints was the mITT population. A last observation carried forward (LOCF) approach was used within each period if a video is missing or unreadable. Also, if either Visit 3 or Visit 4 was available but both Visit 5 and Visit 6 were missing or unreadable, the CI-CS score was assigned the value 0 (stable) for the primary efficacy analysis.

#### 6.2.1.4. Results of Analyses

##### 6.2.1.4.1. Subject Disposition and Baseline Characteristics

#### **Parent Study**

A total of 33 subjects were enrolled in the parent study of Trial IB1001-201 and treated across 9 sites in the United States, the United Kingdom, Germany, Spain, and Slovakia. [Table 8](#) presents subject disposition. Two subjects (6.1%) withdrew from the parent study. Of those two, one subject was withdrawn after Visit 2 due to an AE (increased seizure [n=1; 3.0%]) and was not included in the mITT population. This subject began to have mild seizures after 9 days of treatment. Given their medical history of seizures, the AE was not considered related to study drug. The other subject was withdrawn after Visit 3 due to “Other” reason (“Intake of study drug did not lead to benefit” [n=1; 3.0%]).

**Table 8. Subject Disposition, Parent Study, Trial IB1001-201**

| <b>Disposition</b> | <b>Parent Study</b> |
|--------------------|---------------------|
| Patients screened  | 34                  |
| Patients enrolled  | 33                  |
| ITT population     | 33 (100%)           |
| Safety population  | 33 (100%)           |
| mITT population    | 32 (97.0%)          |
| PPS population     | 18 (54.5%)          |
| Discontinued study | 2 (6.1%)            |
| Adverse event      | 1 (3.0%)            |
| Other <sup>1</sup> | 1 (3.0%)            |

Source: Table 11-1 of Trial IB1001-201 Clinical Study Report and adsl.xpt located at [\\CDSESUB1\evsprod\NDA219132\0001\m5\datasets\lib1001-201\analysis\adam\datasets\](#)

<sup>1</sup> One subject withdrew after Visit 3 due to “Intake of study drug did not lead to benefit.” However, this subject had a fall with head injury and broken ribs that required hospitalization after 44 days of treatment and approximately 1 month before the study discontinuation. The subject has a medical history of recurrent falls, and the SAE is considered unrelated to the study drug. Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat; PPS = per protocol set; SAE = serious adverse event

[Table 9](#) shows the baseline demographic characteristics of subjects enrolled in the parent study. Of the 33 subjects in the ITT population, 23 (69.7%) were male and 10 (30.3%) were female. The overall mean age was 28.8 years (standard deviation [SD]=15.1). Thirty subjects (n=30; 90.9%) used miglustat at baseline. The majority of the subjects were White (n=29; 87.9%) and most subjects were naïve (n=30; 90.9%).

**Table 9. Baseline Demographics and Clinical Characteristics, ITT Population, Trial IB1001-201**

| Characteristic                 | Total<br>N=33     |
|--------------------------------|-------------------|
| Naïve, n (%)                   |                   |
| Naïve                          | 30 (90.9)         |
| Non-naïve                      | 3 (9.1)           |
| Sex, n (%)                     |                   |
| Female                         | 10 (30.3)         |
| Male                           | 23 (69.7)         |
| Age, years                     |                   |
| Mean (SD)                      | 28.8 (15.07)      |
| Median (min, max)              | 29.0 (7.0, 64.0)  |
| Age categories, n (%)          |                   |
| Pediatric (<18 years)          | 10 (30.3)         |
| Adult (≥18 years)              | 23 (69.7)         |
| Age <10 years                  | 2 (6.1)           |
| Age ≥10 years                  | 31 (93.9)         |
| Race, n (%)                    |                   |
| Asian                          | 2 (6.1)           |
| White                          | 29 (87.9)         |
| Other                          | 2 (6.1)           |
| Baseline weight (kg)           |                   |
| Mean (SD)                      | 62.4 (17.48)      |
| Median (min, max)              | 64.0 (21.0, 98.4) |
| Miglustat at baseline, n (%)   |                   |
| No                             | 3 (9.1)           |
| Yes                            | 30 (90.9)         |
| Age at diagnosis, n (%)        |                   |
| Early infantile (<2 years)     | 3 (9.1)           |
| Late infantile (2 to <6 years) | 3 (9.1)           |
| Juvenile (6 to <15 years)      | 12 (36.4)         |
| Adolescent/adult (≥15 years)   | 15 (45.5)         |
| Ethnicity, n (%)               |                   |
| Not Hispanic or Latino         | 30 (90.9)         |
| Unknown                        | 1 (3.0)           |
| Other                          | 2 (6.1)           |
| Country, n (%)                 |                   |
| Netherlands                    | 7 (21.2)          |
| Spain                          | 10 (30.3)         |
| United Kingdom                 | 10 (30.3)         |
| Slovakia                       | 4 (12.1)          |
| United States                  | 2 (6.1)           |

Source: The statistical review team's analysis based on adsl.xpt located at

[\\CDSESUB1\evsprod\NDA219132\0001\m5\datasets\ib1001-201\analysis\adam\datasets\](#)

Abbreviations: ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects; n = number of subjects with given characteristic; SD = standard deviation

### **Extension Phase**

In addition to the 2 subjects who discontinued the parent study, 12 subjects did not consent to the EP. The individual trajectories of endpoints in the discontinued subjects did not show trends of change in either direction before discontinuation. Thus, a total of 19 subjects continued into the EP across 8 sites in the United States, the United Kingdom, Germany, and Slovakia. Of the 19 treated subjects, 17 (89.5%) subjects completed Visit 10 (EP Treatment Period I) and 13 subjects (68.4%) completed Visit 12 (EP Treatment Period II). Of 19 treated subjects in the EP, 11 (57.9%) subjects were male and 8 (42.1%) subjects were female. The overall mean age of the subjects was 24.3 years (SD=11.8).

A total of 6 subjects withdrew from the EP due to withdrawal of consent (n=1; 5.3%), lost to follow-up (n=1; 5.3%), and “Other” (“patient was not receiving any benefit” [n=2; 10.5%], “treatment was considered not sufficient enough” [n=1; 5.3%], or “patient wishes to withdraw from study participation” [n=1; 5.3%]).

**Review team’s comment:** The first visit of the first subject of Trial IB1001-201 EP was (b) (6) and the last visit of the last subject was (b) (6). Given that the review team could not identify any pattern regarding study discontinuation, it is considered that COVID-19 restrictions could likely have impacted the loss of sample size in the EP. Consequently, the review will focus on the efficacy results from the parent study, which preserves the majority of the enrolled subjects.

#### **6.2.1.4.2. Efficacy Results for CI-CS**

The results of the Applicant’s analysis of the primary efficacy endpoint are summarized in [Table 10](#). The analyses of CI-CS were based on the prespecified mITT population that includes all subjects in the ITT population with one recorded video at either Visit 3 or Visit 4, or both. The mITT set includes 28 subjects who have completed all essential visits of the parent study, 3 subjects who have completed Visit 4 (end of treatment period) but have Visit 6 excluded from the analysis due to extremely delayed visits, and 1 early termination subject who was withdrawn after Visit 3 due to an unrelated serious adverse event (SAE). Within the mITT population, the 9HPT-D was selected for 20 subjects (62.5%) and the 8MWT was selected for 12 subjects (37.5%). The mean CI-CS score in the treatment period (Visit 4 versus Visit 2) was 0.5 (SD=1.3) indicating improvement in the subjects’ condition at the end of the treatment period (EOT). The mean CI-CS score in the washout period (Visit 6 versus Visit 4) was -0.4 (SD=1.4) indicating deterioration in the subjects’ condition at the end of the washout period (EOW).

The Applicant provided results based on the Wilcoxon signed-rank test (one-sided p-value =0.03) and the Hodges-Lehmann estimate (median of the difference =1, 90% confidence interval (CI): 0.25, 1.75). The estimated difference in mean CI-CS between the two treatment periods was 0.9 with the p-value of 0.03 based on the one-sample t-test.

**Table 10. Summary of CI-CS Score, mITT Population, Trial IB1001-201**

| Parameter                                             | Parent Study     |
|-------------------------------------------------------|------------------|
| CI-CS comparing Visit 4 to Visit 2                    |                  |
| N <sup>1</sup>                                        | 32               |
| Mean (SD)                                             | 0.5 (1.3)        |
| Median (min, max)                                     | 1.0 (-3.0, 2.5)  |
| CI-CS comparing Visit 6 to Visit 4                    |                  |
| N <sup>2</sup>                                        | 32               |
| Mean (SD)                                             | -0.4 (1.4)       |
| Median (min, max)                                     | -0.2 (-3.0, 3.0) |
| CI-CS Visit 4 vs. Visit 2 – CI-CS Visit 6 vs. Visit 4 |                  |
| N                                                     | 32               |
| Mean (SD)                                             | 0.9 (2.5)        |
| Median (min, max)                                     | 1 (-5.0, 5.0)    |
| Hodges-Lehmann Estimate (90% CI)                      | 1.0 (0.25, 1.75) |
| One-sided p-value <sup>3</sup>                        | 0.03             |

Source: Table 11-4 of Trial IB1001-201 Clinical Study Report and adcics.xpt located at  
[\\CDSESUB1\evsprod\NDA219132\0001\m5\datasets\ib1001-201\analysis\adam\datasets\](#)

<sup>1</sup> One subject discontinued from the study after Visit 3. For a missing Visit 4, a video of the previous visit (Visit 3) was used.

<sup>2</sup> A last observation carried forward (LOCF) was applied to 4 subjects due to missing/unreadable Visit 5 and Visit 6. One subject discontinued the study after Visit 3. Three subjects had delayed Visit 6 after data cut-off on June 22, 2020. The CI-CS value of 0 (stable) was used for the 4 subjects.

<sup>3</sup> Wilcoxon signed-rank test was used.

Abbreviations: CI = confidence interval; CI-CS = clinical impression of change in severity; max = maximum; min = minimum; mITT = modified intent-to-treat; N = number of subjects; SD = standard deviation; vs. = versus

Three subjects had delayed Visit 6 videos outside of the visit schedule due to COVID-19 restrictions. For these subjects, the LOCF was applied and a value of 0 was used for their CI-CS scores comparing the EOW (Visit 6) and the EOT (Visit 4). The review team conducted a sensitivity analysis using observed CI-CS scores comparing Visit 6 and Visit 4 for these three subjects regardless of delayed assessments. The mean difference between the CI-CS in the treatment period and the CI-CS in the washout period was 0.8 (SD=2.55) with a one-sided p-value of 0.04 based on the one-sample t-test.

### **Subgroup Analysis of CI-CS by the Selected Anchor Test**

[Table 11](#) presents descriptive statistics of the CI-CS score in subgroups based on the selected primary anchor test. The mean CI-CS scores in the treatment period (Visit 4 versus Visit 2) were 0.8 and 0.3 for the 8MWT subgroup and the 9HPT-D subgroup, respectively. The mean CI-CS scores in the washout period (Visit 6 versus Visit 4) were -0.8 and -0.2 for the 8MWT subgroup and the 9HPT-D subgroup, respectively. The results indicate improvement in their primary anchor test during the treatment period followed by deterioration during the washout period in both subgroups.

**Table 11. Descriptive Statistics of CI-CS by the Primary Anchor Test, mITT Population, Trial IB1001-201**

| Parameter                          | Primary Anchor Test for CI-CS |                 |
|------------------------------------|-------------------------------|-----------------|
|                                    | 8MWT                          | 9HPT-D          |
| CI-CS comparing Visit 4 to Visit 2 | N=12                          | N=20            |
| Mean (SD)                          | 0.8 (1.1)                     | 0.3 (1.5)       |
| Median (min, max)                  | 1 (-1, 2.5)                   | 0.8 (-3, 2.5)   |
| CI-CS comparing Visit 6 to Visit 4 | N=11                          | N=17            |
| Mean (SD)                          | -0.8 (1.0)                    | -0.2 (1.5)      |
| Median (min, max)                  | -0.5 (-2.5, 0.5)              | 0.0 (-3.0, 3.0) |

Source: Table 14.2.1.6.5 of Trial IB1001-201 Clinical Study Report and adcs.xpt located at

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Last observation carried forward (LOCF) was not applied in this table.

Abbreviations: 8MWT = 8-meter walk test; 9HPT-D = 9-Hole Peg Test of the dominant hand; CI-CS = clinical impression of change in severity; max = maximum; min = minimum; mITT = modified intent-to-treat; N = number of subjects; SD, standard deviation

#### 6.2.1.4.3. Efficacy Results for 8-Meter Walk Test and 9-Hole Peg Test of the Dominant Hand

In addition to evaluation of the subject's performance regarding quality of walking and upper extremity function using the rater-blinded CI-CS endpoint, the quantitative analyses based on speed of gait and dexterity were assessed using the timed 8MWT and 9HPT-D. Both tests were provided as subtests of a secondary endpoint, SCAFI, which was assessed at every visit in the parent study except Visit 0 (screening visit). For each subtest, subjects performed two consecutive trials (Trial 1 and Trial 2). Time was reported within 0.1 second. At every visit, Trial 2 of the 8MWT and 9HPT-D were videoed as the CI-CS primary anchor test.

According to the CI-CS administration and scoring manual version 3.0 dated January 21, 2020, the 8MWT was still administered and video-recorded even if a subject required the use of assistive devices, another person, or wall for support. Per the SAP, if a subject required the unallowable support (another person or wall), the time for the trial was not recorded in the SCAFI scoring but only in the CI-CS scoring.

[Table 12](#) shows descriptive statistics of the timed 8MWT at the EOT and at the EOW. Per the scoring manual, the subjects with assistive devices (n=5) or a remote visit due to COVID-19 restrictions (n=1) were counted as missing data in [Table 12](#). For the ITT population, the mean change from baseline in the 8MWT at the EOT was -1.1 seconds (SD=4.1, median=-0.3). The mean change in the 8MWT at the EOW compared with the start of the washout period was -0.3 second (SD=2.8, median=0.3), indicating nearly no change during the washout period.

The subgroup of subjects whose primary anchor test was the 8MWT for the CI-CS endpoint showed a greater improvement in the 8MWT during the treatment period compared with the subgroup whose primary anchor test was 9HPT-D for the CI-CS endpoint. The former subgroup showed a mean change of -3.5 seconds (SD=5.5), and the latter showed a mean change of 0.1 (SD=2.7) during the treatment period. Considering the mean baseline difference between the subgroups (17.7 versus 8.8 seconds) and the extent of changes in the 8MWT within the 9HPT-D subgroup, the 8MWT subgroup is considered to have shown more notable improvement, while the other subgroup already had stable gait function.

**Table 12. Descriptive Summaries of 8-Meter Walk Test (SCAFI Subtest), ITT Population, Trial IB1001-201**

| Visit              | Timed 8MWT (in Seconds) |                         |                 | Change From the Start of Each Period (in Seconds) |                            |                   |
|--------------------|-------------------------|-------------------------|-----------------|---------------------------------------------------|----------------------------|-------------------|
|                    | 8MWT Subgroup<br>N=12   | 9HPT-D Subgroup<br>N=21 | Overall<br>N=33 | 8MWT<br>Subgroup<br>N=12                          | 9HPT-D<br>Subgroup<br>N=21 | Overall<br>N=33   |
| Baseline (Visit 2) | N=9                     | N=20                    | N=29            |                                                   |                            |                   |
| Mean (SD)          | 17.7 (11.7)             | 8.8 (2.6)               | 11.6 (7.8)      |                                                   |                            |                   |
| Median (min, max)  | 12.7 (6.4, 41.9)        | 8.5 (5, 16.5)           | 9.5 (5.0, 41.9) |                                                   |                            |                   |
| EOT (Visit 4)      | N=9                     | N=18                    | N=27            | N=9                                               | N=18                       | N=27              |
| Mean (SD)          | 14.2 (7.2)              | 8.9 (3.6)               | 10.7 (5.5)      | -3.5 (5.5)                                        | 0.1 (2.7)                  | -1.1 (4.1)        |
| Median (min, max)  | 12.1 (7.1, 27.4)        | 8.3 (4.5, 19)           | 9.1 (4.5, 27.4) | -2.5 (-14.4, 3.3)                                 | -0.2 (-3, 9.5)             | -0.3 (-14.4, 9.5) |
| EOW (Visit 6)      | N=6                     | N=16                    | N=22            | N=6                                               | N=16                       | N=22              |
| Mean (SD)          | 17.1 (8.2)              | 8.2 (2.3)               | 10.6 (6.0)      | 1.2 (1.1)                                         | -0.9 (3.0)                 | -0.3 (2.8)        |
| Median (min, max)  | 13.1 (10.2, 28.2)       | 7.6 (6.3, 14.1)         | 7.8 (6.3, 28.2) | 0.8 (0.4, 3.3)                                    | -0.3 (-10.8, 2.4)          | 0.3 (-10.8, 3.3)  |

Source: The statistical review team's analysis based on adscafi.xpt located at [\\CDSESUB1\evsprod\NDA219132\0001\m5\datasets\ib1001-201\analysis\adam\datasets\](#)

Abbreviations: 8MWT = 8-meter walk test; 9HPT-D = 9-Hole Peg Test of the dominant hand; EOT = end of treatment period; EOW = end of washout period; ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects; SCAFI = Spinocerebellar Ataxia Functional Index; SD = standard deviation

[Table 13](#) shows descriptive summaries of the timed 9HPT-D at the EOT and at the EOW. Per the SCAFI scoring manual, the data were missing if subjects were unable to perform the test due to physical limitations or Trial 1 had a value of >300 seconds. Of note, missing data due to these limitations were observed from the 8MWT subgroup (n=3 in Visit 2; n=4 in Visit 4; n=2 in Visit 6).

For the ITT population, the mean reduction in the 9HPT-D during the treatment period was 1.1 seconds (SD=13.4, median=0.3), whereas the mean change during the washout period was 7.7 seconds (SD=35.1, median=-0.8). While both subgroups by anchor test showed overall no changes in 9HPT-D during the treatment period, the 8MWT subgroup showed a greater deterioration in the mean time for 9HPT-D during the washout period compared with a 9HPT-D subgroup (34 versus -4.7 seconds). Similar to 8MWT in [Table 12](#), the 8MWT subgroup also exhibited higher mean baseline values than the 9HPT-D subgroup, indicating more severe symptoms in both gait and upper extremity function at the baseline.

**Table 13. Descriptive Summaries of 9-Hole Peg Test Dominant Hand (SCAFI Subtest), ITT Population, Trial IB1001-201**

| Visit              | Timed 9HPT-D (in Seconds) |                            |                    | Change From the Start of Each Period (in Seconds) |                            |                   |
|--------------------|---------------------------|----------------------------|--------------------|---------------------------------------------------|----------------------------|-------------------|
|                    | 8MWT<br>Subgroup<br>N=12  | 9HPT-D<br>Subgroup<br>N=21 | Overall<br>N=33    | 8MWT<br>Subgroup<br>N=12                          | 9HPT-D<br>Subgroup<br>N=21 | Overall<br>N=33   |
| Baseline (Visit 2) | N=8                       | N=21                       | N=29               |                                                   |                            |                   |
| Mean (SD)          | 143.5 (83.7)              | 59.3 (19.4)                | 82.5 (59.1)        |                                                   |                            |                   |
| Median (min, max)  | 114.4 (49.2, 290)         | 58.2 (29.4, 98.8)          | 64.1 (29.4, 290)   |                                                   |                            |                   |
| EOT (Visit 4)      | N=6                       | N=19                       | N=25               | N=6                                               | N=19                       | N=25              |
| Mean (SD)          | 110.3 (48.2)              | 61 (24.3)                  | 72.8 (37.3)        | 0.7 (24.8)                                        | 1.3 (8.4)                  | 1.1 (13.4)        |
| Median (min, max)  | 103.6 (50.1, 178.3)       | 61.5 (28, 104.2)           | 68.2 (28, 178.3)   | 9.2 (-36.6, 23.0)                                 | -0.1 (-9.8, 21.9)          | 0.3 (-36.6, 23)   |
| EOW (Visit 6)      | N=8                       | N=17                       | N=25               | N=8                                               | N=17                       | N=25              |
| Mean (SD)          | 169.4, (75.8)             | 57.3 (22.4)                | 93.2 (69.7)        | 34 (51)                                           | -4.7 (14.3)                | 7.7 (35.1)        |
| Median (min, max)  | 157.9 (73.7, 299.6)       | 55.9 (27.2, 121)           | 63.6 (27.2, 299.6) | 40.5 (-37.5, 127)                                 | -4.7 (-39.1, 16.9)         | -0.8 (-39.1, 127) |

Source: The statistical review team's analysis based on adscafi.xpt located at [\\CDSESUB1\evsprod\NDA219132\0001\m5\datasets\ib1001-201\analysis\adam\datasets\](#)

Abbreviations: 8MWT = 8-meter walk test; 9HPT-D = 9-Hole Peg Test of the dominant hand; EOT = end of treatment period; EOW = end of washout period; ITT = intent-to-treat; max = maximum; min = minimum; SCAFI = Spinocerebellar Ataxia Functional Index; N = number of subjects; SD = standard deviation

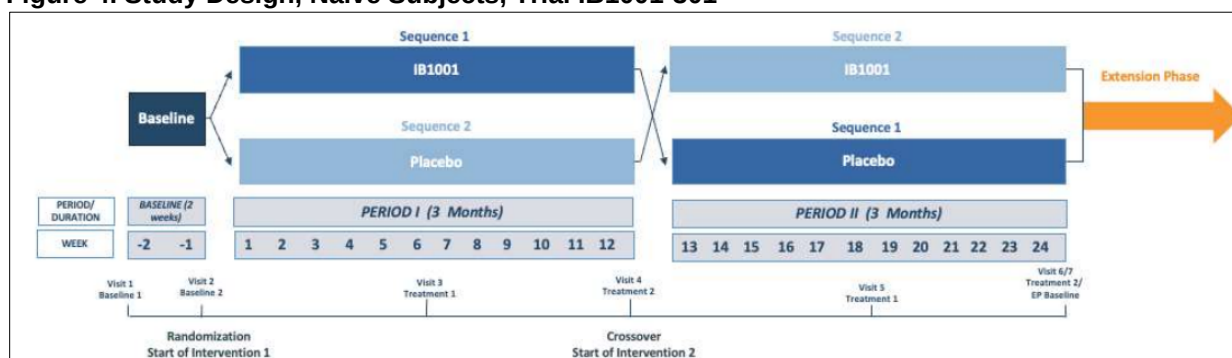
## 6.2.2. Trial IB1001-301

### 6.2.2.1. Design

The clinical benefit of levacetylleucine in patients with NPC was primarily based on a multinational, randomized, double-blinded, placebo-controlled, crossover phase 3 study, Trial IB1001-301. This trial involves 11 trial sites across 7 non-US countries. The trial consists of three periods: a baseline period, a 12-week first treatment period (“Treatment Period I”), and a 12-week second treatment period (“Treatment Period II”). At the screening visit, subjects were classified as either “naïve” or “non-naïve” based on their use of prohibited medications within the past 42 days. A total of 60 subjects aged  $\geq 4$  years with a confirmed diagnosis of NPC at the time of signing the informed consent were enrolled and randomized in a 1:1 ratio to one of the following treatment sequences:

- Sequence 1 (N=30): levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II.
- Sequence 2 (N=30): placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II.

**Figure 4. Study Design, Naïve Subjects, Trial IB1001-301**



Source: Trial IB1001-301 Clinical Study Report, page 31

All of 60 subjects were naïve subjects; they had not used prohibited medications within the past 42 days.

There was no washout period between the two periods. According to Section 2.5.3.1.2 of the submitted Clinical Overview,<sup>2</sup> the mean half-life of levacetylleucine is approximately 1 hour with a peak concentration range values between 0.5 to 2.5 hours after single and repeated oral dose. The Applicant stated that no or minor accumulation was observed after repeated administration.

Upon the completion of the parent study, trial participants were offered the opportunity to participate in a 2-year EP if the safety and tolerability during the parent study was considered acceptable by the Investigator. The EP is ongoing, thus data from the EP were not submitted at the time of the NDA submission (January 24, 2024).

<sup>2</sup> Clinical Overview, received January 24, 2024.

The Applicant's primary endpoint for the U.S. marketing application was a modified scale for the assessment and rating of ataxia (mSARA) total score at the end of treatment period (Visit 4 or Visit 6). The SARA is used to assess eight domains: gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide. The details on the scores for each domain are presented in Section [16.4](#). The SARA total score ranges from 0 to 40, where 0 is the best neurological status and 40 is the worst. The mSARA focuses on six domains: gait, speech disturbance, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test. The mSARA score ranges from 0 to 30. For the U.S. marketing application, the original SARA total score was defined as a key secondary endpoint.

**Review team's comment:** The Agency previously communicated to the Applicant that mSARA was not considered clearly interpretable to convey clinical benefit in daily functioning of patients with NPC. The Agency recommended an fSARA which focuses on four domains: gait, stance, sitting, and speech disturbance. For these four domains, the Agency recommended a modification to the scoring so that each domain has five possible scores: 0 (normal), 1, 2, 3, and 4 (worst severity); thus, the total fSARA score ranges from 0 to 16. Detailed regulatory history and the Agency's recommended scores are available in Section [6.3.1](#). In this review, results based on the fSARA will be considered as primary evidence of efficacy in patients with NPC.

#### 6.2.2.2. Eligibility Criteria

##### **Inclusion Criteria**

Individuals who met all the following criteria were eligible to participate in Trial IB1001-301:

1. Written informed consent signed by the patient and/or their legal representative/parent/impartial witness.
2. Male or female aged 4 years or older with a confirmed diagnosis of NPC at the time of signing informed consent. Confirmed diagnosis includes one of the following:<sup>3</sup>
  - a. Clinical features and positive biomarker screen and/or filipin test without genetic test results (has not been performed).
  - b. Clinical features and positive genetic test.
  - c. Clinical features and positive biomarker screen and/or filipin test but only 1 NPC mutation identified on genetic test.
  - d. Clinical features with positive biomarker screen and/or filipin test and positive genetic test.

---

<sup>3</sup> Note: The U.S. protocol required a confirmed genetic diagnosis of NPC. In the end, all 60 patients enrolled in the trial ultimately had a confirmed genetic diagnosis of NPC.

3. Females of childbearing potential, defined as a premenopausal female capable of becoming pregnant, were included if they were either sexually inactive (sexually abstinent<sup>4</sup> for 14 days prior to the first dose and confirmed to continue through 28 days after the last dose) or using one of the following highly effective contraceptives (i.e., resulting in <1% failure rate when used consistently and correctly) 14 days prior to the first dose continuing through 28 days after the last dose:
  - a. Intrauterine device
  - b. Surgical sterilization of the partner (vasectomy for 6 months minimum)
  - c. Combined (estrogen or progestogen containing) hormonal contraception associated with the inhibition of ovulation (either oral, intravaginal, or transdermal)
  - d. Progestogen only hormonal contraception associated with the inhibition of ovulation (either oral, injectable, or implantable)
  - e. Intrauterine hormone-releasing system
  - f. Bilateral tubal occlusion
4. Females of non-childbearing potential who had to have undergone one of the following sterilization procedures at least 6 months prior to the first dose:
  - a. Hysteroscopic sterilization
  - b. Bilateral salpingectomy
  - c. Hysterectomy
  - d. Bilateral oophorectomy

**OR** be postmenopausal with amenorrhea for at least 1 year prior to the first dose and FSH serum levels consistent with postmenopausal status. FSH analysis for postmenopausal women was done at screening. FSH levels should have been in the postmenopausal range as determined by the central laboratory.
5. Non-vasectomized male patients who agreed to use a condom with spermicide during the trial until 90 days beyond the last dose of study medication and the female partner agreed to comply with inclusion criteria 3 or 4. For a vasectomized male who had his vasectomy 6 months or more prior to study start, it was required that they use a condom during sexual intercourse. A male who had been vasectomized less than 6 months prior to study start had to follow the same restrictions as a non-vasectomized male.
6. If male, patient agreed not to donate sperm from the first dose until 90 days after their last dose.

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<sup>4</sup> Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. In this trial, abstinence was only acceptable if in line with the subject's preferred and usual lifestyle.

Periodic abstinence (calendar, symptothermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method were not acceptable methods of contraception. As well, female condom and male condom were not to be used together.

7. Patients had to have fallen within:
  - a. A SARA score of  $7 \leq x \leq 34$  points (out of 40).

**AND**

  - b. Either:
    - i. Within the 2 to 7 range (0 to 8 range) of the gait subtest of the SARA scale.

**OR**

    - ii. Were able to perform the 9HPT-D (SCAFI subtest) in  $20 \leq x \leq 150$  seconds.
8. Weight  $\geq 15$  kg at screening.
9. Patients were willing to disclose their existing medications/therapies for (the symptoms) of NPC, including those on the prohibited medication list. Non-prohibited medications/therapies (authorized medicines for NPC [e.g., miglustat], speech therapy, and physiotherapy) were permitted, provided:
  - a. The Investigator did not believe the medication/therapy would interfere with the trial protocol/results.
  - b. Patients had been on a stable dose/duration and type of therapy for at least 42 days before Visit 1 (Baseline 1).
  - c. Patients were willing to maintain a stable dose/would not change their therapy throughout the duration of the trial.
10. Had an understanding of the implications of trial participation, provided in the written patient information and informed consent by patients or their legal representative/parent, and demonstrated a willingness to comply with instructions and attend required trial visits (for children this criterion would also be assessed in parents or appointed guardians).

### **Exclusion Criteria**

Individuals who met any of the following criteria were not eligible to participate in Trial IB1001-301:

1. Patients who had any known hypersensitivity or history of hypersensitivity to:
  - a. Acetyl-Leucine (DL-, L-, D-) or derivatives.
  - b. Excipients of the levacetylleucine sachet (namely isomalt, hypromellose, and strawberry flavor).
  - c. Excipients of the placebo sachet (namely isomalt, hypromellose, strawberry flavor, (b) (4)).
2. Simultaneous participation in another clinical trial or participation in any clinical trial involving administration of an IMP ("study drug") for at least 42 days prior to Visit 1. At the discretion of the Investigator, Medical Monitor, and Sponsor, the washout period for specific IMPs may be longer based on the pharmacological activity and PK of the drug.
3. Patients with a physical or psychiatric condition which, at the Investigator's discretion and in consultation with the Medical Monitor and Sponsor (as applicable), could put the patient at risk, confound the study results, or interfere with the patient's participation in the clinical trial, (i.e., reliably perform trial assessments).

4. Known or persistent use, misuse, or dependency of medication, drugs, or alcohol.
5. Current or planned pregnancy or women who were breastfeeding.
6. Patients with severe vision or hearing impairment (that is not corrected by glasses or hearing aids) that, at the Investigator's discretion, interfered with their ability to perform trial assessments.
7. Patients who had been diagnosed with arthritis or other musculoskeletal disorders affecting joints, muscles, ligaments, and/or nerves that by themselves affect patient's mobility and, at the Investigator's discretion, interfered with their ability to perform trial assessments.
8. Patients unwilling and/or who were not able to undergo a 42-day washout period from any of the following prohibited medication prior to Visit 1 (Baseline 1) and remain without prohibited medication through Visit 6:
  - a. N-acetyl-DL-leucine (e.g., Tanganil)
  - b. N-acetyl-L-leucine (prohibited if not provided as IMP in Trial IB1001-301)
  - c. Sulfasalazine
  - d. Rosuvastatin

#### 6.2.2.3. Statistical Analysis Plan

The SAP was finalized on September 29, 2022 (Version 1.0), prior to database lock and unblinding for the parent phase on June 14, 2023. The primary efficacy analysis population was based on the ITT population that consists of all randomized subjects who received at least one dose of IMP (levacetylleucine or placebo). The primary efficacy endpoint, mSARA at Visit 4 or Visit 6, was analyzed using a mixed model for repeated measures (MMRM) with an unstructured covariance structure. The MMRM included treatment, period, sequence, baseline mSARA value at Visit 2, and baseline-by-period interaction as fixed effects.

#### **Handling of Treatment Discontinuation and Use of Rescue Medications**

Per the SAP, a treatment policy strategy was considered for the primary analysis for the following intercurrent events 1) treatment discontinuation due to AEs, 2) taking the rescue/prohibited medications sulfasalazine or rosuvastatin, or 3) taking of prohibited medications N-acetyl-DL-leucine (Tanganil, racemate of D and L enantiomers) or levacetylleucine as a chemical grade substance or supplied outside of Trial IB1001-301. Therefore, all data collected was used regardless of whether the intercurrent events occurred or not. No subjects had the second and third types of intercurrent events. For missing data, a LOCF on a per-period basis was applied.

Of 60 randomized subjects, 2 subjects had missing Visit 4 or Visit 6. One subject (b) (6) died after trial withdrawal. This subject withdrew from the trial after Visit 3 due to AE (pneumonia aspiration) during Treatment Period I on levacetylleucine. The AE occurred after the subject stopped treatment with levacetylleucine in preparation for the pre-planned procedure for a percutaneous endoscopic gastrostomy (PEG) feeding tube placement at a local non-trial site hospital. The subject had not informed the trial site or Investigator about this pre-planned procedure during screening and only informed the Investigator at Visit 3 (b) (6). The complications during the procedure led the subject to be hospitalized and the subject

developed pneumonia. The subject died 88 days after the treatment discontinuation. As this subject discontinued the trial after Visit 3, assessments at essential visits (Visit 4 and Visit 6) were not available.

One subject (b) (6) missed the Visit 6 assessment. On (b) (6) during Visit 6, which was 1 day after the last dose of study drug in the second treatment period (placebo), the Investigator determined that the subject required hospitalization due to worsening of depression. The Investigator confirmed that the subject remained hospitalized for depression (b) (6). (b) (6) The subject had a history of depression and a prior psychiatric hospitalization (b) (6).

The remaining subjects in the trial (n=58) completed both Visit 4 and Visit 6.

**Review team's comment:** The Applicant proposed LOCF per-period basis for missing values in the primary analysis. Therefore, in the primary analysis, the Visit 3 score was carried to Visit 4 for the Subject (b) (6) and the Visit 5 score was carried to Visit 6 for Subject (b) (6). However, a Visit 6 score does not exist for Subject (b) (6) since the subject withdrew from the trial during the first treatment period (levacetylleucine) and died prior to Visit 6. While the SAP specifies a treatment policy strategy to handle withdrawal from study medication due to AEs and states, "Patients who did not provide sufficient data for a LOCF approach were omitted from analysis," Subject (b) (6) was not omitted from the primary analysis and the nonexistent Visit 6 score in the second treatment period was handled by a hypothetical strategy. In other words, the Applicant's MMRM model implicitly imputed the Visit 6 score of Subject (b) (6) under missing-at-random assumption. While the withdrawal of Subject (b) (6) is not considered related to the investigational drug, the review team conducted sensitivity analyses to evaluate robustness of the primary efficacy analysis result based on fSARA (Section 6.2.2.4.3).

## 6.2.2.4. Results of Analyses

### 6.2.2.4.1. Subject Disposition and Baseline Characteristics

A total of 64 patients were screened, of whom 60 were enrolled and treated. Four patients had screen failures due to violation of one or more inclusion criteria. Of the 60 treated subjects, 59 (98.3%) subjects completed both treatment periods, and 58 (96.7%) subjects had assessments at the end of both treatment periods (Visit 4 and Visit 6).

**Table 14. Patient Screening and Enrollment, Trial IB1001-301**

| Disposition                          | Trial IB1001-301 |
|--------------------------------------|------------------|
| Patients screened                    | 64               |
| Screening failures                   | 4 (6.3%)         |
| Inclusion/exclusion criteria not met | 4 (6.3%)         |
| Patients enrolled                    | 60 (93.8%)       |
| Subjects randomized                  | 60 (93.8%)       |

Source: Table 14.1.3 of Trial IB1001-301 Clinical Study Report

**Table 15. Subject Disposition, Trial IB1001-301**

| <b>Parameter</b>                | <b>Levacetylleucine<br/>N=60<br/>n (%)</b> | <b>Placebo<br/>N=60<br/>n (%)</b> |
|---------------------------------|--------------------------------------------|-----------------------------------|
| Subjects randomized             |                                            |                                   |
| ITT population                  | 60 (100)                                   | 60 (100)                          |
| Safety population               | 60 (100)                                   | 60 (100)                          |
| Discontinued trial              | 1 (1.7)                                    | 0 (0)                             |
| Death                           | 0 (0)                                      | 0 (0)                             |
| Lost to follow-up               | 0 (0)                                      | 0 (0)                             |
| Withdrawal by subject           | 0 (0)                                      | 0 (0)                             |
| Physician decision <sup>1</sup> | 1 (1.7)                                    | 0 (0)                             |
| Protocol deviation              | 0 (0)                                      | 0 (0)                             |
| Other                           | 0 (0)                                      | 0 (0)                             |

Source: Table 14.1.3 of Trial IB1001-301 Clinical Study Report and the statistical review team's analysis based on adsl.xpt located at \\CdseSub1\evsprod\NDA219132\0001\m5\datasets\ib1001-301\analysis\adam\datasets\

<sup>1</sup> One subject (b) (6) developed a serious adverse event (SAE) of pneumonia aspiration during the hospitalization for the pre-planned procedure. The SAE developed 2 days after the last dose of study treatment. The subject was withdrawn from the trial by physician's decision due to the procedure complication with pneumonia. The subject died 88 days after the treatment discontinuation and prior to Visit 6.

Abbreviations: ITT = intent-to-treat; N = number of subjects randomized and treated; n = number of subjects in specified population or group

Demographic baseline characteristics are presented in [Table 16](#). The mean age of subjects was 26.4 (SD=15.9) years, ranging from 5 to 67 years old. Overall, 38.3% of subjects were pediatric patients. Most subjects were White (90%), reflecting the demographics of the trial site locations (most trial sites were in Europe). NPC is a genetic disorder, and the pathogenesis and clinical course are not expected to differ amongst different racial and/or ethnic groups. Because there are international management guidelines for NPC ([Geberhiwot et al. 2018](#)), there is reasonable similarity in care practices of the European and American subjects. While there were no FDA-approved treatments for NPC, miglustat is approved for NPC in the non-US countries that participated in the trial and is considered standard of care for patients with NPC. In the United States, despite not being approved for NPC, off-label use is common. Most subjects (85%) in the trial used miglustat at baseline. Miglustat is one of the non-prohibited medications; subjects were allowed to take miglustat during the trial as long as they maintained a stable dose.

**Table 16. Baseline Demographics and Clinical Characteristics by Treatment Sequence, Trial IB1001-301**

| <b>Characteristic</b>    | <b>Sequence 1<br/>N=30<br/>n (%)</b> | <b>Sequence 2<br/>N=30<br/>n (%)</b> | <b>Total<br/>N=60<br/>n (%)</b> |
|--------------------------|--------------------------------------|--------------------------------------|---------------------------------|
| Received both treatments | 29 (96.7)                            | 30 (100)                             | 59 (98.3)                       |
| Completed Visit 4        | 29 (96.7)                            | 30 (100)                             | 59 (98.3)                       |
| Completed Visit 6        | 28 (93.3)                            | 30 (100)                             | 58 (96.7)                       |
| Sex, n (%)               |                                      |                                      |                                 |
| Female                   | 14 (46.7)                            | 13 (43.3)                            | 27 (45.0)                       |
| Male                     | 16 (53.3)                            | 17 (56.7)                            | 33 (55.0)                       |
| Age, years               |                                      |                                      |                                 |
| Mean (SD)                | 24.2 (16.6)                          | 28.6 (15.1)                          | 26.4 (15.9)                     |
| Median (min, max)        | 18.5 (7.0, 63.0)                     | 26.5 (5.0, 67.0)                     | 25.0 (5.0, 67.0)                |

| <b>Characteristic</b>          | <b>Sequence 1<br/>N=30<br/>n (%)</b> | <b>Sequence 2<br/>N=30<br/>n (%)</b> | <b>Total<br/>N=60<br/>n (%)</b> |
|--------------------------------|--------------------------------------|--------------------------------------|---------------------------------|
| Age categories, n (%)          |                                      |                                      |                                 |
| Pediatric (<18 years)          | 15 (50.0)                            | 8 (26.7)                             | 23 (38.3)                       |
| Adult (≥18 years)              | 15 (50.0)                            | 22 (73.3)                            | 37 (61.7)                       |
| 10 years and older             | 25 (83.3)                            | 28 (93.3)                            | 53 (88.3)                       |
| 4 to 9 years old               | 5 (16.7)                             | 2 (6.7)                              | 7 (11.7)                        |
| Race, n (%)                    |                                      |                                      |                                 |
| Asian                          | 2 (6.7)                              | 0 (0)                                | 2 (3.3)                         |
| White                          | 26 (86.7)                            | 28 (93.3)                            | 54 (90.0)                       |
| Other                          | 2 (6.7)                              | 2 (6.7)                              | 4 (6.7)                         |
| Ethnicity, n (%)               |                                      |                                      |                                 |
| Hispanic                       | 0 (0)                                | 0 (0)                                | 0 (0)                           |
| Non-Hispanic                   | 25 (83.3)                            | 26 (86.7)                            | 51 (85.0)                       |
| Not reported                   | 1 (3.3)                              | 1 (3.3)                              | 2 (3.3)                         |
| Unknown                        | 4 (13.3)                             | 3 (10)                               | 7 (11.7)                        |
| Miglustat at baseline, n (%)   |                                      |                                      |                                 |
| No                             | 4 (13.3)                             | 5 (16.7)                             | 9 (15.0)                        |
| Yes                            | 26 (86.7)                            | 25 (83.3)                            | 51 (85.0)                       |
| Age at diagnosis, n (%)        |                                      |                                      |                                 |
| Early infantile (<2 years)     | 5 (16.7)                             | 4 (13.3)                             | 9 (15.0)                        |
| Late infantile (2 to <6 years) | 8 (26.7)                             | 6 (20.0)                             | 14 (23.3)                       |
| Juvenile (6 to <15 years)      | 11 (36.7)                            | 12 (40.0)                            | 23 (38.3)                       |
| Adolescent/adult (≥15 years)   | 6 (20.0)                             | 8 (26.7)                             | 14 (23.3)                       |
| Country, n (%)                 |                                      |                                      |                                 |
| Australia                      | 0 (0.0)                              | 6 (20.0)                             | 6 (10.0)                        |
| Czech Republic                 | 3 (10.0)                             | 1 (3.3)                              | 4 (6.7)                         |
| Germany                        | 8 (26.7)                             | 9 (30.0)                             | 17 (28.3)                       |
| Netherlands                    | 3 (10.0)                             | 6 (20.0)                             | 9 (15)                          |
| Slovakia                       | 0 (0.0)                              | 2 (6.7)                              | 2 (3.3)                         |
| Switzerland                    | 8 (26.7)                             | 4 (13.3)                             | 12 (20.0)                       |
| United Kingdom                 | 8 (26.7)                             | 2 (6.7)                              | 10 (16.7)                       |

Source: Table 14.1.2 of Trial IB1001-301 Clinical Study Report and the statistical team's analysis based on adsl.xpt located at \\Cdseub1\levsprod\NDA219132\0001\m5\datasets\ib1001-301\analysis\adam\datasets\

Subjects in Sequence 1 received levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II. Subjects in Sequence 2 received placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II.

Abbreviations: max = maximum; min = minimum; N = number of subjects in treatment sequence; n = number of subjects with given characteristic; SD = standard deviation

Subjects randomized to the placebo-levacetylleucine treatment sequence had higher mean baseline (Visit 2) mSARA, fSARA, SARA, and 5DNPPCSS total scores than those who were randomized to the other sequence ([Table 17](#)). The 5DNPPCSS total score was a prespecified primary endpoint for the EP of Trial IB1001-301 and has been used as outcome measures in natural history literature for patients with NPC ([Yanjanin et al. 2010](#)) ([Mengel et al. 2020](#)) ([Mengel et al. 2021](#)).

The efficacy endpoints were highly correlated at baseline. The estimated pairwise Spearman correlations between fSARA, mSARA, and SARA total score at baseline were ≥0.91. The estimated Spearman correlations between 5DNPPCSS total score and the total scores of SARA-based endpoints were 0.72 (fSARA), 0.74 (mSARA), and 0.76 (SARA) at baseline. Additional correlation analyses between the endpoints using all available visits are shown in [Section 16.2](#).

**Table 17. Mean Baseline Scores of mSARA, fSARA, SARA, and 5DNPCSS by Treatment Sequence, Trial IB1001-301**

| Parameter         | Sequence 1<br>N=30 | Sequence 2<br>N=30 | Total<br>N=60<br>(b) (4) |
|-------------------|--------------------|--------------------|--------------------------|
| mSARA             |                    |                    |                          |
| Mean (SD)         |                    |                    |                          |
| Median (min, max) |                    |                    |                          |
| fSARA             |                    |                    |                          |
| Mean (SD)         | 5.23 (3.04)        | 6.27 (3.27)        | 5.75 (3.17)              |
| Median (min, max) | 4 (1.0, 14.0)      | 5.5 (2.0, 14.0)    | 5.0 (1.0, 14.0)          |
| SARA              |                    |                    |                          |
| Mean (SD)         | 14.90 (7.49)       | 16.87 (7.51)       | 15.88 (7.50)             |
| Median (min, max) | 13.2 (6.0, 33.0)   | 14.8 (7.0, 31.5)   | 14.0 (6.0, 33.0)         |
| 5DNPCSS           |                    |                    |                          |
| Mean (SD)         | 10.10 (4.78)       | 12.07 (4.53)       | 11.08 (4.72)             |
| Median (min, max) | 9 (3, 21)          | 10.5 (6, 21)       | 10.0 (3.0, 21.0)         |

Source: The statistical team's analysis based on based on adsara2.xpt located at

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The 5DNPCSS total score was a primary endpoint for the extension phase of Trial IB1001-301.

Subjects in Sequence 1 received levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II. Subjects in Sequence 2 received placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II.

Abbreviations: 5DNPCSS = 5-domain Niemann-Pick disease type C clinical severity scale; fSARA = functional Scale for the Assessment and Rating of Ataxia; max = maximum; min = minimum; mSARA = Applicant's modified Scale for the Assessment and Rating of Ataxia; N = number of subjects in treatment sequence; SARA = Scale for the Assessment and Rating of Ataxia; SD = standard deviation

#### 6.2.2.4.2. Efficacy Results for Modified SARA

Figure 5 displays the mean mSARA total score over time per treatment sequence. (b) (4)



**Figure 5. Mean  $\pm$ SE Plot of mSARA Total Score Over Time per Treatment Sequence**

(b) (4)

Table 18 shows efficacy results based on the Applicant's proposed mSARA.

(b) (4)

**Table 18. Summaries of Applicant's Modified SARA (mSARA) Total Score at Each Visit by Treatment Sequence, Trial IB1001-301**

(b) (4)

The statistical review team also conducted a between-subject comparison using only the first-period data that is not affected by any potential carryover effect. [Table 18](#) show

(b) (4)

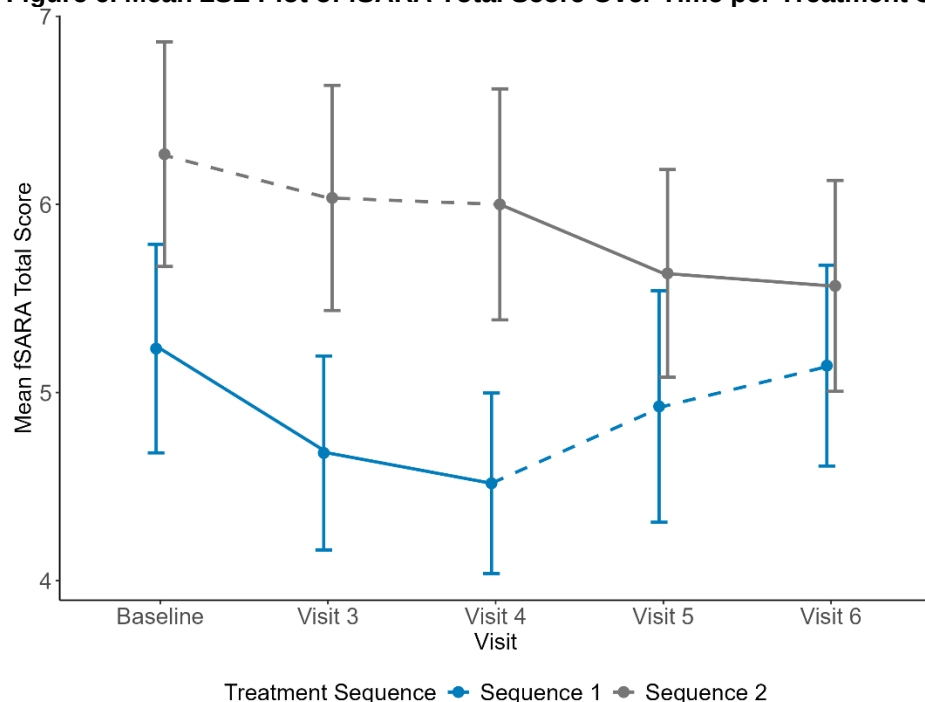
. The estimated treatment difference was -1.29 (95% CI: -2.21, -0.38) with a p-value of 0.007 using two-sample t-test adjusting for baseline value.

#### **6.2.2.4.3. Efficacy Results for Functional SARA**

On March 15, 2024, the Applicant submitted additional analysis results based on the Agency's recommended fSARA. After rescoring SARA, [Figure 6](#) shows a similar pattern to [Figure 5](#) using the Applicant's mSARA. [Table 19](#) shows the results for the fSARA total score using the primary analysis method. The estimated treatment effect for the fSARA was -0.45 (95% CI: -0.70, -0.19) with a p-value <0.001.

**Review team's comment:** The review team considers the efficacy results of fSARA total score highly persuasive given the small p-value and the consistent supportive subgroup analyses results and the results of other efficacy endpoints as described in Section [6.2.2.4](#).

**Figure 6. Mean  $\pm$ SE Plot of fSARA Total Score Over Time per Treatment Sequence**



Source: The statistical review team's analysis based on adsara2.xpt located at  
 \\Cdsub1\evsprod\NDA219132\0011\m5\datasets\lib1001-301\analysis\adam\datasets\  
 Subjects in Sequence 1 received levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II. Subjects in Sequence 2 received placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II.  
 The solid lines represent treatment period with levacetylleucine; the dashed line represents treatment period with placebo. No last observation carried forward (LOCF) approach was used.  
 Abbreviations: fSARA = functional Scale for the Assessment and Rating of Ataxia; SE = standard error

**Table 19. Summaries of fSARA Total Score at Each Visit by Treatment Sequence, Trial IB1001-301**

| Parameter          | Total Score        |                    | Change From Baseline |                    |
|--------------------|--------------------|--------------------|----------------------|--------------------|
|                    | Sequence 1<br>N=30 | Sequence 2<br>N=30 | Sequence 1<br>N=30   | Sequence 2<br>N=30 |
| Baseline (Visit 2) | N=30               | N=30               |                      |                    |
| Mean (SD)          | 5.23 (3.04)        | 6.27 (3.27)        |                      |                    |
| Median (min, max)  | 4 (1.0, 14.0)      | 5.5 (2.0, 14.0)    |                      |                    |
| Period 1 (Visit 4) | N=29               | N=30               | N=29                 | N=30               |
| Mean (SD)          | 4.52 (2.59)        | 6.0 (3.36)         | -0.52 (1.21)         | -0.27 (0.87)       |
| Median (min, max)  | 4.0 (1.0, 11.0)    | 4.5 (2.0, 14.0)    | 0 (-3, 2)            | 0 (-3, 1)          |
| Period 2 (Visit 6) | N=28               | N=30               | N=28                 | N=30               |
| Mean (SD)          | 5.14 (2.82)        | 5.57 (3.07)        | 0.04 (1.53)          | -0.70 (0.88)       |
| Median (min, max)  | 4.0 (2.0, 12.0)    | 5.0 (1.0, 13.0)    | 0 (-2, 3)            | 0 (-3, 0)          |

| Parameter                                              | Total Score        |                      | Change From Baseline |                      |
|--------------------------------------------------------|--------------------|----------------------|----------------------|----------------------|
|                                                        | Sequence 1<br>N=30 | Sequence 2<br>N=30   | Sequence 1<br>N=30   | Sequence 2<br>N=30   |
| Estimated mean fSARA score (SE) from MMRM <sup>1</sup> |                    |                      |                      |                      |
| Levacetylleucine                                       |                    | 5.12 (0.14)          |                      | -0.59 (0.14)         |
| Placebo                                                |                    | 5.57 (0.14)          |                      | -0.14 (0.14)         |
| Levacetylleucine-placebo (95% CI)                      |                    | -0.45 (-0.70, -0.19) |                      | -0.45 (-0.70, -0.19) |
| P-value                                                |                    | 0.0009               |                      | 0.0009               |

Source: The statistical review team's analysis based on adsara2.xpt located at

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<sup>1</sup> MMRM adjusting for period, sequence, treatment, baseline value, and baseline-period interaction. Last observation carried forward (LOCF) was applied for Subject (b) (6) at Visit 6 and Subject (b) (6) at Visit 4.

Subjects in Sequence 1 received levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II. Subjects in Sequence 2 received placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II.

LOCF approach was used for the descriptive summaries in this table.

Abbreviations: CI = confidence interval; fSARA = functional Scale for the Assessment and Rating of Ataxia; max = maximum; min = minimum; MMRM = mixed model for repeated measures; N = number of subjects in treatment sequence; SD = standard deviation; SE = standard error

There was no washout period between the two treatment periods. To address concerns about the carryover effect, the statistical review team assessed a sequence effect in the primary analysis model. The test for the sequence effect implied that there is no significant carryover effect (p-value: 0.6027). In addition, between-subject comparison was conducted based on the first period data only. The estimated treatment difference in the first period data was -0.35 (95% CI: -0.90, 0.19) with a p-value of 0.202 using a two-sample t-test adjusting for baseline. While the between-subject test is not adequately powered, the estimated treatment difference still indicates improvement in fSARA total score with levacetylleucine compared to placebo.

The review team assessed the robustness of the primary efficacy results based on different handling of death and missing data. Subject (b) (6) was randomized to levacetylleucine-placebo sequence, discontinued the trial after Visit 3, and died prior to Visit 6. This subject had the fSARA scores of 11 for both baseline (Visit 2) and Visit 3, showing no changes from baseline before trial discontinuation across all domains in both rescored and original scale. Since Subject (b) (6) did not inform the investigator about the pre-planned surgery at screening, the review team considered that this subject could be removed from the analysis per the eligibility criteria. Using 59 subjects (in which Subject (b) (6) is excluded), there was only a negligible difference in the results compared with the primary analysis results for fSARA. The estimated treatment difference was -0.45 (-0.71, -0.20) with a p-value of <0.001. To evaluate robustness of the primary results to the LOCF per period assumption for Subject (b) (6) the primary analysis was replicated omitting Subject (b) (6) and the best possible fSARA score of 0 for Subject (b) (6) Visit 6 (placebo). The estimated treatment difference was -0.42 (95% CI: -0.70, -0.14) with a p-value of 0.004, confirming the primary analysis. When the primary analysis was performed for completers (n=58), a larger treatment difference was observed (0.48, 95% CI: -0.73, -0.22; p-value <0.001) compared to the primary analysis. This is due to the LOCF assumption for Subject (b) (6) in the primary analysis. To be specific, Subject (b) (6) had observed fSARA scores of 3 at baseline, 3 at Visit 4 (levacetylleucine), and 2 at Visit 5 (placebo). The score of 2 at Visit 5 was carried forward to Visit 6 per the LOCF per period assumption, leading to a treatment difference favoring placebo within this subject in the Applicant's MMRM analysis. Thus, the completer analysis that excludes Subject (b) (6) together with ineligible Subject (b) (6) provides a larger treatment effect than the primary analysis.

The review team also examined the empirical distribution function of the treatment difference at the subject level (Table 20). Among the 58 completers, 22 (38%) subjects had a treatment difference favoring levacetylleucine, 4 (6.9%) subjects had a treatment difference favoring placebo, and 32 (55.2%) subjects had a treatment difference of zero score. The overall estimated treatment difference was -0.5 (95% CI: -0.68, -0.31) with a p-value <0.0006 based on a nonparametric sign test.

**Table 20. Results of Within-Subject Treatment Difference (Levacetylleucine – Placebo) in fSARA Total score (58 Completers)**

| Treatment Difference                                                | -3                                          | -2       | -1         | 0          | 1        |
|---------------------------------------------------------------------|---------------------------------------------|----------|------------|------------|----------|
| n (%)                                                               | 3 (5.2%)                                    | 5 (8.6%) | 14 (24.1%) | 32 (55.2%) | 4 (6.9%) |
| % of subjects with a treatment difference favoring levacetylleucine | 38 (95% CI <sup>1</sup> : 0.28, 0.47)       |          |            |            |          |
| Mean (SD) and (95% CI)                                              | -0.5 (0.94) and (-0.68, -0.31) <sup>1</sup> |          |            |            |          |

Source: The statistical review team's analysis based on adsara2.xpt located at [\\CdseSub1\levsprod\NDA219132\0011\m5\datasets\lib1001-301\analysis\adam\datasets](#)  
<sup>1</sup> Produced using a bootstrap method of sampling (10000 resampling datasets).  
Abbreviations: CI = confidence interval; n = number of subjects with given characteristic; SD = standard deviation

Based on the Clinical Inspection Summary dated July 24, 2024, the review team had a concern regarding data reliability for Visit 6 score of Subject (b) (6) who was taking levacetylleucine at Visit 6. The Visit 6 assessment of this subject was performed remotely over videoconference and the assessments were documented approximately 5 days after Visit 6. In addition, the Investigator made multiple changes to gait, right finger-nose-finger, right heel-shin slide, and left heel-shin slide scores approximately 13 days after the scores were documented on the source record. No justification was provided for the assessment changes. Gait score was changed from 3 to 1 in the original scale, and from 2 to 1 based on the Agency recommended rescoring algorithm. Due to potential recall bias and unjustified score changes, the statistical team conducted a post hoc analysis excluding Subject (b) (6). The analysis excluding both Subjects (b) (6) and (b) (6) provided the similar estimated treatment effect of -0.46 (-0.72, -0.20) with a p-value of <0.001. Despite the concerns with the Visit 6 assessment for Subject (b) (6) the trial appears to be conducted adequately based on the review team's site inspection by Division of Clinical Compliance Evaluation.

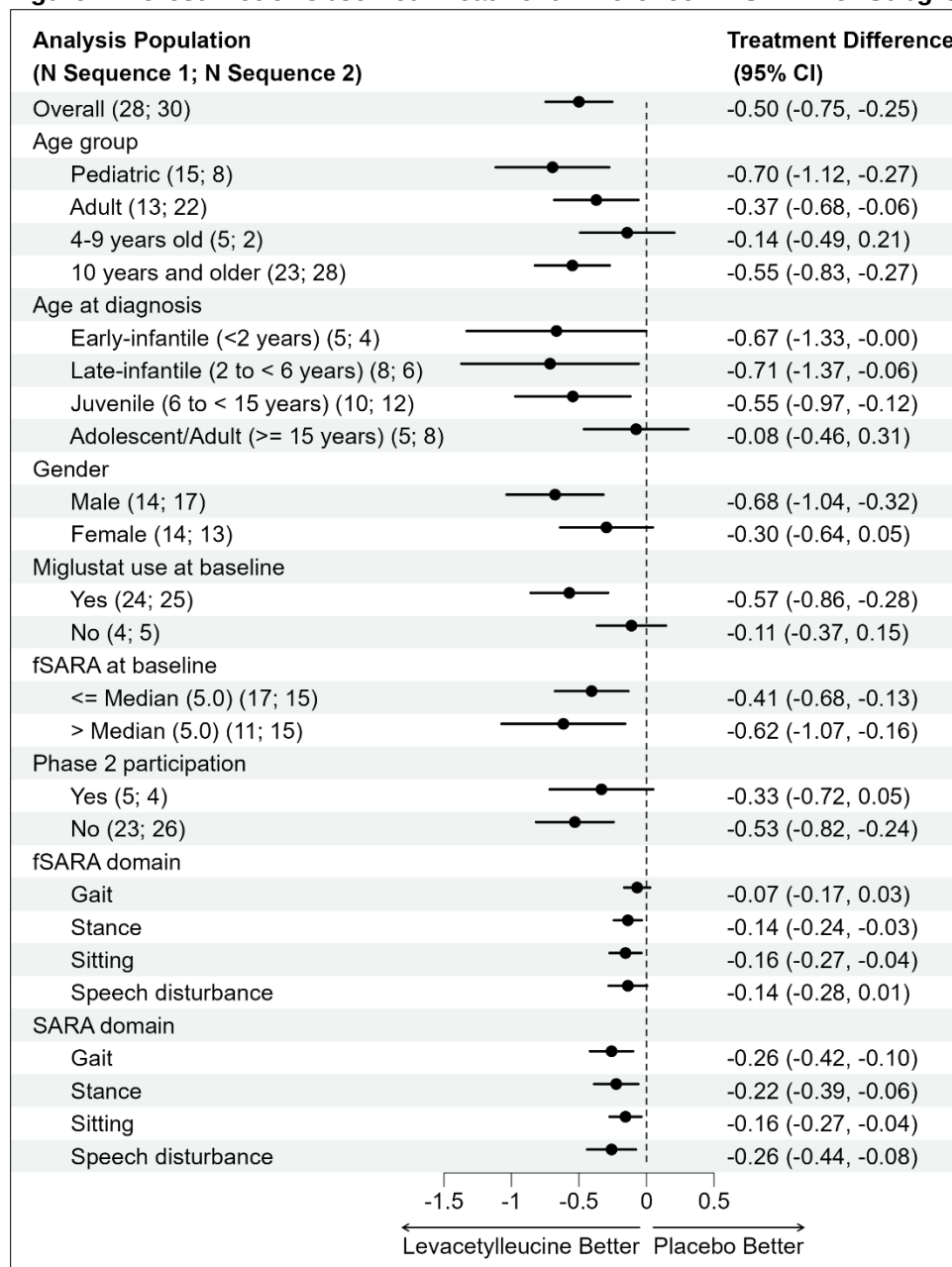
**Subgroup Analysis**

Figure 7 shows subgroup analyses based on the fSARA. Overall, the subgroup analyses showed a consistent trend of treatment difference, including for the subgroup of subjects not on background miglustat. For the subgroup of seven subjects with baseline age under 10 years, six subjects did not show treatment difference, while one subject experienced 1-unit improvement when treated with levacetylleucine. Similarly, among the nine subjects who did not take miglustat at baseline, eight subjects did not show treatment difference while one subject experienced 1-unit improvement with levacetylleucine.

In addition to demographic subgroup analyses, the statistical review team conducted domain-specific analyses for gait, stance, sitting, and speech disturbance domains. The observed treatment differences between levacetylleucine and placebo for rescored domains fSARA were -0.07 (95% CI: -0.17, 0.03) for gait, -0.13 (95% CI: -0.24, -0.03) for stance, -0.13 (95% CI: -0.25, -0.01) for sitting, and -0.13 (95% CI: -0.28, 0.01) for speech disturbance. While the observed difference was minimal in gait, the review team could not find any item that mainly drives the

result for total score. In addition, a consistent trend of treatment difference favoring levacetylleucine was observed in the total score for the four domains scored using the original SARA scale.

**Figure 7. Forest Plot of Observed Treatment Difference in fSARA for Subgroups With 95% CI**



Source: The statistical review team's analysis based on adsara2.xpt located at \\Cdsub1\levsprod\NDA219132\0011\m5\datasets\lib1001-301\analysis\adam\datasets\ No last observation carried forward (LOCF) was applied. Subgroup analyses were based on the observed mean differences from subjects who completed both visits (n=58). A 95% confidence interval was derived from the one-sample t-test based on normality assumption, which may have limited interpretations with small sample size. Subjects in Sequence 1 received levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II. Subjects in Sequence 2 received placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II. Abbreviations: CI = confidence interval; fSARA = functional Scale for the Assessment and Rating of Ataxia; N = number of subjects in treatment sequence; SARA = Scale for the Assessment and Rating of Ataxia

#### 6.2.2.4.4. Efficacy Results for Other Efficacy Endpoints

##### **Original SARA**

For the U.S. marketing application, the original SARA total score was evaluated as a key secondary endpoint. Using the same method as the primary analysis, the results showed an estimated treatment effect of -1.3 (95% CI: -1.9, -0.7) in original SARA total score with levacetylleucine compared to placebo with a p-value of <0.001 (Table 21).

The two-sample t-test adjusting for baseline values based on Period I data showed the estimated treatment difference of -1.39 (95% CI: -2.62, -0.16) with a p-value of 0.03, indicating a greater mean reduction in SARA total score in subjects who received levacetylleucine in the first period compared with those who received placebo.

**Table 21. Summary of Original SARA by Treatment Sequence, Trial IB1001-301**

| Parameter                                             | Total Score        |                      | Change From Baseline |                      |
|-------------------------------------------------------|--------------------|----------------------|----------------------|----------------------|
|                                                       | Sequence 1<br>N=30 | Sequence 2<br>N=30   | Sequence 1<br>N=30   | Sequence 2<br>N=30   |
| Baseline (Visit 2)                                    | N=30               | N=30                 |                      |                      |
| Mean (SD)                                             | 14.90 (7.49)       | 16.87 (7.51)         |                      |                      |
| Median (min, max)                                     | 13.2 (6.0, 33.0)   | 14.8 (7.0, 31.5)     |                      |                      |
| Period 1 (Visit 4)                                    | N=29               | N=30                 | N=29                 | N=30                 |
| Mean (SD)                                             | 12.52 (7.19)       | 16.27 (7.86)         | -1.93 (2.70)         | -0.60 (1.88)         |
| Median (min, max)                                     | 12.0 (1.0, 27.0)   | 13.8 (6.5, 32.0)     | -1.5 (-8.5, 3.5)     | -0.2 (-5.5, 2.0)     |
| Period 2 (Visit 6)                                    | N=28               | N=30                 | N=28                 | N=30                 |
| Mean (SD)                                             | 14.07 (6.53)       | 14.87 (8.09)         | -0.61 (2.88)         | -2.00 (2.18)         |
| Median (min, max)                                     | 13.0 (5.0, 27.5)   | 13.5 (2.5, 30.0)     | -0.2 (-6.5, 5.0)     | -1.5 (-5.5, 2.0)     |
| Estimated mean SARA score (SE) from MMRM <sup>1</sup> |                    |                      |                      |                      |
| Levacetylleucine                                      |                    | 13.87 (0.31)         |                      | -1.91 (0.31)         |
| Placebo                                               |                    | 15.15 (0.32)         |                      | -0.63 (0.32)         |
| Levacetylleucine-placebo<br>(95% CI)                  |                    | -1.28 (-1.91, -0.65) |                      | -1.28 (-1.91, -0.65) |
| P-value                                               |                    | 0.0001               |                      | 0.0001               |

Source: Table 11-10 of Trial IB1001-301 Clinical Study Report and the statistical review team's analysis based on adsara.xpt located at \\CDSESUB1\evsprod\NDA219132\0001\m5\datasets\ib1001-301\analysis\adam\datasets\

<sup>1</sup> MMRM adjusting for period, sequence, treatment, baseline value, and baseline-period interaction. Last observation carried forward (LOCF) was applied for Subject (b) (6) at Visit 6 and Subject (b) (6) at Visit 4.

Subjects in Sequence 1 received levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II. Subjects in Sequence 2 received placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II.

LOCF approach was used for the descriptive summaries in this table.

Abbreviations: CI = confidence interval; MMRM = mixed model for repeated measures; N = number of subjects in treatment sequence; SD = standard deviation; SE = standard error; SARA = Scale for the Assessment and Rating of Ataxia

Results for the following secondary and exploratory endpoints presented in [Table 22](#) also show a numerical trend favoring levacetylleucine:

- SCAFI total score
- Modified disability rating scale composite score (mDRS)
- Axial SARA defined as a sum of SARA item 1 to 4 (gait, stance, sitting, and speech)
- Niemann-Pick disease type C clinical severity scale (NPC-CSS) sum score (15 domains); NPC-CSS sum score (5 domains)

The SARA and SCAFI were used to assess neurological signs and functioning, the modified disability rating scale and NPC-CSS measured overall neurological status. More detailed results for secondary and exploratory analyses are available in Section [16.2](#).

**Table 22. Efficacy Results of Primary, Secondary, and Exploratory Endpoints, Trial IB1001-301**

| Endpoint                     | Change From Baseline       | Change From Baseline | Estimated Treatment Difference (SE) | 95% CI         | P-Value <sup>1</sup> |
|------------------------------|----------------------------|----------------------|-------------------------------------|----------------|----------------------|
|                              | Levacetylleucine Mean (SD) | Placebo Mean (SD)    |                                     |                |                      |
| Primary                      |                            |                      |                                     |                |                      |
| fSARA                        | -0.61 (1.05)               | -0.12 (1.23)         | -0.45 (0.13)                        | (-0.70, -0.19) | 0.0009               |
| Applicant's proposed primary |                            |                      |                                     |                |                      |
| mSARA                        | -1.66 (1.97)               | -0.67 (1.74)         | -0.96 (0.25)                        | (-1.45, -0.46) | 0.0003               |
| Key secondary                |                            |                      |                                     |                |                      |
| SARA                         | -1.97 (2.43)               | -0.60 (2.39)         | -1.28 (0.31)                        | (-1.91, -0.65) | 0.0001               |
| Secondary                    |                            |                      |                                     |                |                      |
| SCAFI total score            | 0.05 (0.27)                | -0.02 (0.31)         | 0.07 (0.04)                         | (0.0, 0.15)    | 0.06                 |
| mDRS                         | -0.03 (0.06)               | 0 (0.06)             | -0.02 (0.01)                        | (-0.04, 0)     | 0.03                 |
| Exploratory                  |                            |                      |                                     |                |                      |
| 15DNPCSS                     | -0.34 (2.24)               | 0.12 (2.12)          | -0.29 (0.34)                        | (-0.97, 0.40)  | 0.40                 |
| 5DNPCSS                      | -0.24 (1.84)               | 0.19 (1.5)           | -0.30 (0.22)                        | (-0.74, 0.15)  | 0.19                 |
| Axial SARA                   | -0.86 (1.38)               | 0.02 (1.66)          | -0.85 (0.19)                        | (-1.24, -0.47) | <0.001               |

Source: Table 7 of Clinical Overview located at [cdsesub1\evsprod\NDA219132\0001\m2\](#) and the statistical review team's analyses based on [adscafi.xpt](#), [adnpccss.xpt](#), [admdrs.xpt](#) located at [\\CDSESUB1\evsprod\NDA219132\0001\m5\datasets\ib1001-301\analysis\adam\datasets\](#) and [adscfi2.xpt](#) located at [\\CDSESUB1\evsprod\NDA219132\0011\m5\datasets\ib1001-301\analysis\adam\datasets\](#)

The mean change from baseline is summarized by pooling treatment at Visit 4 or Visit 6.

<sup>1</sup> Two-sided p-value. Nominal p-values are presented for secondary and exploratory endpoints.

Abbreviations: 5DNPCSS = 5-domain Niemann-Pick disease type C clinical severity scale; 15DNPCSS = 15-domain Niemann-Pick disease type C clinical severity scale; CI = confidence interval; fSARA = functional Scale for the Assessment and Rating of Ataxia; mDRS = modified disability rating scale; mSARA = the Applicant's modified Scale for the Assessment and Rating of Ataxia; SARA = Scale for the Assessment and Rating of Ataxia; SCAFI = Spinocerebellar Ataxia Functional Index; SD = standard deviation; SE = standard error

## 6.3. Key Efficacy Review Issues

### 6.3.1. Interpretability of the Primary Efficacy Endpoint

#### **Issue**

There are two issues that lead to uncertainty regarding whether the observed changes in the primary efficacy endpoint reflect a clinically meaningful benefit to patients with NPC. These issues include scoring and interpretability of the SARA and the assessment of clinically meaningful improvement in neurological symptoms, which are discussed below.

#### 6.3.1.1. SARA Domain Selection and Rescoring

The Applicant and FDA differed on which SARA domains reflected pragmatic, noticeable changes that communicated clinical benefit suitable for inclusion in a primary efficacy endpoint

(b) (4)

#### **Background**

The Agency recommended revising the response categories of the SARA so that the domain response options are distinct and clearly interpretable. The Agency recommended using only the four SARA domains of gait, stance, sitting, and speech (i.e., SARA domains #1, #2, #3, and #4, respectively; advice letter dated December 20, 2021; advice letter dated March 21, 2022). The Applicant defined the primary efficacy endpoint in Trial IB1001-301 based on the mSARA, which comprises 6 or the 8 domains evaluated by the SARA: gait (domain 1), speech disturbance (domain 4), finger chase (domain 5), nose-finger test (domain 6), fast alternating hand movement (domain 7), and heel-shin slide (domain 8). The Applicant stated that NPC clinical experts and patients with NPC/their caregivers indicated that fine motor, ambulation, and speech were the top NPC outcomes to measure, that the selected 6 domains accounted for 90% of the improvements observed in the phase 2 study, and that NPC experts indicated changes in SARA domains 5 through 8 were considered to be associated with functional activities for patients with NPC. Postural balance (sitting, stance) was not accounted for among responses, reflecting expert consensus that it is not a key outcome. Scoring of the SARA domains varies (e.g., gait comprises 9 levels, speech comprises 7 levels), which interferes with the interpretation of the total score.

#### **Assessment**

Consistent with Agency's approach in other rare progressive neurodegenerative indications ([Potashman et al. 2024b](#)), several domains of the SARA (finger chase, nose to finger, fast alternating hand movements, heel to shin slide) assess neurologic exam findings. Evidence demonstrating that a change in SARA domains 5 through 8 was directly associated with functional activities for patients was not available for review. These neurologic exam findings do not directly assess the patient's ability to function, nor do they reflect clinically meaningful change in a patient's ability to perform daily functions, making them unsuitable for inclusion in a primary efficacy endpoint to convey clinical benefit. The Agency acknowledges that postural control is not reported as an important outcome in NPC ([Parseghian 2019](#)); however, the measurement of sitting and stance are functional abilities where a change in scores clearly

correspond to daily functioning. As the Applicant did not revise the response categories of the SARA domains, the Agency rescored to create the same number of response categories across each domain ([Table 23](#)) to ensure equal representation of each domain in the total score and interpretability of a 1-point change as clinically meaningful ([Potashman et al. 2024a](#)).

### **Conclusion**

The Agency accepts the fSARA domains of gait (domain 1), stance (domain 2), sitting (domain 3), and speech (domain 4) with rescoring so that all domains have equal response categories.

#### 6.3.1.2. Interpretability of the SARA in Young Children

Ataxia and related domains are difficult to measure in young children with a progressive condition, a measurement challenge that is not specific to the SARA. SARA scores can have low reliability in developing young children with progressive conditions, which may interfere with interpretability ([Brandtsma et al. 2014](#)) ([Lawerman et al. 2017](#)). The Applicant indicated inter-child variation in SARA ratings may be mitigated by the cross-over study design; however, the small population of subjects <10 years old made interpretation challenging.

### **Conclusion**

Establishing efficacy in pediatric subjects <10 years old will rely on extrapolation from subjects ≥10 years old.

**Table 23. Agency Recommended Modified Domain Scores**

| <b>SARA Domain</b>           | <b>Original Item Score</b>                                                                         | <b>Modified Domain Score</b> |
|------------------------------|----------------------------------------------------------------------------------------------------|------------------------------|
| Domain 1: gait               | 0 = Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)     | 0                            |
|                              | 1 = Slight difficulties, only visible when walking 10 consecutive steps in tandem                  | 1                            |
|                              | 2 = Clearly abnormal, tandem walking >10 steps not possible                                        | 1                            |
|                              | 3 = Considerable staggering, difficulties in half-turn, but without support                        | 2                            |
|                              | 4 = Marked staggering, intermittent support of the wall required                                   | 2                            |
|                              | 5 = Severe staggering, permanent support of one stick or light support by one arm required         | 2                            |
|                              | 6 = Walking >10 m only with strong support (two special sticks or stroller or accompanying person) | 3                            |
|                              | 7 = Walking <10 m only with strong support (two special sticks or stroller or accompanying person) | 3                            |
| Domain 2: stance             | 8 = Unable to walk, even supported                                                                 | 4                            |
|                              | 0 = Normal, able to stand in tandem for >10 s                                                      | 0                            |
|                              | 1 = Able to stand with feet together without sway, but not in tandem for >10s                      | 1                            |
|                              | 2 = Able to stand with feet together for >10 s, but only with sway                                 | 1                            |
|                              | 3 = Able to stand for >10 s without support in natural position, but not with feet together        | 2                            |
|                              | 4 = Able to stand for >10 s in natural position only with intermittent support                     | 3                            |
|                              | 5 = Able to stand >10 s in natural position only with constant support of one arm                  | 3                            |
| Domain 3: sitting            | 6 = Unable to stand for >10 s even with constant support of one arm                                | 4                            |
|                              | 0 = Normal, no difficulties sitting >10 sec                                                        | 0                            |
|                              | 1 = Slight difficulties, intermittent sway                                                         | 1                            |
|                              | 2 = Constant sway, but able to sit >10 s without support                                           | 2                            |
|                              | 3 = Able to sit for >10 s only with intermittent support                                           | 3                            |
| Domain 4: speech disturbance | 4 = Unable to sit for >10 s without continuous support                                             | 4                            |
|                              | 0 = Normal                                                                                         | 0                            |
|                              | 1 = Suggestion of speech disturbance                                                               | 1                            |
|                              | 2 = Impaired speech, but easy to understand                                                        | 1                            |
|                              | 3 = Occasional words difficult to understand                                                       | 2                            |
|                              | 4 = Many words difficult to understand                                                             | 3                            |
|                              | 5 = Only single words understandable                                                               | 4                            |
|                              | 6 = Speech unintelligible / anarthria                                                              | 4                            |

Source: Reviewer generated table adapted from Table 1 of FDA's information request dated March 7, 2024  
Abbreviation: SARA = Scale for the Assessment and Rating of Ataxia

### 6.3.1.3. Clinically Meaningful Benefit in Neurological Symptoms

There is uncertainty regarding whether the observed treatment effect substantiated a clinically meaningful treatment benefit in neurological symptoms in patients with NPC receiving levacetylleucine.

#### **Background**

In rare disease research, there is often no established estimate of clinically meaningful within-subject change for a specific disease or condition. Here, the Applicant's primary endpoint was constructed using the mSARA. The Applicant's proposed meaningful within-subject change threshold<sup>5</sup> to aid in the interpretation of the proposed primary endpoint results in Trial IB1001-301 was based on (b) (4) and the Applicant's interpretation of the original SARA scale. Specifically, the Applicant identified (b) (4) as representing clinically meaningful change to patients with NPC. The Applicant did not provide justification for the proposed (b) (4) change on the mSARA score (b) (4). (b) (4)

Lastly, to evaluate whether the observed treatment effect was clinically meaningful, the Applicant (b) (4) and concluded that there is clinically meaningful treatment benefit with levacetylleucine.

#### **Assessment**

Given the issues with the mSARA discussed in Section 6.3.1.1 and the limited qualitative and quantitative evidence to support the Applicant's proposed clinically meaningful within-subject change threshold, the Agency disagrees with proposed clinically meaningful within-subject change threshold (b) (4) in the mSARA.

The Agency conducted an independent assessment of clinical meaningfulness of the primary efficacy endpoint results based on the fSARA by performing responder analyses, quantitative analyses at the individual subject level, and evaluating exploratory endpoint evidence from exit surveys.

While the Agency recommends the use of anchor-based methods to interpret endpoints for clinical outcome assessments whose scores are not directly interpretable, the review team

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<sup>5</sup> Referred to as "clinically important difference" in the Applicant's submission.

determined the fSARA response options represented distinct and meaningfully different health states, thus making the endpoint scores directly interpretable ([April 2023](#)) such that a 1-point change in any fSARA domain is indicative of a meaningful change (either improvement or worsening) to patients with NPC (see Section [6.3.1.1](#)). Furthermore, because each domain in the fSARA represents an important aspect of daily functioning, improvement in any domain regardless of the absence of change/presence of worsening in other domains provides independent evidence of meaningful clinical benefit to patients.

The Agency conducted responder analyses and defined a responder as a subject who had at least 1-point improvement from baseline in any of the four fSARA domains (i.e., gait, stance, sitting, and speech). The responder analysis was performed for subjects who completed both Visit 4 and Visit 6. Consequently, Subjects (b) (6) were excluded from the analysis. For brevity, the review team will interchange the term ‘treatment period’ and ‘period’. There were 33 treatment responders (56.8%) in the trial: 13 subjects (22.4%) responded in the levacetylleucine period and not in the placebo period, 2 subjects (3.4%) responded in the placebo period and not in the levacetylleucine period, and 18 subjects responded in both periods (31%). The estimated difference in response rates between the subjects who responded in only one of the treatment periods was 18.9% (95% CI using 10,000 resampling datasets: 6.9%, 31.0%). Among subjects who responded in at least one period during the trial, there were a total of 31 responders (53.4%) in the levacetylleucine period, and 20 responders (34.5%) in the placebo period ([Table 24](#)).

To test nonequality of treatment effects between levacetylleucine and placebo in the dichotomous crossover data, the Mainland-Gart test was conducted. Since the number of subjects who contribute to the contingency table is small, we used a Fisher’s exact version of the Mainland-Gart test to evaluate non-equality of treatment effects. The p-value of 0.011 suggests that there is strong evidence that the effects on subjects having at least 1-point improvement in any domain are not equal between placebo and levacetylleucine, favoring levacetylleucine.

**Table 24. Responder Analysis for fSARA**

| Variable                                  | Sequence 1 | Sequence 2 | Total     | p-Value |
|-------------------------------------------|------------|------------|-----------|---------|
| Randomized subjects, N                    | 60         | 60         | 60        |         |
| Completed subjects <sup>1</sup> , n (%)   | 28 (100)   | 30 (100)   | 58 (100)  |         |
| Subjects with response, n (%)             |            |            |           |         |
| Responded to levacetylleucine             | 15 (53.6)  | 16 (53.3)  | 31 (53.4) |         |
| Responded to placebo                      | 11 (39.3)  | 9 (30.0)   | 20 (34.5) |         |
| Subjects with discordant responses, n (%) |            |            |           |         |
| Responded only to levacetylleucine        | 4 (14.3)   | 9 (30.0)   | 13 (22.4) |         |
| Responded only to placebo                 | 0 (0.0)    | 2 (6.7)    | 2 (3.4)   |         |
| Fisher’s exact test <sup>2</sup>          |            |            |           | 0.011   |

Source: The statistical review team’s analysis based on adsara2.xpt located at [\\Cdssub1\evsprod\NDA219132\0011\m5\datasets\lib1001-301\analysis\adam\datasets\](#)

<sup>1</sup> Subjects who completed both Visit 4 and Visit 6. No last observation carried forward (LOCF) was used.

<sup>2</sup> The Mainland-Gart test is a variation on McNemar’s test that takes treatment order into account. Similar to the McNemar’s test, the Mainland-Gart test is based on pairs of discordant responses in Table 7. A two-sided p-value is computed using Fisher’s exact test version of the Mainland-Gart test.

Subjects in Sequence 1 received levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II. Subjects in Sequence 2 received placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II.

Abbreviations: fSARA = functional Scale for the Assessment and Rating of Ataxia; N = number of subjects in treatment sequence; n = number of subjects with given characteristic; SARA = Scale for the Assessment and Rating of Ataxia

Note that an at least 1-point improvement in any fSARA domain does not necessarily imply an at least 1-point improvement in fSARA total score. However, among those who had 1-point improvement in any domain of fSARA, only one subject had total score worsened from baseline in both periods. This subject had an at least 1-point improvement in the speech domain in both periods, but an at least 1-point deterioration in the stance and sitting domains at the same time. Therefore, a responder analysis excluding this subject produces the same results as those in [Table 24](#). [Table 25](#) shows the number of subjects who achieved an at least 1-point improvement in an individual domain, and in any of the four fSARA domains.

**Table 25. Number of Responders in fSARA by Domain and Treatment Sequence**

| Domain<br>Treatment<br>Sequence | N <sup>1</sup> | No Response in<br>Any Treatments | Response in<br>Period I Only | Response in<br>Period II Only | Response in Both<br>Treatments |
|---------------------------------|----------------|----------------------------------|------------------------------|-------------------------------|--------------------------------|
| <b>Gait</b>                     |                |                                  |                              |                               |                                |
| Sequence 1                      | 28             | 23                               | 2                            | 0                             | 3                              |
| Sequence 2                      | 30             | 22                               | 2                            | 4                             | 2                              |
| <b>Stance</b>                   |                |                                  |                              |                               |                                |
| Sequence 1                      | 28             | 21                               | 3                            | 1                             | 3                              |
| Sequence 2                      | 30             | 26                               | 0                            | 4                             | 0                              |
| <b>Sitting</b>                  |                |                                  |                              |                               |                                |
| Sequence 1                      | 28             | 25                               | 0                            | 0                             | 3                              |
| Sequence 2                      | 30             | 22                               | 1                            | 3                             | 4                              |
| <b>Speech</b>                   |                |                                  |                              |                               |                                |
| Sequence 1                      | 28             | 20                               | 2                            | 1                             | 5                              |
| Sequence 2                      | 30             | 14                               | 1                            | 3                             | 2                              |
| <b>Any Domain</b>               |                |                                  |                              |                               |                                |
| Sequence 1                      | 28             | 13                               | 4                            | 0                             | 11                             |
| Sequence 2                      | 30             | 12                               | 2                            | 9                             | 7                              |

Source: The statistical review team's analysis based on adsara2.xpt located at [\\CdseSub1\levsprod\NDA219132\0011\m5\datasets\lib1001-301\analysis\adam\datasets](#)

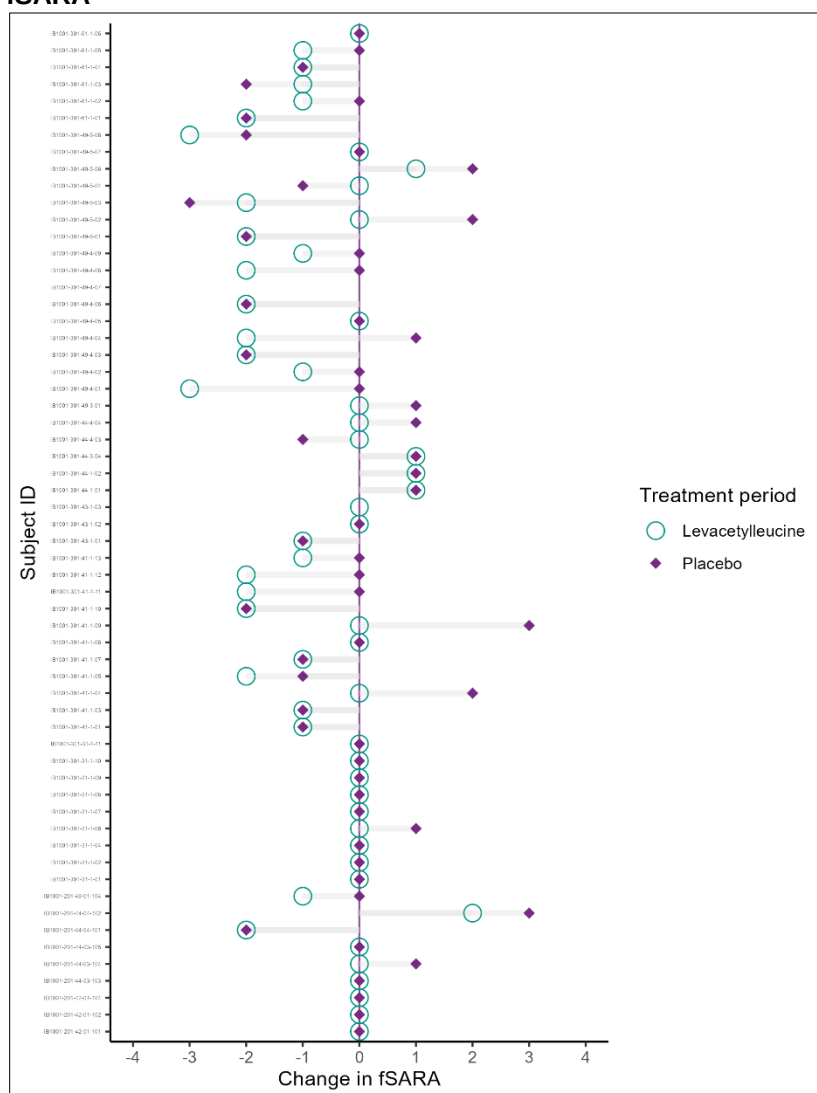
<sup>1</sup> Subjects who completed both Visit 4 and Visit 6. No last observation carried forward (LOCF) is used.

Subjects in Sequence 1 received levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II. Subjects in Sequence 2 received placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II.

Abbreviations: fSARA = functional Scale for the Assessment and Rating of Ataxia; N = number of subjects in treatment sequence

Additionally, given the heterogeneity of NPC, it is important to evaluate individual changes in the total fSARA and in each of its four domains. For that purpose, dumbbell plots of change from baseline to EOT (i.e., Visit 4 or Visit 6) in fSARA ([Figure 8](#)) and each of the four domain scores ([Figure 32](#) to [Figure 35](#) in Section 16.3) were visualized. The dumbbell plot ([Figure 8](#)) shows the change from baseline to end of treatment in fSARA during the levacetylleucine period (green circle) and placebo period (purple diamond) for each subject. During the levacetylleucine period, 72.9% of subjects experienced no change in fSARA from baseline compared to 72.4% of subjects during the placebo period. For those who experienced changes, more subjects experienced improvement while in the levacetylleucine period (20.3%) as compared to when they were in the placebo period (15.5%), whereas more subjects experienced worsening while in the placebo period (12.1%) than while in the levacetylleucine period (6.8%). Subjects in general experienced more improvement in the fSARA when they received levacetylleucine as compared to when they received placebo (i.e., the green open circle is on the left of the purple diamond), with few exceptions (e.g., 4 [6.9%] subjects improved more in the fSARA on placebo than when they were in the levacetylleucine period).

**Figure 8. Dumbbell Plot of Change From Baseline to End of Treatment (i.e., Visit 4 or Visit 6) in fSARA**



Source: Reviewer's Figure using adsara2.xpt

Abbreviation: fSARA = functional Scale for the Assessment and Rating of Ataxia

Overall, similar trends of change described above were observed across the four domains. See Section 16.3 for a detailed discussion.

The Applicant conducted exploratory exit surveys at the conclusion of Trial IB1001-301 (i.e., Visit 6 before unblinding) to provide additional evidence of clinical meaningfulness and subject experiences with levacetylleucine. Subjects and caregivers provided reports of improvements in neurological symptoms (e.g., swallowing, reduction in falls, cataplexy, cognition). The exploratory evidence from the exit surveys may be viewed as supportive for the broad treatment effects related to neurological symptoms. From a clinical perspective, NPC is a progressive, neurodegenerative disease where neurological symptom stabilization and/or improvement of any magnitude for any neurological symptom would not be expected given the known natural history of the disease. Patients, caregivers and clinical experts in NPC have

indicated that slowing of disease progression as well as improvement in neurological symptoms would be meaningful ([Parseghian 2019](#)).

### **Conclusion**

While the observed average treatment effect in fSARA is -0.45, at least a 1-point improvement in any of the four fSARA domains were seen more often when subjects received levacetylleucine than received placebo. As improvements in neurological symptoms would not be expected given the known natural history of NPC, this change is considered to be clinically meaningful.

## **6.3.2. Establishment of Drug Effectiveness in Patients <10 Years Old**

### **6.3.2.1. Body Weight $\geq 15$ kg**

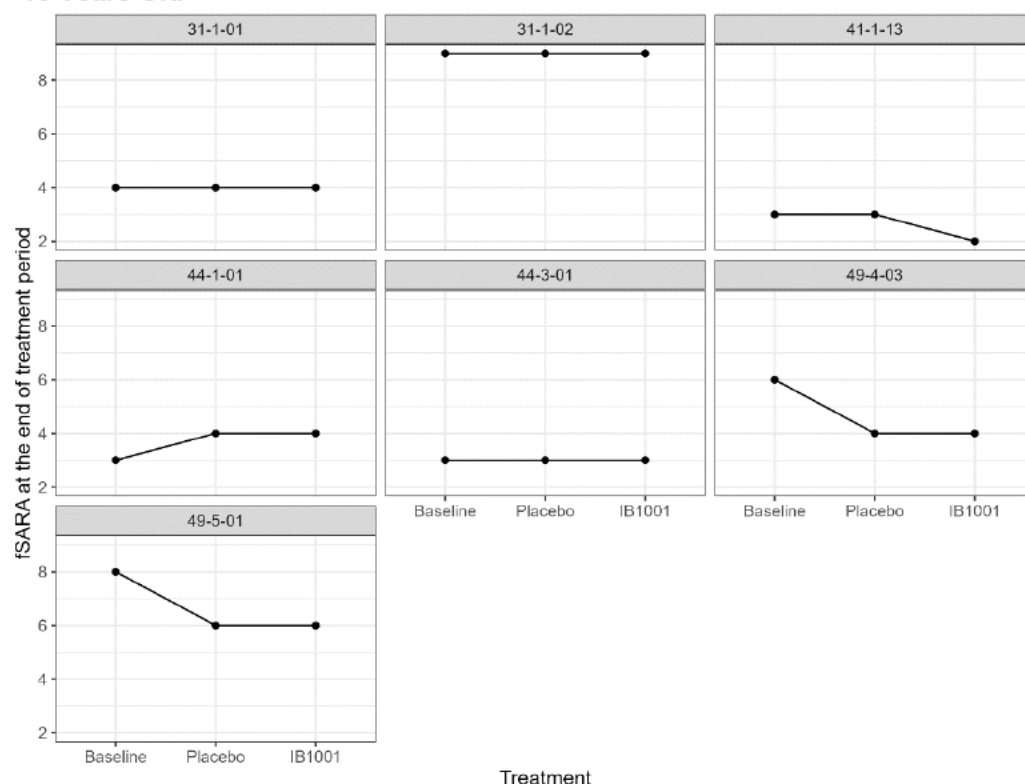
#### **Issue/Background**

Because of the uncertainty regarding the interpretation of the primary efficacy endpoint in subjects <10 years old (body weight  $\geq 15$  kg) and the very limited number of studied subjects in this age group, there was a concern regarding the adequacy of the data from Trial IB1001-301 to establish efficacy patients with NPC who are <10 years old.

#### **Assessment**

Of the 60 randomized subjects in Trial IB1001-301, 7 subjects (11.7%) were <10 years old. According to a subgroup analysis, the observed treatment difference for this subpopulation was -0.14 (95% CI: -0.49, 0.21; [Figure 7](#)). Among the 7 subjects <10 years old, only one subject showed a treatment difference between IB1001 and placebo in fSARA score at the end of treatment periods ([Figure 9](#)). Due to the small number of subjects in this subgroup, the review team determined that the efficacy data from Trial IB1001-301 were not sufficient to demonstrate a treatment benefit in subjects <10 years old.

**Figure 9. Individual Trajectory of fSARA Total Score at the End of Treatment Period for Subjects <10 Years Old**



Source: The statistical review team's analysis based on adsara2.xpt located at <\\CDSESUB1\evsprod\NDA219132\0011\m5\datasets\ib1001-301\analysis\adam\datasets\adsara2.xpt>  
 Subjects (b) (6) were randomized to Sequence 1 (levacetylleucine-placebo) and subjects (b) (6) were randomized to Sequence 2 (placebo-levacetylleucine).  
 Abbreviation: fSARA = functional Scale for the Assessment and Rating of Ataxia

While there can be predominant visceral manifestations with very early symptom onset, when symptoms begin in the late infantile period or afterward, they are predominantly neurodegenerative. Because NPC is a genetic disease with the same underlying disease pathophysiology across age groups, levacetylleucine is expected to exert its treatment effect on the neurological symptoms of NPC similarly across age groups. Given the shared underlying disease pathophysiology and primary manifestations of NPC in subjects <10 years old with those ≥10 years of age, the review team determined that it would be appropriate to extrapolate the efficacy data from subjects ≥10 years to the younger population from Trial IB1001-301 by comparing PK data between subjects in these two age groups from Trials IB1001-201, IB1001-202, and IB1001-301.

### PK Exposures <10 Years Old (Body Weight ≥15 kg) vs. ≥10 Years Old

The exposures (daily AUC and maximum plasma concentration [ $C_{max}$ ]) of IB1001 were estimated for each subject who received the proposed dosing regimen in Trials IB1001-201, IB1001-202, and IB1001-301 and are summarized by age groups (≥10 years and <10 years) in Table 26. The daily AUC and  $C_{max}$  of IB1001 in pediatric subjects <10 years of age were generally similar to those in the older pediatric subject group (≥10 years of age). Thus, the overall PK results would provide support to extrapolate efficacy from older pediatric subjects

(≥10 years old) to younger pediatric subjects (<10 years old). Of note, the youngest pediatric subject included in the analysis was 6 years old.

**Table 26. Exposure Comparison of IB1001 by Age Groups**

| <b>Age Group</b>         | <b>&lt;10 Years Old (n=13)</b> | <b>≥10 Years Old (n=82)</b> |
|--------------------------|--------------------------------|-----------------------------|
| Daily AUC (h·µg/mL)      |                                |                             |
| Mean (SD)                | 32.3 (11.2)                    | 26.6 (7.0)                  |
| C <sub>max</sub> (µg/mL) |                                |                             |
| Mean (SD)                | 7.2 (1.4)                      | 6.5 (2.1)                   |

Source: Reviewer's analysis

Individual PK exposures were derived using the individual predicted PK parameters from population PK analysis.

Abbreviations: AUC = area under the concentration-time curve; C<sub>max</sub> = maximum plasma concentration; n = number of subjects with given characteristic; SD = standard deviation

### **Conclusion**

The establishment of efficacy in pediatric patients <10 years old relies on extrapolation of efficacy seen in subjects ≥10 years old in Trial IB1001-301. The review team determined that extrapolation of efficacy from subjects ≥10 years old to patients <10 years old is scientifically justified based on the same underlying disease pathophysiology, similarity in clinical manifestations, and the expected same therapeutic mechanism of action (MOA) across age groups. The PK findings from Trials IB1001-201, IB1001-202, and IB1001-301 support this extrapolation, as they provide evidence that the evaluated dose in subjects <10 years old results in similar exposure to subjects ≥10 years old. Therefore, the efficacy results from Trial IB1001-301 and PK data from Trials IB1001-201, IB1001-202, and IB1001-301 support the effectiveness of IB1001 in patients <10 years old and support a labeled indication for pediatric patients weighing ≥15 kg (refer to subsection [below](#) for a discussion on why the available data do not support dosing in patients <15 kg).

(b) (4)

### 6.3.3. Adequacy of Confirmatory Evidence

#### **Issue/Background**

SEE, the regulatory requirement for approval (under 21 CFR 314.126), generally consists of evidence from at least two adequate and well-controlled trials. In certain circumstances, a single adequate and well-controlled trial demonstrating efficacy may be sufficient to generate SEE if there is adequate CE. Such circumstances are described in the FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* ([December 2019](#)), which includes: the persuasiveness of the single investigation; the robustness of the CE; the seriousness of the disease, particularly when there is an unmet medical need; the size of the patient population; and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation. These criteria and considerations are all relevant to the levacetylleucine development program for NPC, a rare and serious disease with an unmet need. Because the levacetylleucine NDA includes only one adequate and well-controlled trial, the review team sought to assess whether there is adequate CE to generate SEE. As stated in the FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* ([September 2023](#)), the strength of the single adequate and well-controlled clinical trial informs the quantity and quality of CE needed to substantiate the results of the trial. The highly persuasive results of the single trial, Trial IB1001-301 (described in Section [6.2.2.4.3](#)), influenced the review team's determination of the level of strength needed for the data to serve as CE in this application.

The Applicant submitted data from multiple sources to serve as potential CE of the treatment effect of levacetylleucine observed in Trial IB1001-301. These sources, which included nonclinical studies (mechanistic in vitro and animal disease model) and clinical trials (a phase 2 single arm trial in patients with NPC and a phase 2 single arm trial in patients with GM2 gangliosidosis), are discussed in the *Assessment* section [below](#).

#### **Assessment**

##### **Nonclinical Evidence: Mechanistic Studies (In Vitro)**

Data to support the MOA for levacetylleucine were derived from published literature. The Applicant described data suggesting that in cultured Chinese hamster ovary cells, treatment with levacetylleucine at a concentration of 1mM for 24 hours, was associated with a modest reduction in lysosomal volume, sphingosine, GSLs, and a very modest reduction in stored cholesterol. In NPC patient-derived fibroblasts, treatment with levacetylleucine was also associated with a modest reduction in apparent lysosomal volume when cells were cultured for 7 days with 1mM levacetylleucine. These studies suggest that the drug has the potential to reduce stored intracellular lipid; however, the MOA, including any molecular targets by which it may elicit these effects, is unclear.

##### **Nonclinical Evidence (In Vivo)**

In *Npc1*<sup>-/-</sup> mice, a nonclinical mouse model of NPC, pre-symptomatic (from the age of 3 weeks) treatment with levacetylleucine was also associated with a modest increase in survival and a reduction in markers of neuroinflammation (CD68 staining) in the cerebellum (see

Section [13.2.2](#)). These changes were not monitored in the clinical trial to evaluate the association of change in magnitude of GSL and neuroinflammation with the dose of levacetylleucine and efficacy. Taken together, the nonclinical data support a potential mechanism by which levacetylleucine may reduce intracellular cholesterol and may improve survival when administered pre-symptomatically in mice; however, because the same parameters were not assessed in clinical trials, there is no direct correlation between these data and the efficacy endpoints measured in subjects.

### **Additional Clinical Data**

The additional clinical data submitted by the Applicant as potential sources of clinical CE include the open-label study of levacetylleucine in patients with NPC (Trial IB1001-201), an open-label study of levacetylleucine in individuals with GM2 gangliosidosis (Trial IB1001-202), and several case series detailing off-label use of Tanganil (N-acetyl-DL-leucine) in NPC and GM2 gangliosidosis.

#### **Trial IB1001-201**

The results from Trial IB1001-201 are based on the rater-blinded CI-CS in the parent study. Thirty-three subjects with NPC were enrolled in the trial, which consisted of a 2-week baseline period, a 6-week treatment period, and a 6-week washout period. The CI-CS measured each subject's change in performance on their primary anchor test (8MWT or 9HPT-D) between the beginning and end of the treatment and washout periods. Improvements were observed in the treatment period for the selected anchor test with the mean CI-CS score of 0.5 (median=1), but performance declined by the EOW with the mean CI-CS score of -0.4 (median=-0.2). The Hodges-Lehmann estimate for the median difference of CI-CS score between the two periods was 1.0 (90% CI: 0.25, 1.75), indicating improvement in the treatment period and deterioration during the washout period. The associated Wilcoxon signed rank test resulted in a one-sided p-value of 0.03. The rater-blinded CI-CS endpoint relied on an investigator-selected primary anchor test. Each anchor test was performed by all subjects as a component of the SCAFI (a secondary endpoint). The timed SCAFI subtests showed minimal changes in 8MWT in both periods, with mean changes of -1.1 and -0.3 seconds for the treatment and washout periods, respectively, which were considered within measurement error. The 9HPT-D showed minor changes in the treatment period with a mean change of 1.1 seconds, but a deterioration with a mean change of 7.7 seconds after the washout.

While Trial IB1001-201 was an open-label study and therefore was susceptible to bias that decreases the persuasiveness of these results, the methodology of blinding the CI-CS raters to time and treatment assignment increases the interpretability of the resulting scores by reducing the influence of knowledge of treatment assignment.

The CI-CS results supported by the timed SCAFI subtests indicate either improvement or stability in the treatment period, and either deterioration or stability in the washout period. Consequently, the Agency concludes that Trial IB1001-201 provided sufficient supportive evidence that the subjects' performance on the selected measures of gait and fine motor function is comparatively favorable in the treatment period. Refer to Section [6.2.1](#) for detailed results.

## **Trial IB1001-202**

Trial IB1001-202 was a phase 2 study of levacetylleucine in 30 subjects with GM2 gangliosidosis, a lysosomal storage disorder with some shared pathophysiological mechanisms that could potentially benefit from treatment with levacetylleucine. The trial design was identical to that of Trial IB1001-201 in subjects with NPC, and the results from Trial IB1001-202 are based on the rated-blinded CI-CS in the parent study. Similar to Trial IB1001-201, the Trial IB1001-202 parent study also met its primary endpoint CI-CS. The mean CI-CS in the treatment period was 0.34 (SD=1.59, median=0.50), while the mean CI-CS in the washout period was -0.36 (SD=1.33, median=-0.50). The Hodges-Lehmann estimate was 0.75 (90% CI: 0.00, 1.50), indicating a nominally significant effect for levacetylleucine in terms of improvement during the treatment period followed by deterioration during washout.

Given the similar pathophysiological mechanisms of NPC and GM2 gangliosidosis and the same expected MOA of levacetylleucine in the two diseases, the results from Trial IB1001-202 may provide some support for the effectiveness of levacetylleucine in lysosomal storage disorders such as NPC. However, since levacetylleucine has not been approved in the United States for the treatment of GM2 gangliosidosis (and thus, the efficacy has not been established), the review team determined that the results of IB1001-202 are not adequate to be used as CE of effectiveness of levacetylleucine for NPC.

## **Real World Data**

The Applicant submitted three published case series describing the off-label use of Tanganil (N-acetyl-DL-leucine) (b) (4)

. The exact number of individual patients with NPC is not clear as several may overlap between the submitted publications. Although these publications provided early proof-of-concept for further evaluation of the components of N-acetyl-DL-leucine as a potential treatment for NPC early in the development of levacetylleucine, they were not considered as supportive data of the findings of Trial IB1001-301 (b) (4)

## **Conclusion**

The several different sources of data described above were submitted to serve as CE of the treatment benefit of levacetylleucine observed in Trial IB1001-301. Each of these sources of data has considerable limitations, as detailed above, that preclude their acceptability to serve as CE on their own. However, the review team determined that the integration of the clinical data from Trial IB1001-201 along with the nonclinical data together constitute acceptable CE for this application, which included a highly persuasive clinical trial.

As stated in the FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023), the strength of the single adequate and well-controlled clinical trial informs the quantity and quality of CE needed to substantiate the results of the trial. As detailed in Section 6.2.2.4.3, Trial IB1001-301 was considered highly persuasive due to its randomized, blinded, placebo-controlled trial design and because it demonstrated a clinically meaningful

treatment benefit on the primary endpoint (p-value: <0.001). The review team determined that, in the context of these highly persuasive results from the pivotal trial, the strength of the submitted CE – specifically, the results of Trial IB1001-201 and the supportive mechanistic nonclinical data – was adequate to substantiate the results of Trial IB1001-301. Together, Trial IB1001-301 and the CE establish SEE of levacetylleucine for the treatment of NPC, a rare disease with an unmet therapeutic need. The data from both the adequate and well-controlled trial (Trial IB1001-301) and the CE are adequate to support use of levacetylleucine either with or without background concomitant miglustat.

### 6.3.4. Uncertainty Regarding Durability of Treatment Effect

#### **Issue/Background**

The single adequate and well-controlled trial, Trial IB1001-301, assessed the efficacy of levacetylleucine for NPC over a treatment period of 12 weeks. Because treatment with levacetylleucine beyond 12 weeks occurred only during the OLE periods of Trial IB1001-301 and IB1001-201, the interpretability of the efficacy data to support long-term use was limited.

#### **Assessment**

For the pivotal Trial IB1001-301, the Applicant initially proposed a placebo-controlled trial duration of 6 weeks based on preliminary findings from their open-label study, Trial IB1001-201. During a Type C meeting held on May 27, 2001, a minimum placebo-controlled duration of 12 weeks for Trial IB1001-301 was advised to the Applicant by the FDA. Trial IB1001-301 incorporated 12 weeks of placebo-controlled treatment as agreed upon, followed by an OLE study that is ongoing. Subjects who completed the trial were eligible to continue open-label treatment with levacetylleucine for up to 2 additional years. After a midcycle meeting with the Applicant in May 2024 during the review of this NDA, the Applicant provided a high-level summary of data for the first year of the extension study. The primary endpoint for the EP is not the same as for the parent study, thus a comparison of trial outcomes from 12 weeks of placebo-controlled treatment to the first year of open-label treatment would be challenging due to the different timing of assessments and prespecified endpoints. The endpoint for the EP is the change in 5DNPCCSS from baseline to the EOT.

The Applicant reported that 54 subjects enrolled in the extension study after completion of Trial IB1001-301 and that all have completed the first 6 months of open-label treatment (Visit 8). After 12 months from randomization baseline, the mean change on the 5DNPCCSS was -0.115 ( $\pm 2.60$ ). The Applicant compared the mean change to that of published cohorts, however given the lack of individual subject data for either the EP or the cohorts used for comparison, we did not consider this comparison in our assessment. Generally, NPC is expected to progress after the onset of neurological symptoms, thus a mean change that suggests decrease (rather than a mean increase, which would suggest worsening) of 5DNPCCSS scores may indicate potential disease stabilization and/or improvement in a portion of trial subjects, but this interpretation is limited by the absence of a control group.

The Applicant also provided summary data from their version of the mSARA, the total SARA, and the fSARA, (b) (4)

(b) (4) This information is limited by the lack of a control group as noted above, as well as by the different time periods between treatment groups in terms of their open-label treatment baseline (i.e., depending on whether they were on treatment during the first or second treatment periods of the parent study), and because the high-level and summary nature of this information could not be independently verified by the FDA.

Trial IB1001-201 included a 6-week initial treatment period with a rater-blinded primary endpoint, followed by continued open-label treatment with levacetylleucine for up to a total of 2 years (with a 6-week washout period between years 1 and 2 of additional open-label treatment). The primary endpoint for the EP of Trial IB1001-201 was also the change in 5DNPCCSS from baseline to the EOT. A total of 19 subjects enrolled in the EP and 13 subjects completed 2 additional years of treatment. After 12 months of treatment with levacetylleucine from the start of the EP, the mean change on the 5DNPCCSS for those with available assessments at baseline (Visit 7) and Visit 10 was 0.88 (SD=2.60) based on 17 subjects. After 2 years of EP (Visit 7 versus Visit 12), the mean change on the 5DNPCCSS was 1.75 (SD=2.56) based on 12 subjects.

As detailed in Section 6.2.1, there was a high drop-out rate for the trial that was likely impacted by the COVID-19 pandemic and associated health concerns as well as travel and activity restrictions, thus the results of the EP are difficult to interpret. Additionally, because the neurological symptoms of NPC are expected to progress, a worsening in 5DNPCCSS scores over the course of 2 years is not unexpected; however, without a concurrent control group for comparison, we could not make definitive conclusions regarding the results of the EP of Trial IB1001-201.

### **Conclusion**

The 12 weeks of placebo-controlled data from Trial IB1001-301 followed by high-level summary data from the EP suggesting continued mean improvement and/or relative stability in neurological symptoms after 1 year provide reasonable scientific justification for the long-term use of levacetylleucine. Although some uncertainty remains regarding the long-term efficacy (greater than one year) of levacetylleucine, the data are adequate to support a labeled indication for chronic therapy.

## **6.3.5. Proposed Indication**

### **Issue/Background**

The Applicant proposed an indication (b) (4). During the Midcycle review meeting on May 8, 2024, the Agency noted (b) (4).

### **Assessment**

At the request of the Agency, the Applicant provided their justification (b) (4) indication in a Clinical Information Amendment on May 17, 2024. (b) (4)

(b) (4)

As detailed in Section 6.3.1, the 4-domain fSARA that assesses gait, stance, sitting, and speech disturbance with modified scoring is the Agency-recommended approach to using the SARA for the endpoint and efficacy analyses in Trial IB1001-301.

(b) (4)

The Agency independently applied the Applicant's approach of examining each SARA domain and considering the neurological features and functional changes measured for domains 1 to 4 of the fSARA. Whether these changes may be influenced by other neurological symptoms of NPC, rather than ataxia alone, was then considered. The symptoms in subjects with late-infantile onset of disease or later (>2 years of age) are primarily neurological, including: ataxia, vertical supranuclear gaze palsy, dysarthria, cognitive impairment, dysphagia, dystonia, seizures, cataplexy, and hypotonia (Patterson 1993). For each of the 4 fSARA domains, there are score response options that could reflect either ataxia or another neurological symptom (or, in many cases, likely a combination of several neurological symptoms). Examples are tandem gait or standing with feet together being impacted by dystonia, sway while sitting being impacted by low truncal tone, and speech being impacted by a combination of cognitive impairment and orofacial dyskinesia. The SARA was originally intended to evaluate cerebellar ataxia and was developed in patients with spinocerebellar ataxia. While each category is geared toward identifying features of ataxia specifically, in patients with NPC, there is more likely a combination of ataxia and other heterogeneous neurological symptoms contributing to their scores.

With respect to the other, non-neurological symptoms of NPC, the most common systemic symptoms include neonatal jaundice, hepatomegaly, and splenomegaly. In general, the visceral symptoms tend to predominate and are more severe with early onset of disease symptoms. However, while the proportion of systemic manifestations declines with late age of onset, some patients have a history of neonatal jaundice and/or hepatosplenomegaly as early as in infancy, before the onset of neurological symptoms as late as in adulthood. The systemic manifestations of NPC were not assessed in Trial IB1001-301. Finally, the inclusion criteria for Trial IB1001-301 selected for subjects with neurological symptoms defined as a SARA score of 7 to 34 (out of 40) points and either a score of 2 to 7 (0 to 8) on the SARA Gait domain or were able to perform the 9-Hole Peg Test in 20 to 150 seconds.

In terms of the proposed MOA of levacetylleucine and nonclinical studies that include published data from studies of *Npc1*<sup>-/-</sup> mice treated with levacetylleucine that had reduced ataxia and improved gait and mobility, the impact of levacetylleucine on the neurological symptoms of NPC as evidenced by Trial IB1001-301 is plausible.

### **Conclusion**

Trial IB1001-301 provides evidence of a treatment benefit for the neurological symptoms of NPC. The SARA scale from which the primary endpoint was constructed was developed to measure the symptoms of cerebellar ataxia specifically. However, in the context of (b) (4) different aspects of pragmatic neurological function measured by the fSARA specifically, the data are adequate to support an indication that addresses the neurological manifestations of NPC (b) (4). It is not known what impact (if any) levacetylleucine has on the non-neurological symptoms of NPC.

## **7. Safety (Risk and Risk Management)**

### **7.1. Potential Risks or Safety Concerns Based on Nonclinical Data**

- There were no toxicologically significant findings in the 26-week rat and 39-week dog oral gavage toxicology studies conducted with levacetylleucine. Safety margins achieved at the no-observed-adverse-effect levels were 2- to 3-fold in rats and 6- to 9-fold in dogs compared to the steady-state AUCs in humans at the maximum recommended human dose (MRHD).
- Embryofetal development toxicity, including malformations and embryofetal death, was observed based on dose-ranging embryofetal developmental toxicology studies that were conducted in rats and rabbits at 1.4- and 6-fold the MRHD based on body surface area.
- Juvenile animal studies have not been conducted; therefore, it is unknown whether levacetylleucine may affect developmental processes in children.
- Nonclinical fertility studies have not been conducted; therefore, risks to male and female fertility and early embryonic development are unknown.
- Nonclinical pre- and postnatal development toxicity studies have not been conducted; therefore, risks to pre- and postnatal development are unknown.
- Rodent carcinogenicity studies have not been performed; therefore, carcinogenic risks are unknown.

### **7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors**

Not applicable. There are no other drugs in the same class as levacetylleucine.

### 7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable. This product has not been approved in the United States or in any foreign markets. Therefore, no postmarketing experience is available at the time of this review.

### 7.4. FDA Approach to the Safety Review

Safety data from the trials listed in [Table 3](#) were submitted to support the safety of levacetylleucine. The safety review was primarily based on Trial IB1001-301, the only placebo-controlled study of levacetylleucine in subjects with NPC. Safety results from the open-label, rater-blinded Trial IB1001-201 and the OLEs of both Trials IB1001-301 and IB1001-201 were reviewed separately to evaluate any potential safety signals not identified in the pivotal trial or that occurred after a longer duration of exposure to levacetylleucine. Lastly, summary data from the completed open-label study of levacetylleucine in GM2 gangliosidosis (Trial IB1001-202) was reviewed for additional safety signals, withdrawals, or deaths. An ongoing open-label study of levacetylleucine in Ataxia-Telangiectasia (Trial IB1001-203) was not included because no summary data were provided by the Applicant.

Because there are no clinical safety data for levacetylleucine in subjects under 5 years old, the Agency requested any available real-world data from the literature or from treating clinicians known to the Applicant. The Applicant did not have any available data for levacetylleucine but did provide data supporting the safety of the racemate of levacetylleucine, Tanganil (N-acetyl-DL-leucine) in patients with NPC and GM2 gangliosidosis from a patient registry and a clinician's anecdotal reports. Medical literature including several case reports and case series summarizing off-label use of Tanganil in NPC and other conditions that was included in the NDA submission by the Applicant was not included in the safety evaluation because subject-level data for the age groups represented (which were primarily adults) was available for levacetylleucine in the safety database.

The labelled adverse reactions (ARs) for Tanganil were reviewed as AEs that may overlap with levacetylleucine (skin rashes, urticaria). However, the form of Tanganil marketed in France and other countries uses a wheat-based excipient and is contraindicated in patients with a wheat allergy; thus, it cannot be determined if ARs are related to the excipient rather than the active ingredient. The majority (87%) of subjects in Trial IB1001-301 were taking concomitant miglustat as part of their standard of care therapy and were on a stable dose at the time of enrollment. Labelling for Zavesca (miglustat) for adults with Gaucher disease contains 'Warnings and Precautions' for the following: tremor, gastrointestinal events such as diarrhea and weight loss, peripheral neuropathy, and thrombocytopenia. We considered the potential impact of concomitant miglustat use on reported ARs with levacetylleucine exposure throughout our review.

**Table 28. Clinical Trials Submitted<sup>1</sup> in Support of Efficacy and Safety Determinations for Levacetylleucine**

| <b>Trial Identifier</b> | <b>Trial Population</b>                                             | <b>Trial Design</b>                                                                                                                                                                                                                                                            | <b>Regimen (Number Treated), Duration</b>                                                                                                                                                                                   | <b>Primary and Key Secondary Endpoints</b>                                                                                                                                                                                                                                                | <b>No. of Subjects Planned; Actual Randomized</b>                                                                                        | <b>No. of Centers and Countries</b> |
|-------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| IB1001-301              | Subjects aged >4 y in Europe or the United States with NPC          | Control Type: Placebo concurrent<br><br>Randomization: Standard<br><br>Randomization Ratio: 1:1<br><br>Blinding: Double-blind<br><br>Biomarkers: No biomarkers<br><br>Innovative design features: Crossover                                                                    | Drug (established name): N-acetyl-L-leucine<br><br>Dose: 4 g/day for ≥13 y, otherwise based on body weight<br><br>Number treated: 60<br><br>Duration (quantity and units): 6 months in parent study; 2 y in extension phase | Primary: Difference in the mSARA scores at the end of periods 1 and 2.<br><br>Secondary: Original SARA<br>In the United States, the original SARA was evaluated as a key secondary endpoint.<br><br>Scale for Spinocerebellar Ataxia Functional Index (SCAFI)                             | Planned: 53<br><br>Actual: 60 in parent study; 54 in extension phase                                                                     | Centers: 11<br><br>Countries: 7     |
| IB1001-201              | Subjects aged ≥6 y in Europe or ≥18 y in the United States with NPC | Control Type: No treatment concurrent (single arm)<br><br>Randomization: No randomization (single arm)<br><br>Randomization Ratio: No randomization (single arm)<br><br>Blinding: Open-label<br><br>Biomarkers: No biomarkers<br><br>Innovative design features: Rater-blinded | Drug (established name): N-acetyl-L-leucine<br><br>Dose: 4 g/day for ≥13 y, otherwise based on body weight<br><br>Number treated: 33<br><br>Duration (quantity and units): 6 weeks in parent study; 2 y in extension phase  | Primary: CI-CS comparing the end of treatment with baseline minus the CI-CS comparing the end of washout with the end of treatment.<br><br>Secondary: The individual components of the primary endpoint, that is the CI-CS from Visit 2 to Visit 4 and the CI-CS from Visit 4 to Visit 6. | Planned: 39<br><br>Actual: 33 in parent study; 19 in extension phase<br><br>Primary endpoint for OLE was change from baseline on 5DNPCSS | Centers: 9<br><br>Countries: 5      |

NDA 219132  
Aqneursa (levacetylleucine)

| <b>Trial Identifier</b> | <b>Trial Population</b>                                                             | <b>Trial Design</b>                                                                                                                                                                                                                                                            | <b>Regimen (Number Treated), Duration</b>                                                                                                                                                                                                                                                                                                                | <b>Primary and Key Secondary Endpoints</b>                                                                                                                                                                                                                                              | <b>No. of Subjects Planned; Actual Randomized</b> | <b>No. of Centers and Countries</b> |
|-------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|-------------------------------------|
| IB1001-202              | Subjects aged ≥6 y in Europe and ≥18 y in the United States with GM2 Gangliosidosis | Control Type: No treatment concurrent (single arm)<br><br>Randomization: No randomization (single arm)<br><br>Randomization Ratio: No randomization (single arm)<br><br>Blinding: Open-label<br><br>Biomarkers: No biomarkers<br><br>Innovative design features: Rater-blinded | Drug (established name): N-acetyl-L-leucine<br><br>Dose: 4 g/day for ≥13 y in Europe, ≥18 y in the United States and 6 to 12 y weighing ≥35 kg; 3 g/day for 6 to 12 y weighing 25 to <35 kg; 2 g/day for 6 to 12 y weighing 15 to <25 kg<br><br>Number treated: 30<br><br>Duration (quantity and units): 42 days in parent study; 2 y in extension phase | Primary: CI-CS comparing the end of treatment with baseline minus the CI-CS comparing the end of washout with the end of treatment.<br><br>Secondary: CI-CS comparing the end of treatment period with baseline minus the CI-CS comparing the end of washout with the end of treatment. | Planned: 39<br><br>Actual: 30                     | Centers: 8<br><br>Countries: 4      |

NDA 219132  
Aqneursa (levacetylleucine)

| <b>Trial Identifier</b> | <b>Trial Population</b>                                              | <b>Trial Design</b>                                                                                                                                                                                                                                                               | <b>Regimen (Number Treated), Duration</b>                                                                                                                                                                          | <b>Primary and Key Secondary Endpoints</b>                                                                                                                                                                                                | <b>No. of Subjects Planned; Actual Randomized</b> | <b>No. of Centers and Countries</b> |
|-------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|-------------------------------------|
| IB1001-203              | Subjects aged ≥6 y in Europe and ≥18 y in the United States with A-T | Control Type: No treatment concurrent (single arm)<br><br>Randomization: No randomization (single arm)<br><br>Randomization Ratio: No randomization (single arm)<br><br>Blinding: Open-label<br><br>Biomarkers: No biomarkers<br><br>Innovative design features:<br>Rater-blinded | Drug (established name): N-acetyl-L-leucine<br><br>Dose: 4 g/day for ≥13 y in Europe, ≥18 y in the United States and 6 to 12 y weighing ≥35 kg; 3 g/day for 6 to 12 y weighing 25 to <35 kg; 2 g/day for 6 to 12 y | Primary: CI-CS comparing the end of treatment with baseline minus the CI-CS comparing the end of washout with the end of treatment.<br><br>Secondary: The individual components of the primary endpoint will be summarized descriptively. | Planned: 39<br><br>Actual: ongoing                | Centers: 5<br><br>Countries: 4      |

Source: Clinical Study Report and adsl.xpt

<sup>1</sup> Includes all submitted clinical trials, even if not reviewed in-depth, except for Period 1 and pharmacokinetic studies.

Abbreviations: 5DNPCSS = 5-domain Niemann-Pick disease type C clinical severity scale; A-T = ataxia telangiectasia; CI-CS = clinical impression of change in severity; mSARA = modified Scale for the Assessment and Rating of Ataxia; No. = number; NPC = Niemann-Pick disease type C; OLE = open-label extension; SARA = Scale for the Assessment and Rating of Ataxia; SCAFI = Spinocerebellar Ataxia Functional Index; y = years

The NPC safety population (including Trials IB1001-301 and IB1001-201) consisted of a total of 84 subjects who were between 5 to 67 years old. The lowest weight of a subject was 20.6 kg. There were nine subjects who participated in both parent studies and were only counted once for this total. Between the two trials, there were 28 pediatric subjects (7 were under 10 years old) and 56 adult subjects.

First, the data from each trial with submitted datasets was examined for the required and standardized components and for completeness of data. The review team then confirmed that the AEs reported by the Applicant accurately described the AEs reported by the investigators. Once accuracy was confirmed, the frequencies of each AE were assessed. The review team reviewed all deaths, SAEs, discontinuations, and withdrawals.

Trial IB1001-301 was assessed and is reported separately as the only placebo-controlled study of levacetylleucine in subjects with NPC. Trial IB1001-301 is a cross-over study where subjects were randomized 1:1 to either levacetylleucine or placebo in addition to their baseline standard of care for 12 weeks (Treatment Period I), followed by immediate crossover to Treatment Period II, in which subjects previously on placebo began treatment with levacetylleucine and subjects previously on levacetylleucine began treatment with Placebo for 12 weeks. Because there may be carryover effects or repeated AEs (such as worsening of the same AE in the same subject) from Treatment Period I in Treatment Period II, Treatment Period I was the primary portion of Trial IB1001-301 reviewed for common ARs. Eligible subjects who completed Trial IB1001-301 enrolled in an ongoing OLE (IB1001-301) for 2 additional years of treatment, thus Trial IB1001-301 (including Treatment Period I and Treatment Period II) is referred to as the “parent study.” All subjects included in the 120-day safety update for Trial IB1001-301 have completed at least 1 year of open-label treatment (only summary data were available for review of this ongoing trial).

Trial IB1001-201 was an open-label (single arm) study with a rater-blinded primary efficacy endpoint. In the parent study, subjects were treated with levacetylleucine for 6 weeks, followed by a 6-week washout period. Eligible subjects had the option to enroll in an OLE (IB1001-201 OLE) that allowed subjects to continue treatment with levacetylleucine for approximately 2 additional years. IB1001-201 OLE consisted of treatment with levacetylleucine for 1 year (OLE Treatment Period I), followed by a 6-week washout period, and then a second year of treatment with levacetylleucine (OLE Treatment Period II).

In addition, the review team separately assessed summary data from an open-label trial of levacetylleucine in GM2 gangliosidosis, primarily for SAEs, withdrawals, and/or deaths.

## 7.5. Adequacy of the Clinical Safety Database

The safety database was adequate for a sufficient safety assessment of levacetylleucine (IB1001) for the indication of NPC in children and adults weighing 15 kg or greater. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review. No major issues were identified with respect to coding of AEs.

[Table 29](#) shows the baseline demographics of subjects enrolled in Trial IB1001-301, the only placebo-controlled trial in NPC. The two trial arms were generally well-balanced apart from there being fewer pediatric subjects in the placebo arm than in the levacetylleucine treatment arm. There were fewer pediatric participants than adult participants enrolled overall. 23 children

total enrolled, 7 of whom were 10 years old or younger at the time of enrollment. There were 37 adults enrolled. While Trial IB1001-301 intended to enroll patients aged 4 years and older, the youngest participant was 5 years old.

Most subjects (90%) were White, which is not representative of the global population with NPC but may reflect the trial site locations, which were primarily in Europe and Great Britain.

Because treatment recommendations and guidelines for NPC are international and the disease manifestations are expected to be similar across different races and ethnic groups, it is not likely that care practices and preferences would differ significantly.

**Table 29. Baseline Demographic and Clinical Characteristics, Safety Population, Period I, Trial IB1001-301**

| Characteristic                  | IB1001<br>N=30 | Placebo<br>N=30 | Overall<br>N=60 |
|---------------------------------|----------------|-----------------|-----------------|
| Sex, n (%)                      |                |                 |                 |
| Female                          | 14 (46.7)      | 13 (43.3)       | 27 (45.0)       |
| Male                            | 16 (53.3)      | 17 (56.7)       | 33 (55.0)       |
| Age, years                      |                |                 |                 |
| Mean (SD)                       | 24.2 (16.6)    | 28.6 (15.2)     | 26.4 (15.9)     |
| Median (min, max)               | 18.5 (7, 63)   | 26.5 (5, 67)    | 25 (5, 67)      |
| Age group, years, n (%)         |                |                 |                 |
| Adult (≥18)                     | 15 (50.0)      | 22 (73.3)       | 37 (61.7)       |
| Pediatric (<18)                 | 15 (50.0)      | 8 (26.7)        | 23 (38.3)       |
| Age group ≥65, years, n (%)     |                |                 |                 |
| ≥65                             | 0              | 2 (6.7)         | 2 (3.3)         |
| Race, n (%)                     |                |                 |                 |
| Asian                           | 2 (6.7)        | 0               | 2 (3.3)         |
| Other                           | 2 (6.7)        | 2 (6.7)         | 4 (6.7)         |
| White                           | 26 (86.7)      | 28 (93.3)       | 54 (90.0)       |
| Ethnicity, n (%)                |                |                 |                 |
| Not Hispanic or Latino          | 25 (83.3)      | 26 (86.7)       | 51 (85.0)       |
| Not reported                    | 1 (3.3)        | 1 (3.3)         | 2 (3.3)         |
| Unknown                         | 4 (13.3)       | 3 (10.0)        | 7 (11.7)        |
| Country of participation, n (%) |                |                 |                 |
| Australia                       | 0              | 6 (20.0)        | 6 (10.0)        |
| Switzerland                     | 8 (26.7)       | 4 (13.3)        | 12 (20.0)       |
| Czech Republic                  | 3 (10.0)       | 1 (3.3)         | 4 (6.7)         |
| Germany                         | 8 (26.7)       | 9 (30.0)        | 17 (28.3)       |
| Great Britain                   | 8 (26.7)       | 2 (6.7)         | 10 (16.7)       |
| Netherlands                     | 3 (10.0)       | 6 (20.0)        | 9 (15.0)        |
| Slovakia                        | 0              | 2 (6.7)         | 2 (3.3)         |

Source: adsl.xpt; Software: R

Abbreviations: max = maximum; min = minimum; N = number of subjects in treatment arm; n = number of subjects in specified population or group; SD = standard deviation

[Table 30](#) summarizes the levacetylleucine exposure for Trial IB1001-301. Most subjects were treated for 84 days or greater but less than 127 days.

**Table 30. Duration of Exposure, Safety Population, Trial IB1001-301**

| Parameter                            | Period I       |                 | Period II      |                 | Overall        |                 |
|--------------------------------------|----------------|-----------------|----------------|-----------------|----------------|-----------------|
|                                      | IB1001<br>N=30 | Placebo<br>N=30 | IB1001<br>N=30 | Placebo<br>N=29 | IB1001<br>N=60 | Placebo<br>N=59 |
| Duration of treatment, days          |                |                 |                |                 |                |                 |
| Mean (SD)                            | 86.5 (4.9)     | 86.2 (3.3)      | 85.9 (4.6)     | 88.4 (5.8)      | 86.2 (4.7)     | 87.3 (4.8)      |
| Median (Q1, Q3)                      | 86 (85, 90.8)  | 85.5 (85, 88.8) | 85 (84, 88.8)  | 88 (85, 90)     | 85 (84, 90)    | 86 (85, 89)     |
| Min, max                             | 69, 92         | 78, 92          | 76, 97         | 81, 113         | 69, 97         | 78, 113         |
| Total exposure <sup>1</sup>          | 7              | 7               | 7              | 7               | 14             | 14              |
| Subjects treated, by duration, n (%) |                |                 |                |                 |                |                 |
| <42 days                             | 0              | 0               | 0              | 0               | 0              | 0               |
| ≥42 to <84 days                      | 2 (6.7)        | 2 (6.7)         | 6 (20.0)       | 1 (3.3)         | 8 (13.3)       | 3 (5.0)         |
| ≥84 to <127 days                     | 28 (93.3)      | 28 (93.3)       | 24 (80.0)      | 28 (93.3)       | 52 (86.7)      | 56 (93.3)       |
| ≥127 days                            | 0              | 0               | 0              | 0               | 0              | 0               |
| Missing                              | 0              | 0               | 0              | 1 (3.3)         | 0              | 1 (1.7)         |

Source: adex.xpt and adsl.xpt; Software: R

<sup>1</sup> in person years.

Abbreviation: max = maximum; min = minimum; N = number of subjects in treatment arm; n = number of subjects in specified population or group; Q1 = first quartile; Q3 = third quartile; SD = standard deviation

[Table 31](#) shows the baseline demographics of subjects enrolled in Trial IB1001-201, an open-label study of levacetylleucine (IB1001) in NPC. Like Trial IB1001-301, there were fewer pediatric subjects enrolled than adults. There were 10 children enrolled, only 2 of whom are 10 years old or younger. There were 23 adults enrolled. The youngest subject enrolled was 7 years old.

Most subjects (87.9%) were White. Most of the trial sites were again in Europe and Great Britain. Trial IB1001-201 enrolled 2 subjects in the United States.

**Table 31. Baseline Demographic and Clinical Characteristics, Safety Population, Trial IB1001-201**

| Characteristic          | Overall<br>N=33 |
|-------------------------|-----------------|
| Sex, n (%)              |                 |
| Female                  | 10 (30.3)       |
| Male                    | 23 (69.7)       |
| Age, years              |                 |
| Mean (SD)               | 28.8 (15.1)     |
| Median (min, max)       | 29 (7, 64)      |
| Age group, years, n (%) |                 |
| Adult (≥18)             | 23 (69.7)       |
| Pediatric (<18)         | 10 (30.3)       |
| Race, n (%)             |                 |
| Asian                   | 2 (6.1)         |
| Other                   | 2 (6.1)         |
| White                   | 29 (87.9)       |
| Ethnicity, n (%)        |                 |
| Not Hispanic or Latino  | 30 (90.9)       |
| Other                   | 2 (6.1)         |
| Unknown                 | 1 (3.0)         |

| <b>Characteristic</b>           | <b>Overall<br/>N=33</b> |
|---------------------------------|-------------------------|
| Country of participation, n (%) |                         |
| Germany                         | 7 (21.2)                |
| Spain                           | 10 (30.3)               |
| Great Britain                   | 10 (30.3)               |
| Slovakia                        | 4 (12.1)                |
| United States                   | 2 (6.1)                 |
| Is in United States, n (%)      |                         |
| United States                   | 2 (6.1)                 |
| Non-United States               | 31 (93.9)               |

Source: adsl.xpt; Software: R  
Abbreviations: max = maximum; min = minimum; N = number of subjects; n = number of subjects with given characteristic; SD = standard deviation

**Table 32** summarizes the levacetylleucine exposure for Trial IB1001-201. Most subjects were treated for 42 days or greater but less than 84 days.

**Table 32. Duration of Exposure, Safety Population, Trial IB1001-201**

| <b>Parameter</b>                     | <b>IB1001<br/>N=33</b> |
|--------------------------------------|------------------------|
| Duration of treatment, days          |                        |
| Mean (SD)                            | 52.2 (23.8)            |
| Median (Q1, Q3)                      | 44 (43, 48)            |
| Min, max                             | 36, 134                |
| Total exposure (person years)        | 5                      |
| Subjects treated, by duration, n (%) |                        |
| <42 days                             | 2 (6.1)                |
| ≥42 to <84 days                      | 28 (84.8)              |
| ≥84 to <127 days                     | 1 (3.0)                |
| ≥127 to <169 days                    | 2 (6.1)                |
| ≥169 days                            | 0                      |
| Missing                              | 0                      |

Source: adex.xpt and adsl.xpt; Software: R  
Duration is 6 weeks in treatment and 6 weeks in washout  
Abbreviations: max = maximum; min = minimum; N = number of subjects randomized and treated; n = number of subjects in specified population or group; Q1 = first quartile; Q3 = third quartile; SD = standard deviation

## 7.6. Safety Results

### 7.6.1. Safety Findings and Concerns, Trial IB1001-301

#### **Overall Summary**

The demonstrated safety profile of levacetylleucine is acceptable at the doses intended for marketing. ARs that occurred in two or more subjects were abdominal pain, dysphagia, upper respiratory infections, vomiting, and thrombocytopenia on laboratory analysis.

There were no SAEs that led to withdrawal from the trial. There was one death of a subject in Trial IB1001-301 that occurred after withdrawal from the trial due to complications from a planned surgical procedure. While the duration of IB1001-301 was relatively short (made up of two 12-week treatment periods in the crossover study design), the data from this study in combination with the other submitted safety data for levacetylleucine are adequate to support

chronic use. The review team concluded that the risks observed are acceptable with appropriate product labeling and routine pharmacovigilance.

### 7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Trial IB1001-301

**Table 33** provides a summary of AEs reported during the parent study. To avoid the potential impact of carry over effects from Treatment Period I to Treatment Period II, the risk difference is only presented for Treatment Period I. One or more TEAEs were reported by more subjects exposed to levacetylleucine (IB1001) than placebo during Treatment Period I (63% versus 43%, with a risk difference of 20). In the overall cohort (Treatment Period I and Treatment Period II), there were two SAEs in one subject while randomized to levacetylleucine, one SAE of which was ultimately fatal after withdrawal from the trial.

**Table 33. Overview of Adverse Events, Safety Population, Trial IB1001-301**

| Event Category                                        | Period I                |                          |                                                        | Period II               |                          | Overall                 |                          |
|-------------------------------------------------------|-------------------------|--------------------------|--------------------------------------------------------|-------------------------|--------------------------|-------------------------|--------------------------|
|                                                       | IB1001<br>N=30<br>n (%) | Placebo<br>N=30<br>n (%) | IB1001 vs.<br>Placebo<br>Risk Difference<br>% (95% CI) | IB1001<br>N=30<br>n (%) | Placebo<br>N=29<br>n (%) | IB1001<br>N=30<br>n (%) | Placebo<br>N=59<br>n (%) |
| SAE                                                   | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                       | 1 (3.3)                 | 2 (6.9)                  | 2 (3.3)                 | 2 (3.4)                  |
| SAEs with fatal outcome                               | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                       | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Life-threatening SAEs                                 | 0                       | 0                        | 0.0 (-11.5, 11.5)                                      | 0                       | 0                        | 0                       | 0                        |
| SAEs requiring hospitalization                        | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                       | 1 (3.3)                 | 2 (6.9)                  | 2 (3.3)                 | 2 (3.4)                  |
| Other                                                 | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                       | 0                       | 0                        | 1 (1.7)                 | 0                        |
| AE leading to permanent discontinuation of study drug | 0                       | 0                        | 0.0 (-11.5, 11.5)                                      | 0                       | 0                        | 0                       | 0                        |
| AE leading to dose modification of study drug         | 2 (6.7)                 | 1 (3.3)                  | 3.3 (-11.1, 18.7)                                      | 0                       | 1 (3.4)                  | 2 (3.3)                 | 2 (3.4)                  |
| AE leading to interruption of study drug              | 2 (6.7)                 | 1 (3.3)                  | 3.3 (-11.1, 18.7)                                      | 0                       | 1 (3.4)                  | 2 (3.3)                 | 2 (3.4)                  |
| AE leading to reduction of study drug                 | 0                       | 0                        | 0.0 (-11.5, 11.5)                                      | 0                       | 0                        | 0                       | 0                        |
| AE leading to dose delay of study drug                | 0                       | 0                        | 0.0 (-11.5, 11.5)                                      | 0                       | 0                        | 0                       | 0                        |
| Any AE                                                | 19<br>(63.3)            | 13<br>(43.3)             | 20.0 (-5.4, 43.0)                                      | 17<br>(56.7)            | 17<br>(58.6)             | 36<br>(60.0)            | 30<br>(50.8)             |
| AE with fatal outcome                                 | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                       | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Severe and worse                                      | 2 (6.7)                 | 0                        | 6.7 (-5.2, 21.5)                                       | 1 (3.3)                 | 3 (10.3)                 | 3 (5.0)                 | 3 (5.1)                  |
| Moderate                                              | 5 (16.7)                | 4 (13.3)                 | 3.3 (-16.0, 22.8)                                      | 4 (13.3)                | 5 (17.2)                 | 9 (15.0)                | 9 (15.3)                 |
| Mild                                                  | 12<br>(40.0)            | 9 (30.0)                 | 10.0 (-14.2, 33.2)                                     | 12<br>(40.0)            | 9 (31.0)                 | 24<br>(40.0)            | 18<br>(30.5)             |

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 3 months for Period I and 3 months for Period II.

Risk difference (with 95% CI) is shown between total treatment and comparator.

Severity as assessed by the investigator.

Abbreviations: AE = adverse event; CI = confidence interval; N = number of subjects in treatment arm; n = number of subjects with at least one event; SAE = serious adverse event

The most reported TEAE in the overall trial population was upper respiratory tract infection, occurring in 10% of subjects. The most common system organ class with TEAE was infections and infestations (27%). The most common ARs in the overall population were gastrointestinal disorders including abdominal pain, dysphagia, and vomiting (See Section [7.7.1](#)). While there were no reported ARs of thrombocytopenia, laboratory analysis demonstrated thrombocytopenia in a higher portion of subjects on levacetylleucine compared to placebo during Treatment Period I (See Section [7.6.1.6](#)).

#### 7.6.1.2. Deaths, Trial IB1001-301

There was one subject with two SAEs unrelated to the study drug that led to withdrawal from the trial (physician decision) and that ultimately had a fatal outcome during Treatment Period I of the parent study of Trial IB1001-301.

Subject (b) (6) was an adult male at the time of enrollment in Trial IB1001-301. This subject had severe dystonia requiring multiple medications (gabapentin, trihexiphenidyl, clonazepam and a THC/CBD oil) in addition to other symptoms of NPC. The subject was status-post placement of a deep brain stimulator for dystonia and was also taking miglustat. The subject had a planned elective procedure to place a PEG tube on Study Day 67 (the trial staff was not previously aware of this planned procedure). The study drug (levacetylleucine) was stopped for this procedure. After the procedure, the subject experienced an episode of aspiration on Study Day 70 that lead to pneumonia, and the subject remained hospitalized while being treated with antibiotics and parenteral nutrition. During this hospitalization the subject also suffered a neurologic regression with dystonic crises and worsening agitation that progressed to psychosis before they were withdrawn from the trial by the trial investigator due to their inability to participate in future trial visits. The subject died from respiratory failure 37 days after being withdrawn from the trial. The SAEs of aspiration pneumonia and psychosis were both assessed as not related to the study medication. This reviewer agrees with this assessment.

#### 7.6.1.3. Serious Treatment-Emergent Adverse Events, Trial IB1001-301

The SAEs reported in Trial IB1001-301 are noted in [Table 34](#). There were three SAEs during the parent study in subjects randomized to levacetylleucine: two in Treatment Period I (aspiration pneumonia and psychosis in one subject during the same prolonged hospitalization), and one in Treatment Period II (incisional hernia repair).

**Table 34. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial IB1001-301**

| System Organ Class<br>Preferred Term  | Period I                |                          |                                                        | Period II               |                          | Overall                 |                          |
|---------------------------------------|-------------------------|--------------------------|--------------------------------------------------------|-------------------------|--------------------------|-------------------------|--------------------------|
|                                       | IB1001<br>N=30<br>n (%) | Placebo<br>N=30<br>n (%) | IB1001 vs.<br>Placebo<br>Risk Difference<br>% (95% CI) | IB1001<br>N=30<br>n (%) | Placebo<br>N=29<br>n (%) | IB1001<br>N=60<br>n (%) | Placebo<br>N=59<br>n (%) |
| Any SAE                               | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                       | 1 (3.3)                 | 2 (6.9)                  | 2 (3.3)                 | 2 (3.4)                  |
| Infections and infestations (SOC)     | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                       | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Pneumonia aspiration                  | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                       | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Nervous system disorders (SOC)        | 0                       | 0                        | 0.0 (-11.5, 11.5)                                      | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Epilepsy                              | 0                       | 0                        | 0.0 (-11.5, 11.5)                                      | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Psychiatric disorders (SOC)           | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                       | 0                       | 1 (3.4)                  | 1 (1.7)                 | 1 (1.7)                  |
| Psychotic disorder                    | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                       | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Depression                            | 0                       | 0                        | 0.0 (-11.5, 11.5)                                      | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Surgical and medical procedures (SOC) | 0                       | 0                        | 0.0 (-11.5, 11.5)                                      | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Incisional hernia repair              | 0                       | 0                        | 0.0 (-11.5, 11.5)                                      | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 3 months for Period I and 3 months for Period II.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI = confidence interval; N = number of subjects in treatment group; n = number of subjects with adverse event; SAE = serious adverse event; SOC = system organ class

### **Aspiration Pneumonia and Psychosis**

The SAEs that occurred in Treatment Period I (aspiration pneumonia and psychosis) are described in Section 7.6.1.2. Both occurred in the same subject during a prolonged hospitalization due to complications of a planned medical procedure after the study drug had been stopped. Neither event was assessed as related to study drug. This reviewer agrees with this assessment.

### **Hernia Repair**

Subject (b) (6) is an adult male at the time of enrollment in Trial IB1001-301. The subject had a past medical history of a caecum volvulus and ileus operation in addition to his symptoms of NPC. They were randomized to placebo during Treatment Period I and then switched to treatment with levacetylleucine during Treatment Period II. During Treatment Period II (Study Day 136) the subject developed an abdominal wall hernia secondary to his previous abdominal surgeries and required surgical repair, which was followed by an 8-day hospitalization. The subject was discharged home after the procedure on Study Day 144 without incident and continued the study drug during the hospitalization. This event was assessed as not related to the study medication. This reviewer agrees with this assessment.

### **SAEs in Placebo Group During Treatment Period II**

Two subjects experienced SAEs while on placebo in Treatment Period II after having received levacetylleucine during Treatment Period I.

### **Worsening Epilepsy**

Subject (b) (6) is an adolescent male at the time of enrollment. The subject had a past medical history of epilepsy on three anti-seizure medications (levetiracetam, sodium valproate, clobazam). The subject first experienced an increase in duration and frequency of his seizures during Treatment Period I, however they did not require hospitalization, thus this was reported as a severe (i.e., not serious) AE. On Study Day 14 in Treatment Period II, the subject required hospitalization for control of worsening seizures and medication management. During the hospitalization, the subject received benzodiazepines and fluids. The subject also had an AE of aspiration pneumonia during this hospitalization that was attributed to sedation from their medications causing worsening dysphagia. The subject was discharged home on Study Day 30 of Treatment Period II. There were no interruptions in the subject's study drug dosing and this SAE was assessed as not related to study drug. In the setting of their prior history of treatment-refractory epilepsy requiring three anti-seizure medications and with the hospitalization occurring 2 weeks into treatment during Period II while taking placebo, this reviewer concurs that worsening epilepsy is not likely related to the study drug.

### **Major Depression**

Subject (b) (6) was an adult male at the time of trial enrollment. The subject's past medical history was significant for a prior psychiatric hospitalization in 2013 in addition to other symptoms of NPC. The subject was taking sertraline and amantadine daily and clonazepam and quetiapine as needed for depression. The subject began having worsening symptoms of depression (moderate) during Treatment Period I, when they were randomized to levacetylleucine. On the last day of Treatment Period II (during which the subject received placebo) while being assessed for trial Visit 6, the trial investigator recognized severe symptoms of depression and determined that urgent hospitalization was needed. Symptoms were described as similar to catatonia and the subject experienced a significant decline in daily functioning requiring a prolonged hospitalization. This SAE was assessed as not related to study drug. In the context of this subject's prior history of depression requiring hospitalization and worsening over time (and at the EOT II while on placebo), this reviewer agrees that the SAE major depression is unlikely related to the study drug.

#### **7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Trial IB1001-301**

There were no AEs that led to treatment discontinuation.

#### **7.6.1.5. Treatment-Emergent Adverse Events, Trial IB1001-301**

The frequency and severity of TEAEs were evaluated to assess the general safety profile of levacetylleucine. TEAEs are AEs that developed, worsened, or became serious during the treatment period. Overall, 58% of subjects experienced a TEAE while on treatment versus 51% while on placebo. Because there was no washout period between Treatment Period I and Treatment Period II, the assessment of TEAEs is primarily focused on Treatment Period I, when there are no potential carryover effects from treatment in the prior period. During Treatment

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Period I. 63% of subjects randomized to levacetylleucine (IB1001) experienced TEAEs compared to 43% taking placebo.

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**Table 35. Subjects With Common Adverse Events, Safety Population, Trial IB1001-301**

| Preferred Term                    | Period I                |                          |                                                     | Period II               |                          | Overall                 |                          |
|-----------------------------------|-------------------------|--------------------------|-----------------------------------------------------|-------------------------|--------------------------|-------------------------|--------------------------|
|                                   | IB1001<br>N=30<br>n (%) | Placebo<br>N=30<br>n (%) | IB1001 vs. Placebo<br>Risk Difference<br>% (95% CI) | IB1001<br>N=30<br>n (%) | Placebo<br>N=29<br>n (%) | IB1001<br>N=60<br>n (%) | Placebo<br>N=59<br>n (%) |
| Any AE                            | 19 (63.3)               | 13 (43.3)                | 20.0 (-5.4, 43.0)                                   | 16 (53.3)               | 17 (58.6)                | 35 (58.3)               | 30 (50.8)                |
| Abdominal pain                    | 2 (6.7)                 | 0                        | 6.7 (-5.2, 21.5)                                    | 0                       | 0                        | 2 (3.3)                 | 0                        |
| Dysphagia                         | 2 (6.7)                 | 0                        | 6.7 (-5.2, 21.5)                                    | 1 (3.3)                 | 0                        | 3 (5.0)                 | 0                        |
| Nasopharyngitis                   | 2 (6.7)                 | 0                        | 6.7 (-5.2, 21.5)                                    | 0                       | 3 (10.3)                 | 2 (3.3)                 | 3 (5.1)                  |
| Upper respiratory tract infection | 3 (10.0)                | 1 (3.3)                  | 6.7 (-8.2, 23.0)                                    | 3 (10.0)                | 2 (6.9)                  | 6 (10.0)                | 3 (5.1)                  |
| Vomiting                          | 2 (6.7)                 | 0                        | 6.7 (-5.2, 21.5)                                    | 0                       | 1 (3.4)                  | 2 (3.3)                 | 1 (1.7)                  |
| Bone fissure                      | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Clavicle fracture                 | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| COVID-19                          | 2 (6.7)                 | 1 (3.3)                  | 3.3 (-11.1, 18.7)                                   | 0                       | 1 (3.4)                  | 2 (3.3)                 | 2 (3.4)                  |
| Depression                        | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 1 (3.4)                  | 1 (1.7)                 | 1 (1.7)                  |
| Dizziness                         | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Dystonia                          | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Epilepsy                          | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 1 (3.4)                  | 1 (1.7)                 | 1 (1.7)                  |
| Epistaxis                         | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Gastroenteritis                   | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Gastroenteritis viral             | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 1 (3.3)                 | 0                        | 2 (3.3)                 | 0                        |
| Influenza                         | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Non-cardiac chest pain            | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Pneumonia aspiration              | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 1 (3.4)                  | 1 (1.7)                 | 1 (1.7)                  |
| Psychotic disorder                | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Respiratory tract infection       | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Sinusitis                         | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Sleep apnea syndrome              | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Vision blurred                    | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Weight decreased                  | 1 (3.3)                 | 0                        | 3.3 (-8.4, 16.8)                                    | 0                       | 0                        | 1 (1.7)                 | 0                        |
| Aggression                        | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Anemia                            | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Anxiety                           | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Aphasia                           | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Cough                             | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Decreased vibratory sense         | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Dermatitis contact                | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Gait disturbance                  | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Growth disorder                   | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |

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| Preferred Term                       | Period I                |                          |                                                     | Period II               |                          | Overall                 |                          |
|--------------------------------------|-------------------------|--------------------------|-----------------------------------------------------|-------------------------|--------------------------|-------------------------|--------------------------|
|                                      | IB1001<br>N=30<br>n (%) | Placebo<br>N=30<br>n (%) | IB1001 vs. Placebo<br>Risk Difference<br>% (95% CI) | IB1001<br>N=30<br>n (%) | Placebo<br>N=29<br>n (%) | IB1001<br>N=60<br>n (%) | Placebo<br>N=59<br>n (%) |
| Headache                             | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Incisional hernia repair             | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Nail bed bleeding                    | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Oropharyngeal pain                   | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Otitis media                         | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Pneumonia                            | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 1 (3.4)                  | 1 (1.7)                 | 1 (1.7)                  |
| Proteinuria                          | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Rash maculo-papular                  | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Rosacea                              | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Spinal fracture                      | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 0                       | 1 (3.4)                  | 0                       | 1 (1.7)                  |
| Tinea pedis                          | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Urinary incontinence                 | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Vitamin A deficiency                 | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Vitamin D deficiency                 | 0                       | 0                        | 0.0 (-11.5, 11.5)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 0                        |
| Contusion                            | 1 (3.3)                 | 1 (3.3)                  | -0.0 (-13.9, 13.9)                                  | 0                       | 0                        | 1 (1.7)                 | 1 (1.7)                  |
| Fall                                 | 3 (10.0)                | 3 (10.0)                 | -0.0 (-17.5, 17.5)                                  | 1 (3.3)                 | 6 (20.7)                 | 4 (6.7)                 | 9 (15.3)                 |
| Acne                                 | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Blood alkaline phosphatase decreased | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Cataplexy                            | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Cystitis                             | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Drooling                             | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Drug eruption                        | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Electrocardiogram QT prolonged       | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Influenza like illness               | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 1 (1.7)                  |
| Scarlet fever                        | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Seizure                              | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 1 (1.7)                  |
| Swelling                             | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Tendonitis                           | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |

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|                       | Period I                |                          |                                                     | Period II               |                          | Overall                 |                          |
|-----------------------|-------------------------|--------------------------|-----------------------------------------------------|-------------------------|--------------------------|-------------------------|--------------------------|
|                       | IB1001<br>N=30<br>n (%) | Placebo<br>N=30<br>n (%) | IB1001 vs. Placebo<br>Risk Difference<br>% (95% CI) | IB1001<br>N=30<br>n (%) | Placebo<br>N=29<br>n (%) | IB1001<br>N=60<br>n (%) | Placebo<br>N=59<br>n (%) |
| <b>Preferred Term</b> |                         |                          |                                                     |                         |                          |                         |                          |
| Traumatic hematoma    | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Viral infection       | 0                       | 1 (3.3)                  | -3.3 (-16.8, 8.4)                                   | 0                       | 0                        | 0                       | 1 (1.7)                  |
| Anal incontinence     | 0                       | 2 (6.7)                  | -6.7 (-21.5, 5.2)                                   | 1 (3.3)                 | 0                        | 1 (1.7)                 | 2 (3.4)                  |
| Diarrhea              | 1 (3.3)                 | 3 (10.0)                 | -6.7 (-23.0, 8.2)                                   | 0                       | 1 (3.4)                  | 1 (1.7)                 | 4 (6.8)                  |
| Pyrexia               | 0                       | 3 (10.0)                 | -10.0 (-25.8, 2.1)                                  | 1 (3.3)                 | 0                        | 1 (1.7)                 | 3 (5.1)                  |

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 3 months for Period I and 3 months for Period II.

Coded as MedDRA preferred terms.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Nail bed bleeding replaces: Traumatic hematoma.

Nasopharyngitis replaces: Rhinitis.

Pyrexia replaces: Viral infection.

Viral infection replaces: Viral infection.

Abbreviations: AE = adverse event; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment arm; n = number of subjects with adverse event

During Treatment Period I, TEAEs with a risk difference  $\geq 6.7$  were abdominal pain, dysphagia, nasopharyngitis, upper respiratory tract infections, and vomiting. The review team assessed frequent TEAEs to be ARs if they could be reasonably explained by the proposed MOA of levacetylleucine. While it is not clear how levacetylleucine could lead to an increase in upper respiratory infections directly, upper respiratory infections and nasopharyngitis were included due to the increased risk for dysphagia and known risk of aspiration in this disorder as it may be difficult to assess a cause-and-effect relationship of these symptoms during the course of medical care for NPC while on treatment with levacetylleucine. Seasonal allergies were not considered ARs due to the seasonal nature of the symptoms, which would be difficult to attribute to any of the proposed mechanisms of action for levacetylleucine in subjects with NPC.

**Table 36. Subjects With Common Treatment-Emergent Adverse Events With a Risk Difference of  $\geq 6.7$ , Period 1, Trial IB1001-301**

| Preferred Term                    | Period I                |                          |                                                           | Period II               |                          | Overall                 |                          |
|-----------------------------------|-------------------------|--------------------------|-----------------------------------------------------------|-------------------------|--------------------------|-------------------------|--------------------------|
|                                   | IB1001<br>N=30<br>n (%) | Placebo<br>N=30<br>n (%) | IB1001 vs.<br>Placebo<br>Risk<br>Difference<br>% (95% CI) | IB1001<br>N=30<br>n (%) | Placebo<br>N=29<br>n (%) | IB1001<br>N=60<br>n (%) | Placebo<br>N=59<br>n (%) |
| Any AE                            | 19 (63.3)               | 13 (43.3)                | 20.0 (-5.4, 43.0)                                         | 16 (53.3)               | 17 (58.6)                | 35 (58.3)               | 30 (50.8)                |
| Abdominal pain                    | 2 (6.7)                 | 0                        | 6.7 (-5.2, 21.5)                                          | 0                       | 0                        | 2 (3.3)                 | 0                        |
| Dysphagia                         | 2 (6.7)                 | 0                        | 6.7 (-5.2, 21.5)                                          | 1 (3.3)                 | 0                        | 3 (5.0)                 | 0                        |
| Nasopharyngitis                   | 2 (6.7)                 | 0                        | 6.7 (-5.2, 21.5)                                          | 0                       | 3 (10.3)                 | 2 (3.3)                 | 3 (5.1)                  |
| Upper respiratory tract infection | 3 (10.0)                | 1 (3.3)                  | 6.7 (-8.2, 23.0)                                          | 3 (10.0)                | 2 (6.9)                  | 6 (10.0)                | 3 (5.1)                  |
| Vomiting                          | 2 (6.7)                 | 0                        | 6.7 (-5.2, 21.5)                                          | 0                       | 1 (3.4)                  | 2 (3.3)                 | 1 (1.7)                  |

Source: Reviewer's table adapted from [Table 35](#), above

Abbreviations: AE = adverse event; CI = confidence interval; N = number of subjects in treatment arm; n = number of subjects with adverse event

### **Treatment-Emergent Events of Interest**

AEs reported for the racemate of levacetylleucine, Tanganil, in the label in France (skin rash, urticaria, hypersensitivity reactions, anaphylactic shock and laryngeal edema and abdominal pain) as well as those listed in current U.S. labeling for Zavesca (miglustat as approved for adults with Gaucher disease: peripheral neuropathy, tremor, diarrhea, weight loss, and reductions in platelet count) were reviewed with heightened interest and included as ARs if they occurred during treatment with levacetylleucine at a more frequent rate than when treated with placebo. ARs reported during treatment with levacetylleucine that also have been reported in labeling for miglustat are gastrointestinal and metabolic symptoms including vomiting, abdominal pain, and weight loss. One subject who was also taking miglustat experienced an AR of weight loss during Treatment Period I. There were 4 subjects randomized to levacetylleucine with laboratory analysis demonstrating a platelet count of  $<100$  in Treatment Period I compared to 2 subjects on placebo. When comparing decreased platelet counts of the overall trial population during Treatment Periods I and II, there was a similar occurrence of decreased platelet counts in both the treatment and placebo groups, which may reflect background miglustat use and/or underlying disease (see further discussion Laboratory Findings, [below](#)). There were more subjects in Treatment Period I who were randomized to placebo (n=3) who had diarrhea (an AR reported for miglustat) than those who were randomized to levacetylleucine (n=1). There were no clear hypersensitivity reactions like those reported with Tanganil in Trial IB1001-301. One subject

experienced an exacerbation of a previous diagnosis of rosacea during Treatment Period II while randomized to levacetylleucine that responded to their typical treatment for rosacea exacerbations and did not require a change in dose or discontinuation of levacetylleucine.

#### 7.6.1.6. Laboratory Findings, Trial IB1001-301

Routine safety monitoring bloodwork (hematology, clinical chemistry, creatine kinase) and urinalysis were obtained throughout the trials. The mean values for most of these tests remained within normal ranges except for low platelets (thrombocytopenia) in both the treatment and placebo cohorts as detailed below. There were two instances of decreased potassium during Treatment Period I and one instance of mildly elevated blood urea nitrogen during Treatment Period II that are not likely CS.

##### **Hematology**

[Table 37](#) demonstrates abnormalities in hematology laboratory values during Trial IB1001-301. There were several isolated low and high white blood cell count values during Period I that are not likely CS, and most other hematology laboratory values were within normal limits except for platelets, discussed in further detail in Thrombocytopenia, [below](#).

**Table 37. Subjects With One or More Hematology Analyte Values Outside of Specified Levels, Safety Population, Trial IB1001-301**

| Laboratory Parameter                      | Period I                               |                                         |                                                     | Period II                              |                                         | Overall                                |                                         |
|-------------------------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------------|-----------------------------------------|
|                                           | IB1001<br>N=30<br>n/N <sub>w</sub> (%) | Placebo<br>N=30<br>n/N <sub>w</sub> (%) | IB1001 vs. Placebo<br>Risk Difference<br>% (95% CI) | IB1001<br>N=30<br>n/N <sub>w</sub> (%) | Placebo<br>N=29<br>n/N <sub>w</sub> (%) | IB1001<br>N=60<br>n/N <sub>w</sub> (%) | Placebo<br>N=59<br>n/N <sub>w</sub> (%) |
| <b>Complete Blood Count</b>               |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| WBC, low (10 <sup>3</sup> cells/uL)       |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Level 1 (<3.5)                            | 1/30 (3.3)                             | 0/30 (0)                                | 3.3 (-8.4, 16.8)                                    | 1/30 (3.3)                             | 1/29 (3.4)                              | 2/60 (3.3)                             | 1/59 (1.7)                              |
| Level 2 (<3)                              | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Level 3 (<1)                              | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| WBC, high (10 <sup>3</sup> cells/uL)      |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Level 1 (>10.8)                           | 3/30 (10.0)                            | 0/30 (0)                                | 10.0 (-2.1, 25.8)                                   | 2/30 (6.7)                             | 2/29 (6.9)                              | 5/60 (8.3)                             | 2/59 (3.4)                              |
| Level 2 (>13)                             | 1/30 (3.3)                             | 0/30 (0)                                | 3.3 (-8.4, 16.8)                                    | 0/30 (0)                               | 0/29 (0)                                | 1/60 (1.7)                             | 0/59 (0)                                |
| Level 3 (>15)                             | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Hemoglobin, low (g/dL)                    |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Level 2 (>1.5 g/dL dec. from baseline)    | 0/30 (0)                               | 1/30 (3.3)                              | -3.3 (-16.8, 8.4)                                   | 0/30 (0)                               | 3/29 (10.3)                             | 0/60 (0)                               | 4/59 (6.8)                              |
| Level 3 (>2 g/dL dec. from baseline)      | 0/30 (0)                               | 1/30 (3.3)                              | -3.3 (-16.8, 8.4)                                   | 0/30 (0)                               | 1/29 (3.4)                              | 0/60 (0)                               | 2/59 (3.4)                              |
| Hemoglobin, high (g/dL)                   |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Level 2 (>2 g/dL inc. from baseline)      | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 1/30 (3.3)                             | 1/29 (3.4)                              | 1/60 (1.7)                             | 1/59 (1.7)                              |
| Level 3 (>3 g/dL inc. from baseline)      | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Platelets, low (10 <sup>3</sup> cells/uL) |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Level 1 (<140)                            | 13/30 (43.3)                           | 13/30 (43.3)                            | -0.0 (-24.6, 24.6)                                  | 9/30 (30.0)                            | 8/28 (28.6)                             | 22/60 (36.7)                           | 21/58 (36.2)                            |
| Level 2 (<125)                            | 7/30 (23.3)                            | 6/30 (20.0)                             | 3.3 (-18.1, 24.6)                                   | 6/30 (20.0)                            | 7/28 (25.0)                             | 13/60 (21.7)                           | 13/58 (22.4)                            |
| Level 3 (<100)                            | 4/30 (13.3)                            | 2/30 (6.7)                              | 6.7 (-10.3, 24.4)                                   | 1/30 (3.3)                             | 2/28 (7.1)                              | 5/60 (8.3)                             | 4/58 (6.9)                              |

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| Laboratory Parameter                         | Period I                               |                                         |                                                     | Period II                              |                                         | Overall                                |                                         |
|----------------------------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------------|-----------------------------------------|
|                                              | IB1001<br>N=30<br>n/N <sub>w</sub> (%) | Placebo<br>N=30<br>n/N <sub>w</sub> (%) | IB1001 vs. Placebo<br>Risk Difference<br>% (95% CI) | IB1001<br>N=30<br>n/N <sub>w</sub> (%) | Placebo<br>N=29<br>n/N <sub>w</sub> (%) | IB1001<br>N=60<br>n/N <sub>w</sub> (%) | Placebo<br>N=59<br>n/N <sub>w</sub> (%) |
| <b>WBC Differential</b>                      |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Lymphocytes, low (10 <sup>3</sup> cells/uL)  |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Level 1 (<1)                                 | 5/30 (16.7)                            | 3/30 (10.0)                             | 6.7 (-11.9, 25.5)                                   | 3/30 (10.0)                            | 2/29 (6.9)                              | 8/60 (13.3)                            | 5/59 (8.5)                              |
| Level 2 (<0.75)                              | 1/30 (3.3)                             | 1/30 (3.3)                              | -0.0 (-13.9, 13.9)                                  | 1/30 (3.3)                             | 1/29 (3.4)                              | 2/60 (3.3)                             | 2/59 (3.4)                              |
| Level 3 (<0.5)                               | 0/30 (0)                               | 1/30 (3.3)                              | -3.3 (-16.8, 8.4)                                   | 1/30 (3.3)                             | 0/29 (0)                                | 1/60 (1.7)                             | 1/59 (1.7)                              |
| Lymphocytes, high (10 <sup>3</sup> cells/uL) |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Level 1 (>4)                                 | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Level 2 (>10)                                | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Level 3 (>20)                                | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Neutrophils, low (10 <sup>3</sup> cells/uL)  |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Level 1 (<2)                                 | 2/30 (6.7)                             | 1/30 (3.3)                              | 3.3 (-11.1, 18.7)                                   | 1/30 (3.3)                             | 2/29 (6.9)                              | 3/60 (5.0)                             | 3/59 (5.1)                              |
| Level 2 (<1)                                 | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Level 3 (<0.5)                               | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Eosinophils, high (10 <sup>3</sup> cells/uL) |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Level 1 (>0.65)                              | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Level 2 (>1.5)                               | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Level 3 (>5)                                 | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| <b>Coagulation Studies</b>                   |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| PT, high (sec)                               |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Missing                                      | NA                                     | NA                                      | NA                                                  | NA                                     | NA                                      | NA                                     | NA                                      |
| PTT, high (sec)                              |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Missing                                      | NA                                     | NA                                      | NA                                                  | NA                                     | NA                                      | NA                                     | NA                                      |

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 3 months for Period I and 3 months for Period II.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI = confidence interval; dec = decrease; inc. = increase; N = number of subjects in treatment arm; n = number of subjects meeting criteria; NA = not applicable; N<sub>w</sub> = number of subjects with data; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cells

### **Thrombocytopenia**

There were no AEs of thrombocytopenia reported; however, there were subjects in both treatment groups with low platelets, called thrombocytopenia (typically defined as  $<150 \times 10^3$  cells/uL), identified via routine laboratory analysis during the trial. Patients with NPC can have thrombocytopenia related to their underlying diagnosis. Baseline values in Trial IB1001-301 ranged from 65 to  $345 \times 10^3$  cells/uL (mean  $170.45 \times 10^3$  cells/uL). Additionally, labelling for miglustat (Zavesca) lists thrombocytopenia as a known risk with its use. All subjects in Trial IB1001-301 with laboratory values consistent with thrombocytopenia received concomitant miglustat therapy.

During Treatment Period I, there was an equal number of subjects with platelets  $<140 \times 10^3$  cells/uL in those randomized to levacetylleucine (13/30, 43.3%) as those randomized to placebo (13/30, 43.3%). A similar proportion of subjects also had platelets  $<125 \times 10^3$  cells/uL (7/30 subjects randomized to levacetylleucine and 6/30 subjects randomized to placebo). There were four subjects randomized to levacetylleucine who had platelets  $<100 \times 10^3$  cells/uL, compared to two subjects randomized to placebo.

For these four subjects with platelets  $<100 \times 10^3$  cells/uL, two had baseline values of  $<100 \times 10^3$  cells/uL that then fluctuated throughout the course of Treatment Period I (on levacetylleucine) and Treatment Period II (on placebo), ranging from 53 to  $112 \times 10^3$  cells/uL, as detailed in [Table 38](#). There were no values  $<50 \times 10^3$  cells/uL. Two subjects had baseline values  $>100 \times 10^3$  cells/uL that decreased during the treatment period to 81 and  $60 \times 10^3$  cells/uL, respectively. However, in both instances, their platelet levels increased again to  $>100 \times 10^3$  cells/uL during Treatment Period II.

**Table 38. Subjects With Post Baseline Platelet Values  $<100 \times 10^3$  Cells/uL**

| Subject ID          | Treatment Period I |          |         |         | Treatment Period II |         |         |
|---------------------|--------------------|----------|---------|---------|---------------------|---------|---------|
|                     | Treatment          | Baseline | Visit 3 | Visit 4 | Treatment           | Visit 5 | Visit 6 |
| IB1001-201- (b) (6) | IB1001             | 154      | 152     | 96      | Placebo             | 155     | 164     |
| IB1001-301- (b) (6) | IB1001             | 65       | 65      | 68      | Placebo             | 92      | 53      |
| IB1001- (b) (6)     | IB1001             | 80       | 112     | 75      | Placebo             | 74      | 83      |
| IB1001-301- (b) (6) | IB1001             | 125      | 120     | 81      | Placebo             | 105     | 118     |
| IB1001-301- (b) (6) | Placebo            | 85       | 150     | 95      | IB1001              | 114     | 133     |
| IB1001-301- (b) (6) | Placebo            | 123      | 99      | 192     | IB1001              | 126     | 108     |
| IB1001-301- (b) (6) | Placebo            | 98       | 123     | 110     | IB1001              | 94      | 113     |

Source: adlb.xpt; Software: R

While there are no symptoms typically associated with thrombocytopenia with platelets  $>50 \times 10^3$  cells/uL because patients with NPC are at risk for thrombocytopenia as part of their underlying disease and miglustat use is common, the potential for any additional risk associated with levacetylleucine may be clinically important. These laboratory findings will be included in labeling.

### **Chemistry**

There were no CS outliers in general chemistry and renal function laboratory analyses in Trial IB1001-301, as detailed in [Table 39](#) and [Table 40](#).

**Table 39. Subjects With Chemistry Values Outside of Specified Levels<sup>1</sup> for General Chemistry, Pooled Analyses,<sup>2</sup> Safety Population, Trial IB1001-301**

| Laboratory Parameter              | Period I                               |                                         |                                                        | Period II                              |                                         | Overall                                |                                         |
|-----------------------------------|----------------------------------------|-----------------------------------------|--------------------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------------|-----------------------------------------|
|                                   | IB1001<br>N=30<br>n/N <sub>w</sub> (%) | Placebo<br>N=30<br>n/N <sub>w</sub> (%) | IB1001 vs.<br>Placebo<br>Risk Difference<br>% (95% CI) | IB1001<br>N=30<br>n/N <sub>w</sub> (%) | Placebo<br>N=29<br>n/N <sub>w</sub> (%) | IB1001<br>N=60<br>n/N <sub>w</sub> (%) | Placebo<br>N=59<br>n/N <sub>w</sub> (%) |
| Potassium, low (mEq/L)            |                                        |                                         |                                                        |                                        |                                         |                                        |                                         |
| Level 1 (<3.6)                    | 1/30 (3.3)                             | 0/30 (0)                                | 3.3 (-8.4, 16.8)                                       | 0/30 (0)                               | 0/29 (0)                                | 1/60 (1.7)                             | 0/59 (0)                                |
| Level 2 (<3.4)                    | 1/30 (3.3)                             | 0/30 (0)                                | 3.3 (-8.4, 16.8)                                       | 0/30 (0)                               | 0/29 (0)                                | 1/60 (1.7)                             | 0/59 (0)                                |
| Level 3 (<3)                      | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                      | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Blood urea nitrogen, high (mg/dL) |                                        |                                         |                                                        |                                        |                                         |                                        |                                         |
| Level 1 (>23)                     | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                      | 1/30 (3.3)                             | 0/29 (0)                                | 1/60 (1.7)                             | 0/59 (0)                                |
| Level 2 (>27)                     | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                      | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Level 3 (>31)                     | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                      | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |

Source: adlb.xpt; Software: R

<sup>1</sup> Threshold levels 1, 2, and 3 as defined in the Standard Safety Tables and Figures Integrated Guide.<sup>2</sup> Duration = Duration is 3 months for Period I and 3 months for Period II.Abbreviations: CI = confidence interval; N = number of subjects in treatment arm; n = number of subjects meeting criteria; N<sub>w</sub> = number of subjects with data

## **Kidney Function**

**Table 40. Subjects With One or More Kidney Function Analyte Values Outside of Specified Levels, Safety Population, Trial IB1001-301**

| Laboratory Parameter                    | Period I                               |                                         |                                                        | Period II                              |                                         | Overall                                |                                         |
|-----------------------------------------|----------------------------------------|-----------------------------------------|--------------------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------------|-----------------------------------------|
|                                         | IB1001<br>N=30<br>n/N <sub>w</sub> (%) | Placebo<br>N=30<br>n/N <sub>w</sub> (%) | IB1001 vs.<br>Placebo<br>Risk Difference<br>% (95% CI) | IB1001<br>N=30<br>n/N <sub>w</sub> (%) | Placebo<br>N=29<br>n/N <sub>w</sub> (%) | IB1001<br>N=60<br>n/N <sub>w</sub> (%) | Placebo<br>N=59<br>n/N <sub>w</sub> (%) |
| Creatinine, high (mg/dL)                |                                        |                                         |                                                        |                                        |                                         |                                        |                                         |
| Level 1 ( $\geq 1.5X$ baseline)         | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                      | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Level 2 ( $\geq 2X$ baseline)           | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                      | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Level 3 ( $\geq 3X$ baseline)           | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                      | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| eGFR, low (mL/min/1.73 m <sup>2</sup> ) |                                        |                                         |                                                        |                                        |                                         |                                        |                                         |
| Level 1 ( $\geq 25\%$ decrease)         | 0/28 (0)                               | 0/28 (0)                                | 0.0 (-12.3, 12.3)                                      | 0/28 (0)                               | 0/27 (0)                                | 0/56 (0)                               | 0/55 (0)                                |
| Level 2 ( $\geq 50\%$ decrease)         | 0/28 (0)                               | 0/28 (0)                                | 0.0 (-12.3, 12.3)                                      | 0/28 (0)                               | 0/27 (0)                                | 0/56 (0)                               | 0/55 (0)                                |
| Level 3 ( $\geq 75\%$ decrease)         | 0/28 (0)                               | 0/28 (0)                                | 0.0 (-12.3, 12.3)                                      | 0/28 (0)                               | 0/27 (0)                                | 0/56 (0)                               | 0/55 (0)                                |

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 3 months for Period I and 3 months for Period II.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

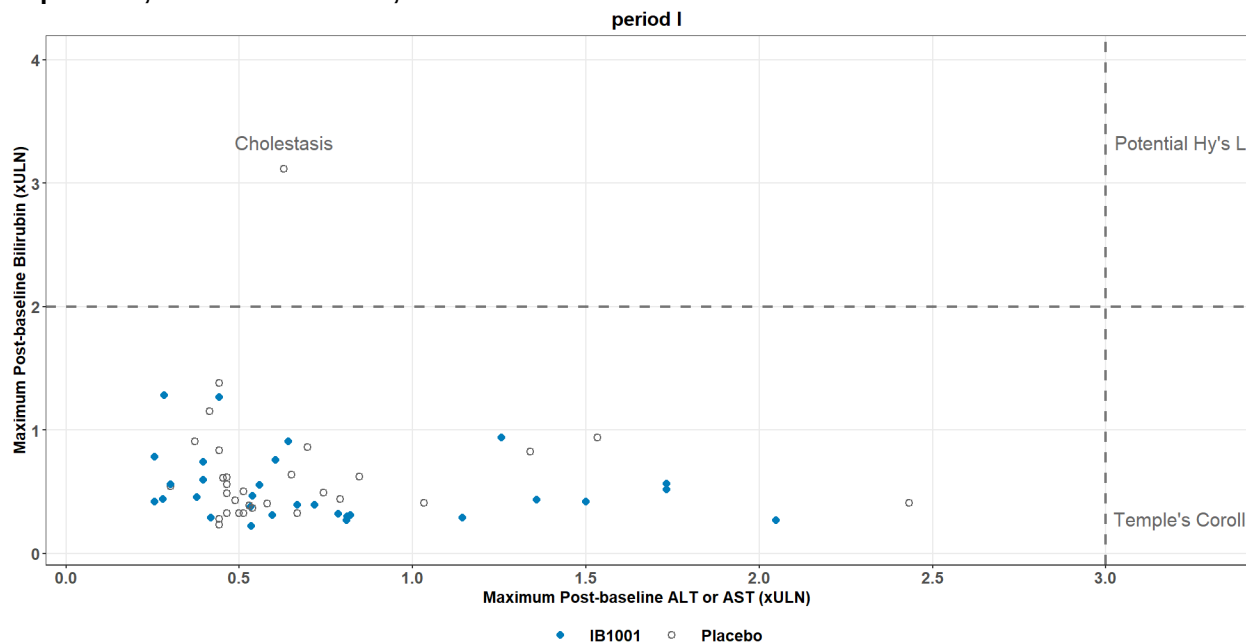
Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; N = number of subjects in treatment arm; n = number of subjects meeting criteria; N<sub>w</sub> = number of subjects with data

### 7.6.1.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Trial IB1001-301

The review team performed additional analyses to discern the prevalence and severity of elevated liver enzyme levels during the trials, focusing on ALT and AST. [Figure 12](#) shows a

screening assessment for potential cases of serious drug-induced liver injury during Treatment Period I. There was one subject randomized to placebo in Treatment Period I with elevated bilirubin (2X ULN). There were no subjects with elevated liver transaminases (AST/ALT).

**Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Pooled Analyses, Safety Population, Treatment Period I, Trial IB1001-301**



Source: adlb.xpt; Software: R

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug-induced liver injury; ULN = upper limit of normal

#### 7.6.1.8. Vital Signs, Trial IB1001-301

There were no specific trends of abnormalities for vital signs in Trial IB1001-301.

#### 7.6.1.9. Subgroups, Trial IB1001-301

AEs by demographic subgroup are detailed in [Table 41](#), which demonstrates a similar rate of occurrence of AEs. Adults over the age of 18 and pediatric subjects under the age of 18 had a similar number of AEs reported.

**Table 41. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial IB1001-301**

| Characteristic         | Period I                               |                                         |                                                     | Period II                              |                                         | Overall                                |                                         |
|------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------------|-----------------------------------------|
|                        | IB1001<br>N=30<br>n/N <sub>s</sub> (%) | Placebo<br>N=30<br>n/N <sub>s</sub> (%) | IB1001 vs. Placebo<br>Risk Difference<br>% (95% CI) | IB1001<br>N=30<br>n/N <sub>s</sub> (%) | Placebo<br>N=29<br>n/N <sub>s</sub> (%) | IB1001<br>N=60<br>n/N <sub>s</sub> (%) | Placebo<br>N=59<br>n/N <sub>s</sub> (%) |
| Sex                    |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Female                 | 7/14 (50.0)                            | 6/13 (46.2)                             | 3.8 (-32.5, 39.2)                                   | 9/13 (69.2)                            | 8/14 (57.1)                             | 16/27 (59.3)                           | 14/27 (51.9)                            |
| Male                   | 12/16 (75.0)                           | 7/17 (41.2)                             | 33.8 (-0.4, 60.9)                                   | 8/17 (47.1)                            | 9/15 (60.0)                             | 20/33 (60.6)                           | 16/32 (50.0)                            |
| Age group, years       |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Adult (≥18)            | 9/15 (60.0)                            | 8/22 (36.4)                             | 23.6 (-9.3, 52.0)                                   | 12/22 (54.5)                           | 8/14 (57.1)                             | 21/37 (56.8)                           | 16/36 (44.4)                            |
| Paediatric (<18)       | 10/15 (66.7)                           | 5/8 (62.5)                              | 4.2 (-33.3, 44.0)                                   | 5/8 (62.5)                             | 9/15 (60.0)                             | 15/23 (65.2)                           | 14/23 (60.9)                            |
| Age group ≥65, years   |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| ≥65                    | 0/0 (NA)                               | 1/2 (50.0)                              | NA                                                  | 1/2 (50.0)                             | 0/0 (NA)                                | 1/2 (50.0)                             | 1/2 (50.0)                              |
| Age group ≥75, years   |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| ≥75                    | 0/30 (0)                               | 0/30 (0)                                | 0.0 (-11.5, 11.5)                                   | 0/30 (0)                               | 0/29 (0)                                | 0/60 (0)                               | 0/59 (0)                                |
| Race                   |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Asian                  | 1/2 (50.0)                             | 0/0 (NA)                                | NA                                                  | 0/0 (NA)                               | 2/2 (100)                               | 1/2 (50.0)                             | 2/2 (100)                               |
| Other                  | 1/2 (50.0)                             | 1/2 (50.0)                              | -0.0 (-74.9, 74.9)                                  | 1/2 (50.0)                             | 1/2 (50.0)                              | 2/4 (50.0)                             | 2/4 (50.0)                              |
| White                  | 17/26 (65.4)                           | 12/28 (42.9)                            | 22.5 (-4.3, 46.3)                                   | 16/28 (57.1)                           | 14/25 (56.0)                            | 33/54 (61.1)                           | 26/53 (49.1)                            |
| Ethnicity              |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Not Hispanic or Latino | 18/25 (72.0)                           | 13/26 (50.0)                            | 22.0 (-5.1, 46.1)                                   | 15/26 (57.7)                           | 16/25 (64.0)                            | 33/51 (64.7)                           | 29/51 (56.9)                            |
| Not reported           | 0/1 (0)                                | 0/1 (0)                                 | 0.0 (-88.5, 88.5)                                   | 0/1 (0)                                | 1/1 (100)                               | 0/2 (0)                                | 1/2 (50.0)                              |
| Unknown                | 1/4 (25.0)                             | 0/3 (0)                                 | 25.0 (-43.8, 72.3)                                  | 2/3 (66.7)                             | 0/3 (0)                                 | 3/7 (42.9)                             | 0/6 (0)                                 |
| Is in United States    |                                        |                                         |                                                     |                                        |                                         |                                        |                                         |
| Non-United States      | 19/30 (63.3)                           | 13/30 (43.3)                            | 20.0 (-5.4, 43.0)                                   | 17/30 (56.7)                           | 17/29 (58.6)                            | 36/60 (60.0)                           | 30/59 (50.8)                            |

Source: adae.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI = confidence interval; N = number of subjects in treatment arm; n = number of subjects with adverse event; NA = not applicable; N<sub>s</sub> = total number of subjects for each specific subgroup that were assigned to that specific arm

#### 7.6.1.10. Open-Label Extension, Trial IB1001-301

Eligible subjects who completed Trial IB1001-301 had the option to enroll in the ongoing OLE (IB1001-301 OLE) for up to 2 years of treatment with levacetylleucine. A total of 54 subjects entered the EP. The median duration of exposure at the 120-day safety update cut-off was 290 days (62 to 355). Safety information reported for the OLE consists primarily of summary data because the trial is ongoing.

There have been no deaths reported in the OLE period thus far. There were five SAEs that occurred in three subjects, none of which were assessed as related to study drug.

One subject was withdrawn after an SAE reported as multi-organ dysfunction due to inability to participate in future trial visits.

##### 7.6.1.10.1. Serious Adverse Events, Trial IB1001-301 OLE

Three subjects had a total of five SAEs during the OLE. This trial is ongoing and the available details for each event provided by the Applicant are summarized below.

#### **Multi-Organ Dysfunction**

Subject (b) (6) was an adult male at the time of enrollment in IB1001-301. On Study Day 269 of the OLE, the subject was hospitalized due to multi-organ failure in the setting of an influenza A infection. The subject developed bilateral multifocal pneumonia which led to cardiorespiratory failure requiring cardiopulmonary resuscitation and assisted ventilation. Their hospitalization was also complicated by bacterial superinfection and septic shock, acute perimyocarditis, pulmonary edema, and acute renal failure requiring intermittent hemodialysis. The subject had a tracheostomy and gastrostomy tube placed and a brain computerized tomography scan revealed brain atrophy. The subject was ultimately withdrawn by the clinical investigator at their trial site due to inability to participate in future trial visits and was placed on hospice care. The study drug was stopped at the time of his hospitalization and not restarted thereafter. The SAE of multi-organ dysfunction was assessed as unrelated to the study drug. This reviewer agrees that multi-organ dysfunction was related to the complications of influenza A infection with pneumonia and not likely related to the study drug.

#### **Urinary Tract Infection, Mycoplasma Pneumonia**

Subject (b) (6) was an adolescent male at the time of enrollment in IB1001-301. The subject has a significant medical history of a previous liver transplant in addition to their diagnosis of NPC with recurrent gastrointestinal hemorrhage, an enlarged spleen, platelet dysfunction, recurrent diarrhea, and epilepsy. The subject was taking miglustat, ergocalciferol, sodium valproate, tranexamic acid, and tacrolimus in addition to levacetylleucine during the trial. Six weeks into the OLE, the subject was hospitalized for a urinary tract infection that was treated with antibiotics and resolved. No changes to the study drug were made during this hospitalization.

Approximately 9 months into the OLE (during the first year), the subject was hospitalized with mycoplasma pneumonia confirmed via chest X-ray and a polymerase chain reaction test for mycoplasma. The subject was treated with antibiotics first in the hospital and then with an

outpatient course. The study drug was interrupted during his hospitalization for 3 days and then restarted at the same dose.

Both SAEs were assessed as not related to the study drug. This reviewer agrees that both the urinary tract infection and the mycoplasma pneumonia are more likely to be related to the subject's underlying disease and not likely related to the study drug.

### **Seizure**

Subject (b) (6) was an elementary school age female at the time of enrollment in IB1001-301. At the time of enrollment, the subject's relevant past medical history in addition to their diagnosis of NPC included delayed motor skills, impaired expressive language, ataxia, vertical gaze palsy, and splenomegaly. The subject was taking miglustat in addition to levacetylleucine during the trial. After approximately 9 months of open-label treatment with levacetylleucine, the subject experienced new onset seizures described as "stereotypical movements of the arm with grimacing and was not responsive to her parents." An electroencephalogram confirmed seizures with focal onset. A magnetic resonance image of the subject's brain was completed and did not note any specific findings related to her new onset seizures. The subject was hospitalized for 2 days to complete a work-up of new-onset seizures and started on levetiracetam, after which the AE of "seizure" was considered resolved. No changes to the study drug were made.

Approximately 1 month after her initial diagnosis of epilepsy as detailed above (i.e., after about 10 months of open-label treatment with levacetylleucine), the subject was hospitalized for management of breakthrough seizures on levetiracetam. The subject was started on lamotrigine and discharged home after 1 day. No changes were made to the study drug.

The Applicant and investigator assessed both events of seizure as unrelated to the study drug. In the setting of the subject's diagnosis of NPC and progressive neurological symptoms as well as them taking the study drug for >9 months at the time of their initial diagnosis of epilepsy, this reviewer agrees that the subject's seizures are more likely due to progression of NPC and less likely due to levacetylleucine, although because this was a new diagnosis of epilepsy it is not possible to make definitive conclusions.

#### **7.6.1.10.2. Common Adverse Events, Trial IB1001-301 OLE**

Forty-three percent of subjects in the OLE experienced any treatment AE during the OLE. Like the parent study, the most common system organ classes were infections and infestations (16.7%) followed by gastrointestinal disorders (13%). Most reported AEs (preferred terms) occurred just once except for COVID-19 (n=3) and fall (n=2). The recurrence of COVID-19 diagnoses is not unexpected given the incidence in the general population during this time-period following the worldwide pandemic.

AEs that are also ARs for the concomitant medication miglustat were gastrointestinal disorders and weight loss. Rash (reported with Tanganil use, which uses a wheat starch excipient) occurred in two subjects (eczema and rash erythematous).

Data were presented in summary form only for this ongoing trial. Overall, the adverse events reported in the OLE period were similar to those reported during the parent study and did not raise any specific new safety concerns.

**Table 42. Treatment-Emergent Adverse Events, Open-Label Extension, Trial IB1001-301**

| System Organ Class<br>Preferred Term                       | Total (N=54) |    |
|------------------------------------------------------------|--------------|----|
|                                                            | N (%)        | m  |
| Any treatment-emergent adverse event                       | 23 (42.6%)   | 43 |
| Infections and infestations (SOC)                          | 9 (16.7%)    | 13 |
| COVID-19                                                   | 3 (5.6%)     | 3  |
| Erysipelas                                                 | 1 (1.9%)     | 1  |
| Gastrointestinal infection                                 | 1 (1.9%)     | 1  |
| Influenza                                                  | 1 (1.9%)     | 1  |
| Nasopharyngitis                                            | 1 (1.9%)     | 1  |
| Pneumonia                                                  | 1 (1.9%)     | 1  |
| Pneumonia mycoplasma                                       | 1 (1.9%)     | 1  |
| Rhinitis                                                   | 1 (1.9%)     | 1  |
| Upper respiratory tract infection                          | 1 (1.9%)     | 1  |
| Urinary tract infection                                    | 1 (1.9%)     | 1  |
| Viral infection                                            | 1 (1.9%)     | 1  |
| Gastrointestinal disorders (SOC)                           | 7 (13%)      | 8  |
| Anal fissure                                               | 1 (1.9%)     | 1  |
| Constipation                                               | 1 (1.9%)     | 1  |
| Diarrhea                                                   | 1 (1.9%)     | 1  |
| Dysphagia                                                  | 1 (1.9%)     | 1  |
| Enteritis                                                  | 1 (1.9%)     | 1  |
| Hematochezia                                               | 1 (1.9%)     | 1  |
| Stomatitis                                                 | 1 (1.9%)     | 1  |
| Vomiting                                                   | 1 (1.9%)     | 1  |
| Nervous system disorders (SOC)                             | 5 (9.3%)     | 6  |
| Amnesia                                                    | 1 (1.9%)     | 1  |
| Cataplexy                                                  | 1 (1.9%)     | 1  |
| Gelastic seizure                                           | 1 (1.9%)     | 1  |
| Headache                                                   | 1 (1.9%)     | 1  |
| Seizure                                                    | 1 (1.9%)     | 2  |
| Injury, poisoning and procedural complications (SOC)       | 4 (7.4%)     | 6  |
| Contusion                                                  | 1 (1.9%)     | 1  |
| Fall                                                       | 2 (3.7%)     | 3  |
| Head injury                                                | 1 (1.9%)     | 1  |
| Ligament sprain                                            | 1 (1.9%)     | 1  |
| General disorders and administration site conditions (SOC) | 3 (5.6%)     | 3  |
| Gait disturbance                                           | 1 (1.9%)     | 1  |
| Multiple organ dysfunction syndrome                        | 1 (1.9%)     | 1  |
| Pyrexia                                                    | 1 (1.9%)     | 1  |
| Respiratory, thoracic and mediastinal disorders (SOC)      | 2 (3.7%)     | 2  |
| Epistaxis                                                  | 1 (1.9%)     | 1  |
| Sleep apnea syndrome                                       | 1 (1.9%)     | 1  |
| Skin and subcutaneous tissue disorders (SOC)               | 2 (3.7%)     | 2  |
| Eczema                                                     | 1 (1.9%)     | 1  |
| Rash erythematous                                          | 1 (1.9%)     | 1  |
| Investigations (SOC)                                       | 1 (1.9%)     | 1  |
| Weight decreased                                           | 1 (1.9%)     | 1  |
| Metabolism and nutrition disorders (SOC)                   | 1 (1.9%)     | 1  |
| Vitamin K deficiency                                       | 1 (1.9%)     | 1  |
| Musculoskeletal and connective tissue disorders            | 1 (1.9%)     | 1  |
| Bursitis                                                   | 1 (1.9%)     | 1  |

Source: FDA recreation of the Applicant's submitted table of TEAEs in Trial IB1001-301 OLE.

Abbreviations: m = number of events, n (%) = number of subjects; OLE = open-label extension; SOC = system organ class; TEAE = treatment-emergent adverse events

## 7.6.2. Safety Results, Trial IB1001-201

### Overall Summary

Trial IB1001-201 was an open-label treatment study, thus it did not have a placebo-control group and was not the primary focus of our safety assessment. A total of 33 subjects with NPC between the ages of 7 and 64 years were enrolled, of which 31 completed treatment with levacetylleucine for 6 weeks followed by a 6-week washout period during the parent study. AEs that occurred in two subjects or more while on treatment with levacetylleucine were diarrhea, seizures, epistaxis, fall, rash, rhinitis, and upper respiratory tract infections. All these AEs were also reported in at least one subject during the placebo-controlled Trial IB1001-301 and remained relatively infrequent, thus no new specific treatment related risks were identified.

There were no SAEs that led to withdrawal from the trial. There were no deaths during the parent study. There was one withdrawal due to worsening epilepsy that was reported as mild in intensity and assessed as not related to the study drug.

### 7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Trial IB1001-201

[Table 43](#) provides a summary of AEs reported during the parent study, Trial IB1001-201. One or more TEAEs were reported by more subjects exposed to levacetylleucine (IB1001) than during the washout period (70% versus 21%). In the overall cohort, there were six SAEs in four subjects and no deaths.

**Table 43. Overview of Treatment-Emergent Adverse Events,<sup>1</sup> Safety Population, Trial IB1001-201**

| <b>Event Category</b>                                 | <b>IB1001<br/>N=33<br/>n (%)</b> | <b>Washout<br/>N=33<br/>n (%)</b> | <b>Overall<br/>N=33<br/>n (%)</b> |
|-------------------------------------------------------|----------------------------------|-----------------------------------|-----------------------------------|
| SAEs                                                  | 4 (12.1)                         | 0                                 | 4 (12.1)                          |
| SAEs with fatal outcome                               | 0                                | 0                                 | 0                                 |
| Life-threatening SAEs                                 | 0                                | 0                                 | 0                                 |
| SAEs requiring hospitalization                        | 4 (12.1)                         | 0                                 | 4 (12.1)                          |
| AE leading to permanent discontinuation of study drug | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| AE leading to dose modification of study drug         | 5 (15.2)                         | 0                                 | 5 (15.2)                          |
| AE leading to interruption of study drug              | 5 (15.2)                         | 0                                 | 5 (15.2)                          |
| AE leading to reduction of study drug                 | 0                                | 0                                 | 0                                 |
| AE leading to dose delay of study drug                | 0                                | 0                                 | 0                                 |
| Any AE                                                | 23 (69.7)                        | 7 (21.2)                          | 24 (72.7)                         |
| Severe and worse                                      | 4 (12.1)                         | 0                                 | 4 (12.1)                          |
| Moderate                                              | 3 (9.1)                          | 3 (9.1)                           | 5 (15.2)                          |
| Mild                                                  | 16 (48.5)                        | 4 (12.1)                          | 15 (45.5)                         |

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AEs that appeared during or after study treatment and was absent before, or an AE which was present before treatment and worsened while on treatment.

Duration is 6 weeks in treatment and 6 weeks in washout.

Severity as assessed by the investigator.

Abbreviations: AE = adverse event; N = number of subjects in treatment arm; n = number of subjects with at least one event; SAE = serious adverse event

The most frequently reported system organ class terms were infections and infestations (27%), nervous system disorders (27%), injury, positioning, and procedural complications (15%),

gastrointestinal disorders (15%), and respiratory, thoracic, and mediastinal disorders (15%). The most common AEs for the overall trial population (treatment period and washout period) during the parent study were diarrhea, seizure, fall, and rhinitis (see Section 7.6.2.5).

#### 7.6.2.2. Deaths, Trial IB1001-201

There were no deaths during the parent study of Trial IB1001-201.

#### 7.6.2.3. Serious Treatment-Emergent Adverse Events, Trial IB1001-201

The SAEs reported in Trial IB1001-201 are noted in Table 44. There were six SAEs reported in four subjects during the parent study. All six SAEs of upper respiratory infection, lower respiratory tract infection, dehydration, and a fall with resultant head injury and rib fracture were reported during the treatment period (none were during the washout period).

**Table 44. Subjects With Serious Treatment-Emergent Adverse Events<sup>1</sup> by System Organ Class and Preferred Term, Safety Population, Trial IB1001-201<sup>2</sup>**

| System Organ Class<br>Preferred Term                 | IB1001<br>N=33<br>n (%) | Washout<br>N=33<br>n (%) | Overall<br>N=33<br>n (%) |
|------------------------------------------------------|-------------------------|--------------------------|--------------------------|
| Any SAE                                              | 4 (12.1)                | 0                        | 4 (12.1)                 |
| Infections and infestations (SOC)                    | 2 (6.1)                 | 0                        | 2 (6.1)                  |
| Lower respiratory tract infection                    | 1 (3.0)                 | 0                        | 1 (3.0)                  |
| Upper respiratory tract infection                    | 1 (3.0)                 | 0                        | 1 (3.0)                  |
| Injury, poisoning and procedural complications (SOC) | 1 (3.0)                 | 0                        | 1 (3.0)                  |
| Fall                                                 | 1 (3.0)                 | 0                        | 1 (3.0)                  |
| Head injury                                          | 1 (3.0)                 | 0                        | 1 (3.0)                  |
| Rib fracture                                         | 1 (3.0)                 | 0                        | 1 (3.0)                  |
| Metabolism and nutrition disorders (SOC)             | 1 (3.0)                 | 0                        | 1 (3.0)                  |
| Dehydration                                          | 1 (3.0)                 | 0                        | 1 (3.0)                  |

Source: adae.xpt; Software: R

<sup>1</sup> Treatment-emergent adverse events defined as any AEs that appeared during or after study treatment and was absent before, or an AE which was present before treatment and worsened while on treatment.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

<sup>2</sup> Duration is 6 weeks in treatment and 6 weeks in washout.

Abbreviations: AE = adverse event; N = number of subjects in treatment arm; n = number of subjects with adverse event; SAE = serious adverse event; SOC = system organ class

#### Upper Respiratory Tract Infection

Subject (b) (6) was an adolescent male at the time of enrollment Trial IB1001-201. The subject was hospitalized on Study Day 14 for an upper respiratory infection, which resolved on Study Day 16. The study drug was interrupted briefly during the hospitalization and restarted. This event was assessed as not related to the study medication by the Applicant. This reviewer agrees that the upper respiratory tract infection was likely related to his underlying disease, not the study drug.

### **Lower Respiratory Tract Infection**

Subject (b) (6) was an adolescent male at the time of enrollment in Trial IB1001-201. The subject's past medical history was relevant for prior gastrostomy tube placement, sialorrhea, epilepsy, cataplexy, and recurrent respiratory infection in addition to their diagnosis of NPC. The subject was hospitalized on Study Day 30 for a lower respiratory tract infection that required intravenous antibiotics and resolved on Study Day 39. The study drug was continued throughout the hospitalization. This event was assessed as not related to the study medication by the clinical investigator. This reviewer agrees that the AE of lower respiratory tract infection is likely related to progression of NPC, sialorrhea, and recurrent lung infection.

### **Dehydration**

Subject (b) (6) was an elementary school age male at the time of enrollment in Trial IB1001-201. The subject's relevant past medical history besides a diagnosis of NPC is significant for a liver transplant, chronic gastrointestinal inflammation, recurrent gastrointestinal hemorrhage, and anemia. On Study Day 23, the subject developed a "chest" infection treated with amoxicillin and was hospitalized for dehydration for 24 hours on Study Day 26. The study drug was interrupted during the hospital stay only and restarted at the same dose. The SAE of dehydration was assessed as unrelated to the study drug and attributed to amoxicillin by the clinical investigator. It is difficult to determine whether amoxicillin was the culprit based on the information provided; however, this reviewer agrees that the hospitalization was likely related to either the infection or the associated treatment, not the study drug.

### **Fall With Head Injury and Rib Fracture**

Subject (b) (6) was an adult female at the time of enrollment in Trial IB1001-201. The subject had a history of previous recurrent falls. The subject had a fall that resulted in a closed head injury and multiple rib fractures resulting in a hospitalization from Study Day 44 to Study Day 50. The study drug was interrupted for 6 days during the hospitalization. The event was reported as resolved 1 month later. This SAE was assessed as not related to the study drug because there were no features suggesting a drug-related cause (e.g., new onset hypotension). This reviewer agrees that a traumatic fall was unlikely related to the study drug and more likely related to symptoms of ataxia or abnormal gait due to NPC or an unrelated accidental fall.

#### **7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Trial IB1001-201**

One subject discontinued the trial due to worsening epilepsy (seizures increased).

Subject (b) (6) was an adolescent male at the time of enrollment in Trial IB1001-201. Relevant medical history besides a diagnosis of NPC was epilepsy requiring three antiseizure medications (ethosuximide, valproate, and clobazam). The subject had additional seizures reported as "mild" on Study Day 10. The subject was treated with three additional antiseizure medications with some improvement but was ultimately withdrawn from the trial at the discretion of the clinical investigator on Study Day 36. This reviewer agrees that the increase in seizures of mild intensity was unlikely to be related to the study drug and more likely related to progression of NPC with treatment-refractory epilepsy.

### 7.6.2.5. Treatment-Emergent Adverse Events, Trial IB1001-201

Overall, 73% of subjects experienced a TEAE while on treatment with levacetylleucine versus 21% during the washout period.

**Table 45. Subjects With Adverse Events, Trial IB1001-201**

| <b>Preferred Term</b>                | <b>IB1001<br/>N=33<br/>n (%)</b> | <b>Washout<br/>N=33<br/>n (%)</b> | <b>Overall<br/>N=33<br/>n (%)</b> |
|--------------------------------------|----------------------------------|-----------------------------------|-----------------------------------|
| Any AE                               | 23 (69.7)                        | 7 (21.2)                          | 24 (72.7)                         |
| Diarrhea                             | 3 (9.1)                          | 1 (3.0)                           | 3 (9.1)                           |
| Seizure                              | 3 (9.1)                          | 1 (3.0)                           | 4 (12.1)                          |
| Epistaxis                            | 2 (6.1)                          | 0                                 | 2 (6.1)                           |
| Fall                                 | 2 (6.1)                          | 1 (3.0)                           | 3 (9.1)                           |
| Lower respiratory tract infection    | 2 (6.1)                          | 0                                 | 2 (6.1)                           |
| Rash pruritic                        | 2 (6.1)                          | 0                                 | 2 (6.1)                           |
| Rhinitis                             | 2 (6.1)                          | 1 (3.0)                           | 3 (9.1)                           |
| Upper respiratory tract infection    | 2 (6.1)                          | 0                                 | 2 (6.1)                           |
| Aggression                           | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Anal incontinence                    | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Arthralgia                           | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Asthenia                             | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Balance disorder                     | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Blood alkaline phosphatase increased | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Contusion                            | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Coordination abnormal                | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Dehydration                          | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Dementia                             | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Dropped head syndrome                | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Dysphagia                            | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Fatigue                              | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Flatulence                           | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Gastroenteritis                      | 1 (3.0)                          | 1 (3.0)                           | 2 (6.1)                           |
| Head injury                          | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Headache                             | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Increased appetite                   | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Nasopharyngitis                      | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Neck pain                            | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Obstructive airways disorder         | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Petit mal epilepsy                   | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Productive cough                     | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Restlessness                         | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Rib fracture                         | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Sleep disorder                       | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Traumatic hematoma                   | 1 (3.0)                          | 0                                 | 1 (3.0)                           |
| Blood pressure increased             | 0                                | 1 (3.0)                           | 1 (3.0)                           |

| Preferred Term      | IB1001<br>N=33<br>n (%) | Washout<br>N=33<br>n (%) | Overall<br>N=33<br>n (%) |
|---------------------|-------------------------|--------------------------|--------------------------|
| Cough               | 0                       | 1 (3.0)                  | 1 (3.0)                  |
| Drooling            | 0                       | 1 (3.0)                  | 1 (3.0)                  |
| Ejaculation failure | 0                       | 1 (3.0)                  | 1 (3.0)                  |
| Illiteracy          | 0                       | 1 (3.0)                  | 1 (3.0)                  |
| Indifference        | 0                       | 1 (3.0)                  | 1 (3.0)                  |
| Rash                | 0                       | 2 (6.1)                  | 2 (6.1)                  |

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AEs that appeared during or after study treatment and was absent before, or an AE which was present before treatment and worsened while on treatment.

Duration is 6 weeks in treatment and 6 weeks in washout.

Coded as MedDRA preferred terms.

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment arm; n = number of subjects with adverse event

During treatment with levacetylleucine, the AEs that occurred most were diarrhea and seizure in three subjects, followed by fall, lower respiratory tract infection, rash pruritic, rhinitis, and upper respiratory infection, which occurred in two subjects each. Diarrhea, seizure, fall and rhinitis all occurred in one subject each during the washout period as well. All other AEs occurred in one subject each. These TEAEs are generally similar to those seen in Trial IB1001-301. Because the parent study of Trial IB1001-201 was both an open-label study and of shorter duration than the pivotal trial, it would be challenging to determine whether any of the AEs that occurred infrequently during Trial IB1001-201 and only once during Trial IB1001-301 are more likely to be attributable to levacetylleucine rather than NPC or concomitant medications. Thus, labeling will reflect the AEs identified during the double-blind placebo-controlled trial during Treatment Period I.

#### 7.6.2.6. Laboratory Findings, Trial IB1001-201

Routine safety monitoring bloodwork (hematology, clinical chemistry, creatine kinase, liver function analyses) and urinalysis were obtained. The mean values for most of these tests remained within normal ranges except for platelet levels, which were in the range of thrombocytopenia both during treatment with levacetylleucine and during the washout period.

#### Hematology

[Table 46](#) demonstrates abnormalities in hematology laboratory values during Trial IB1001-201. Most of the hematology laboratory values were within normal limits except for platelet levels, which revealed thrombocytopenia ( $<150 \times 10^3$  cells/uL) both during open-label treatment with levacetylleucine and during the washout period.

**Table 46. Subjects With One or More Hematology Analyte Values Outside of Specified Levels, Safety Population, Trial IB1001-201**

| Laboratory Parameter                      | IB1001<br>N=33<br>n/N <sub>w</sub> (%) | Washout<br>N=33<br>n/N <sub>w</sub> (%) | Overall<br>N=33<br>n/N <sub>w</sub> (%) |
|-------------------------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------|
| <b>Complete Blood Count</b>               |                                        |                                         |                                         |
| WBC, low (10 <sup>3</sup> cells/uL)       |                                        |                                         |                                         |
| Level 1 (<3.5)                            | 0/33 (0)                               | 0/31 (0)                                | 0/33 (0)                                |
| Level 2 (<3)                              | 0/33 (0)                               | 0/31 (0)                                | 0/33 (0)                                |
| Level 3 (<1)                              | 0/33 (0)                               | 0/31 (0)                                | 0/33 (0)                                |
| WBC, high (10 <sup>3</sup> cells/uL)      |                                        |                                         |                                         |
| Level 1 (>10.8)                           | 1/33 (3.0)                             | 0/31 (0)                                | 1/33 (3.0)                              |
| Level 2 (>13)                             | 0/33 (0)                               | 0/31 (0)                                | 0/33 (0)                                |
| Level 3 (>15)                             | 0/33 (0)                               | 0/31 (0)                                | 0/33 (0)                                |
| Hemoglobin, low (g/dL)                    |                                        |                                         |                                         |
| Level 2 (>1.5 g/dL dec. from baseline)    | 0/33 (0)                               | 2/31 (6.5)                              | 2/33 (6.1)                              |
| Level 3 (>2 g/dL dec. from baseline)      | 0/33 (0)                               | 0/31 (0)                                | 0/33 (0)                                |
| Hemoglobin, high (g/dL)                   |                                        |                                         |                                         |
| Level 2 (>2 g/dL inc. from baseline)      | 0/33 (0)                               | 0/31 (0)                                | 0/33 (0)                                |
| Level 3 (>3 g/dL inc. from baseline)      | 0/33 (0)                               | 0/31 (0)                                | 0/33 (0)                                |
| Platelets, low (10 <sup>3</sup> cells/uL) |                                        |                                         |                                         |
| Level 1 (<140)                            | 14/33 (42.4)                           | 12/31 (38.7)                            | 17/33 (51.5)                            |
| Level 2 (<125)                            | 8/33 (24.2)                            | 7/31 (22.6)                             | 11/33 (33.3)                            |
| Level 3 (<100)                            | 2/33 (6.1)                             | 1/31 (3.2)                              | 2/33 (6.1)                              |

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 6 weeks in treatment and 6 weeks in washout.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: dec. = decrease; inc. = increase; N = number of subjects in treatment arm; n = number of subjects meeting criteria; NA = not applicable; N<sub>w</sub> = number of subjects with data; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cells

## Thrombocytopenia

There was a similar number of subjects during the treatment and washout periods with thrombocytopenia. During the treatment period, 14/33 (42%) subjects had platelets <140 10<sup>3</sup> cells/uL compared to 12/31 (39%) during the washout period. There were 8/33 (24%) compared to 7/31 (23%) with platelets <125 10<sup>3</sup> cells/uL, and 2 subjects during the treatment period and 1 subject during the washout period with platelets <100 10<sup>3</sup> cells/uL. Because patients with NPC can have thrombocytopenia and because thrombocytopenia is also a known risk of miglustat, it is not clear if there is an increased risk of thrombocytopenia attributable to levacetylleucine from this data. Because this risk was similarly demonstrated in Trial IB1001-301, these results from Trial IB101-201 did not raise additional safety concerns.

### 7.6.2.7. Open-Label Extension, Trial IB1001-201

Eligible subjects who completed Trial IB1001-201 had the option to enroll in an OLE (IB1001-201 OLE) for up to 2 years of treatment with levacetylleucine. A total of 19 subjects entered the EP, of which 13 subjects completed the trial. There were two open-label treatment periods, Treatment Period I consisted of 1 year of open-label treatment, followed by a 6-week washout period, and then Treatment Period II, which consisted of a second year of open-label treatment. The total duration of exposure during the OLE ranged from 176 to 816 days.

There were no deaths reported in the OLE. There were 22 SAEs reported in five subjects, none of which were assessed as related to study drug. There were no AEs that lead to trial withdrawal.

Of note, the EP encompassed the beginning and much of the duration of the COVID-19 pandemic, during which there were worldwide restrictions on travel and heightened health concerns, especially for medically complex individuals. Twelve subjects who had completed IB1001-201 did not enroll in the OLE, and six subjects withdrew consent from the OLE without a clear explanation, which the Agency suspects may have been impacted by the COVID-19 pandemic, as noted in Section [6.2.1.2](#).

#### 7.6.2.7.1. Serious Adverse Events, IB1001-201 Open-Label Extension

Five subjects had a total of 22 SAEs during the OLE. There were three subjects who experienced aspiration pneumonia, otherwise each SAE was unique and included the following: gastrointestinal hemorrhage and melena, seizure, a uterine leiomyoma requiring hysterectomy, gastric device dislocation causing gastric perforation, cataplexy, and viral pneumonia. Most of the SAEs reported occurred in one subject who had multiple complications of NPC during the OLE phase, as detailed below. All SAEs were assessed as not related to the study drug by the Applicant.

##### **Aspiration Pneumonia**

Subject (b) (6) was an adult female at the time of enrollment in Trial IB1001-201. The subject had a history of dysphagia and was hospitalized for aspiration pneumonia on Study Day 468 until Study Day 482. The subject continued the study drug during their hospitalization. The AE of aspiration pneumonia was assessed as not related to the study drug. This reviewer agrees that this event was more likely related to NPC and/or dysphagia and not likely related to the study drug.

##### **Gastrointestinal Hemorrhage/Melena**

Subject (b) (6) was an elementary school age male at the time of enrollment in Trial IB1001-201. This subject's medical history in addition to a diagnosis of NPC is relevant for a history of liver transplantation, recurrent gastrointestinal hemorrhage, an enlarged spleen, and platelet dysfunction.

This subject had multiple gastrointestinal complications during the OLE of IB1001-201, including the following hospitalizations:

- On Study Days 181 to 182 for investigations for a cause of melena.
- Study Days 713 to 715 for gastrointestinal hemorrhage.
- Study Days 730 to 733 for gastrointestinal hemorrhage, the study drug was interrupted during this hospital stay and then restarted at the same dose.
- Study Days 766 to 799 for gastrointestinal hemorrhage, the study drug was interrupted during this hospital stay and then restarted at the same dose.
- Study Days 860 to 862 for gastrointestinal hemorrhage.

All the SAEs of melena and gastrointestinal hemorrhage were assessed as unrelated to study drug and instead related to NPC and a history of liver transplantation with complications of liver disease and platelet dysfunction with recurrent gastrointestinal hemorrhage. This reviewer agrees with this assessment.

### **Seizure**

Subject (b) (6) was an adolescent male at the time of enrollment in Trial IB1001-201. This subject had a known history of epilepsy related to his diagnosis of NPC and was on three anti-seizure medications (valproic acid, clobazam and lamotrigine). This subject experienced a seizure requiring a change in his baseline seizure medications on Study Day 684, and this SAE resolved on Study Day 686. The study drug was continued, and the seizure was attributed to NPC and associated epilepsy and not assessed as related to the study drug. This reviewer agrees that the seizure was more likely attributable to the subject's underlying disease/epilepsy.

### **Pneumonia, Aspiration Pneumonia, Multiple Medical Complications**

Subject (b) (6) was an adult male at the time of enrollment in Trial IB1001-201. This subject had a complicated past medical history including recurrent pneumonia with or without aspiration in addition to his other symptoms of NPC. During the trial, this subject continued to have a complicated medical course with multiple hospitalizations as follows:

- On Study Day 140 to 147 for pneumonia and treated with antibiotics.
- Study Day 155 to 157 for viral pneumonia.
- Study Day 203 to 205 for "bronchopneumonia."
- Study Day 253 to 254 for aspiration pneumonia.
- Study Day 276 to 287 for aspiration pneumonia, with a second aspiration event during the hospitalization.
- Study Day 295 to 309 for pneumonia.
- Study Day 315 to 322 for aspiration pneumonia.
- Study Day 335 to 342 for placement of a PEG tube due to weight loss and recurrent pulmonary infections. This hospitalization was complicated by his PEG tube becoming dislodged and causing a gastric perforation with peritonitis. The subject required a laparotomy and intravenous (IV) antibiotics prior to discharge home and the study drug was interrupted during part of his hospital stay.
- Study Day 464 (during the washout period) the subject experienced multiple episodes of cataplexy on the same day and was briefly hospitalized for observation and IV fluids.

All these SAEs were assessed as not related to the study drug. This reviewer agrees that, in the context of this subject's severe and complicated medical history, these events most likely represent progression of NPC and associated complications.

### **Uterine Leiomyoma Requiring Hysterectomy and Aspiration Pneumonia**

Subject (b) (6) was an adult female of age at the time of enrollment in Trial IB1001-201. This subject was hospitalized on Study Day 413 with abdominal pain and found to have a uterine

leiomyoma requiring hysterectomy. This subject was discharged from the hospital on Study Day 429. There were no changes made to the study medication during the hospitalization. This SAE was assessed as unrelated to the study medication. This reviewer agrees that the uterine mass was unlikely due to the study medication. Leiomyomas are also not known to be associated with NPC.

On Study Day 707, this subject had a second SAE of aspiration pneumonia that required hospitalization and treatment with IV antibiotics followed by a course of oral antibiotics. The SAE was reported as resolved on Study Day 737. There were no changes made to the study medication. Prior history was relevant for a feeding tube that was placed many years prior to enrollment in the trial, presumably in the setting of dysphagia and/or poor nutrition. This reviewer agrees with that the SAE of pneumonia is likely related to progression of this subject's underlying disease.

#### 7.6.2.7.2. Common Adverse Events, IB1001-201 Open-Label Extension

Overall, 93.6% of subjects experienced a TEAE while on treatment with levacetylleucine during Treatment Periods I and II versus 26.3% during the washout period.

**Table 47. Subjects With Adverse Events, Open-Label Extension, Trial IB1001-201**

| <b>Preferred Term</b>                    | <b>Extension I<br/>N=19<br/>n (%)</b> | <b>Extension<br/>Washout<br/>N=19<br/>n (%)</b> | <b>Extension II<br/>N=16<br/>n (%)</b> | <b>Overall<br/>(Extension I &amp; II)<br/>N=16<br/>n (%)</b> |
|------------------------------------------|---------------------------------------|-------------------------------------------------|----------------------------------------|--------------------------------------------------------------|
| Any AE                                   | 16 (84.2)                             | 5 (26.3)                                        | 11 (68.8)                              | 15 (93.8)                                                    |
| Fall                                     | 8 (42.1)                              | 2 (10.5)                                        | 2 (12.5)                               | 9 (56.2)                                                     |
| Contusion                                | 3 (15.8)                              | 0                                               | 1 (6.2)                                | 3 (18.8)                                                     |
| Corona virus infection                   | 3 (15.8)                              | 0                                               | 2 (12.5)                               | 4 (25.0)                                                     |
| Dysphagia                                | 2 (10.5)                              | 0                                               | 1 (6.2)                                | 2 (12.5)                                                     |
| Pneumonia aspiration                     | 2 (10.5)                              | 0                                               | 1 (6.2)                                | 3 (18.8)                                                     |
| Rash                                     | 2 (10.5)                              | 0                                               | 0                                      | 1 (6.2)                                                      |
| Aggression                               | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Alanine aminotransferase increased       | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Anal incontinence                        | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Aspiration                               | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Asthenia                                 | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Attention deficit/hyperactivity disorder | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Cataplexy                                | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Cognitive disorder                       | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Constipation                             | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Cough                                    | 1 (5.3)                               | 1 (5.3)                                         | 0                                      | 1 (6.2)                                                      |
| Decubitus ulcer                          | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Device dislocation                       | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Diarrhea haemorrhagic                    | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Dysarthria                               | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Dyskinesia                               | 1 (5.3)                               | 0                                               | 1 (6.2)                                | 2 (12.5)                                                     |
| Dyspepsia                                | 1 (5.3)                               | 0                                               | 1 (6.2)                                | 1 (6.2)                                                      |
| Dystonia                                 | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Epilepsy                                 | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Eye contusion                            | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Face injury                              | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Fatigue                                  | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Gastric perforation                      | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Gastroenteritis viral                    | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Gastrooesophageal reflux disease         | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Gastrostomy                              | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Hypersensitivity                         | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Hysterectomy                             | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |

| <b>Preferred Term</b>             | <b>Extension I<br/>N=19<br/>n (%)</b> | <b>Extension<br/>Washout<br/>N=19<br/>n (%)</b> | <b>Extension II<br/>N=16<br/>n (%)</b> | <b>Overall<br/>(Extension I &amp; II)<br/>N=16<br/>n (%)</b> |
|-----------------------------------|---------------------------------------|-------------------------------------------------|----------------------------------------|--------------------------------------------------------------|
| Incontinence                      | 1 (5.3)                               | 0                                               | 1 (6.2)                                | 2 (12.5)                                                     |
| Influenza                         | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Injury                            | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Insomnia                          | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Joint injury                      | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Lower respiratory tract infection | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Major depression                  | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Medical device removal            | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Melaena                           | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Memory impairment                 | 1 (5.3)                               | 0                                               | 1 (6.2)                                | 2 (12.5)                                                     |
| Mobility decreased                | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Motor dysfunction                 | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Nausea                            | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Ophthalmoplegia                   | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Pharyngitis                       | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Platelet count decreased          | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Pneumonia                         | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Pneumonia viral                   | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Sciatica                          | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Seizure                           | 1 (5.3)                               | 1 (5.3)                                         | 2 (12.5)                               | 2 (12.5)                                                     |
| Skin abrasion                     | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Skin laceration                   | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Sleep disorder                    | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Tooth injury                      | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Traumatic haematoma               | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Urinary incontinence              | 1 (5.3)                               | 0                                               | 0                                      | 0                                                            |
| Urinary retention                 | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Uterine leiomyoma                 | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Victim of crime                   | 1 (5.3)                               | 0                                               | 0                                      | 1 (6.2)                                                      |
| Vomiting                          | 1 (5.3)                               | 0                                               | 1 (6.2)                                | 2 (12.5)                                                     |
| Agitation                         | 0                                     | 0                                               | 1 (6.2)                                | 1 (6.2)                                                      |

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|                              | Extension I<br>N=19<br>n (%) | Extension<br>Washout<br>N=19<br>n (%) | Extension II<br>N=16<br>n (%) | Overall<br>(Extension I & II)<br>N=16<br>n (%) |
|------------------------------|------------------------------|---------------------------------------|-------------------------------|------------------------------------------------|
| <b>Preferred Term</b>        |                              |                                       |                               |                                                |
| Coronavirus test positive    | 0                            | 2 (10.5)                              | 0                             | 0                                              |
| Diarrhoea                    | 0                            | 0                                     | 2 (12.5)                      | 2 (12.5)                                       |
| Disturbance in attention     | 0                            | 0                                     | 1 (6.2)                       | 1 (6.2)                                        |
| Gastrointestinal haemorrhage | 0                            | 0                                     | 1 (6.2)                       | 1 (6.2)                                        |
| Hypoacusis                   | 0                            | 0                                     | 1 (6.2)                       | 1 (6.2)                                        |
| Nasopharyngitis              | 0                            | 1 (5.3)                               | 0                             | 0                                              |
| Paroxysmal arrhythmia        | 0                            | 0                                     | 1 (6.2)                       | 1 (6.2)                                        |
| Rhinitis                     | 0                            | 0                                     | 1 (6.2)                       | 1 (6.2)                                        |

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AEs that appeared during or after study treatment and was absent before, or an AE which was present before treatment and worsened while on treatment.

Duration is 1 year in first extension period, 1 year in second extension period.

Coded as MedDRA preferred terms.

Abbreviations: N = number of subjects in treatment arm; n = number of subjects with adverse event

The most common AEs that occurred during either of the 1-year-long open-label treatment periods included falls (nine subjects), coronavirus infection (four subjects), contusion and aspiration pneumonia (three subjects), and dysphagia (two subjects). There were more falls reported during the first year of open-label treatment (8) compared to the second year of open-label treatment (2). Because there is no control group for comparison, conclusions regarding increased frequency of falls with prolonged treatment could not be drawn.

Generally, the AEs reported during both the parent study and OLE of Trial IB1001-201 were similar to those reported during Trial IB1001-301 with the exception of multiple coronavirus infections, which reflects the timing of the trial during the coronavirus pandemic. There were no additional new safety concerns raised during the OLE of Trial IB1001-201.

### 7.6.3. Safety Results, Other Indications

#### 7.6.3.1. Trial IB1001-202

##### **Summary**

Trial IB1001-202, an open-label treatment study in GM2 gangliosidosis, was reviewed only for SAEs, withdrawals, and deaths. GM2 gangliosidosis is another autosomal recessive lysosomal storage disorder with some overlapping signs and symptoms seen in NPC.

In general, levacetylleucine was well-tolerated in Trial IB1001-202 and there were no SAEs, AEs leading to withdrawal from the trial, or deaths that raised any new safety concerns in our review of levacetylleucine.

##### **Trial IB1001-202, Parent Study**

A total of 30 subjects between the ages of 6 and 55 years were enrolled, of which 27 subjects completed treatment with levacetylleucine for 6 weeks followed by a 6-week washout period during the parent study. The duration of levacetylleucine exposure in the parent study ranged from 16 to 132 days.

There were four SAEs that occurred in two subjects, none of which were assessed as related to the study drug. There were no deaths during the parent study. There was one withdrawal after 16 days of treatment with levacetylleucine for tremor without any further follow-up for an assessment and determination of causation, and one withdrawal due to COVID-19 pandemic-related travel restrictions.

SAEs that occurred during Trial IB1001-201 include a fall causing a vertebral fracture in one subject and an exacerbation of previously diagnosed bipolar disorder with psychotic features in another subject; neither of these SAEs were assessed as related to the study drug.

##### **IB1001-202 Open-Label Extension**

Subjects who completed the parent study were eligible to enroll in an open-label extension study for up to 2 additional years of open-label treatment with a 6-week washout period in between the two open-label treatment periods. Fourteen subjects enrolled in the EP, and just seven subjects completed both years of treatment. The duration of levacetylleucine exposure during the OLE ranged from 266 to 754 days.

Like Trial IB1001-201, this trial coincided with the emergence of the COVID-19 pandemic, and there were multiple withdrawals from the trial with limited details regarding the reason for the withdrawal.

There was one SAE reported in one subject during the OLE. This SAE was an exacerbation of bipolar disorder that occurred during the washout period of the OLE and assessed as not related to the study drug. There were no TEAEs that led to withdrawal from the trial. There were no deaths.

## 7.7. Key Safety Review Issues

### 7.7.1. Embryofetal Development Toxicity in Rodents and Non-Rodents

#### **Issue**

Dose-range finding animal embryo-fetal development (EFD) toxicity studies in rats and rabbits demonstrate EFD toxicity including induction of malformations following administration of levacetylleucine during pregnancy. However, final study reports for EFD toxicity studies in rats and rabbits have not been submitted. Additionally, because the protocols for EFD toxicity studies in rats and rabbits were not submitted to the agency, it is uncertain if the doses that were selected for definitive studies were adequate to evaluate the risk to EFD.

#### **Background**

In pregnant rats, increases in resorptions, post-implantation loss, and skeletal malformation were seen due to exposure to levacetylleucine at doses of 600 mg/kg/day and at the human-equivalent dose of 97 mg/kg/day. In pregnant rabbits, increased resorptions, post-implantation loss, decreased fetal body weight, and increased skeletal malformations were observed following exposure to levacetylleucine at doses of 1250 mg/kg/day and at the human-equivalent dose of 403 mg/kg/day.

#### **Assessment**

Concern for a CS risk to EFD was demonstrated in animal studies. Specifically, nonclinical effects occurred in both nonclinical species. A Warning and Precaution for EFD toxicity that describes the potential risk to a fetus with recommendations to mitigate the risk (i.e., effective contraception) should be included in labeling. In addition, information was also described in Section 8.1 *Pregnancy* and in Section 8.3 *Females and Males of Reproductive Potential* subsections of the label ([Table 89](#)). See Section [8.4](#) of this review for details.

#### **Conclusion**

A Warning and Precaution for EFD toxicity recommends that females of reproductive potential avoid pregnancy and use effective contraception during treatment with levacetylleucine. Submission of final study reports for EFD toxicity studies in rats and rabbits will be required as a postmarketing requirement (PMR). Additionally, because it is uncertain if the doses and trial design for definitive studies were appropriate for reasons described above, the Applicant may be required to repeat the EFD toxicity studies in rats and rabbits after the dose selection and trial protocols have been reviewed by the Agency.

### 7.7.2. Juvenile Toxicology Profile Unknown

#### **Issue**

A juvenile toxicity study with levacetylleucine has not been conducted. Evaluation of toxicity of levacetylleucine in juvenile animals is needed because onset of NPC ranges from infancy into adulthood, and treatment with levacetylleucine may be lifelong. Data in the rat and rabbit EFD studies indicate levacetylleucine crossed the placenta and modulated growth of bones, and it is expected that levacetylleucine will modulate the growth of bones in juvenile animals as well. Because levacetylleucine crosses the blood brain barrier and because its major metabolite, leucine, causes defects in ossification of the skull, torsion of the neck, and depression of the brain waves ([Bergstrom et al. 1967](#)), levacetylleucine has the potential to influence growth, neurological development (learning and memory), sexual development, and general health. Hence, there is need for a juvenile toxicity study to determine the toxic effects of levacetylleucine in juvenile animals and to inform patients of potential risks of this medication. These risks cannot be readily characterized in patients in the postmarketing setting.

#### **Conclusion**

While the current clinical safety and efficacy data appear to be adequate to support approval in pediatric patients, the available data are limited; therefore, a juvenile toxicity study will be required as a PMR.

### 7.7.3. Effects on Male and Female Fertility and Early Embryonic Development Unknown

#### **Issue**

Rodent male and female fertility and early embryonic development toxicity studies with levacetylleucine has not been conducted. Evaluation of effects of levacetylleucine on fertility and early embryonic development is needed because there are adult-onset forms of NPC and because treatment with levacetylleucine for early onset NPC may continue into reproductive age. As such, some patients of reproductive age are likely to be exposed. Additionally, levacetylleucine is a modified amino acid that appears to have widespread distribution; therefore, placental transfer is expected, and there may be an impact on embryo implantation, as suggested by data from the non-good laboratory practice dose-ranging embryofetal development studies that were submitted in the NDA. Levacetylleucine appeared to reduce the number of implantations in dams treated in an EFD study; therefore, the purpose of this study is to evaluate whether levacetylleucine may affect fertility through inhibition of implantation or through other effects on gametogenesis.

#### **Conclusion**

Information was described in the impairment of fertility subsection of labeling ([Table 89](#); [Section 13.1](#)) to indicate that studies of fertility and early embryonic development and pre- and postnatal toxicology were not conducted with the drug. These risks cannot be readily characterized in patients. Rodent male and female fertility and early embryonic development toxicity studies will be required as PMRs to support risk communication to patients and caregivers.

#### 7.7.4. Effects on Pre- and Postnatal Development Unknown

##### **Issue**

A rodent pre- and postnatal development toxicity study with levacetylleucine has not been conducted. Evaluation of the effects of levacetylleucine on pre- and postnatal development is needed because onset of NPC ranges from infancy into adulthood, and treatment with levacetylleucine may begin in infancy and be lifelong. Levacetylleucine was found to cause increases in post-implantation loss and malformation in skeletal bones in a dose-range finding EFD study in rabbits. Leucine, a metabolite of levacetylleucine, as a single 0.2 mL injection of a 1% solution in the amniotic sac of a nine-day-old chicken embryo is reported to cause morphological anomalies of the legs (including inward flexion of the toes, leg extension or flexion at hip joint), defects in ossification of the skull, torsion of the neck, and depression of the brain waves ([Bergstrom et al. 1967](#)). Therefore, exposure to levacetylleucine has the potential to cause adverse effects on growth and development (neurological, physical, and sexual) from prenatal and into postnatal stages of life. This possibility requires investigation. Additionally, levacetylleucine is a modified amino acid that appears to have widespread distribution; therefore, placental and lactational transfer are expected. Significant exposure to a fetus and/or neonate is likely. This study will evaluate the effect of the drug on growth, maturation, and reproduction when offspring are exposed during pregnancy and lactation. This risk cannot be readily characterized in patients.

##### **Conclusion**

Information was described in the impairment of fertility subsection of labeling ([Table 89](#); Section [8.1](#)) to indicate that study of pre- and postnatal toxicology has not been conducted. A rodent pre- and postnatal development toxicity study will be required as a PMR.

#### 7.7.5. Carcinogenic Risk Unknown

##### **Issue**

Carcinogenicity studies with levacetylleucine have not been conducted. Leucine, a metabolite of levacetylleucine, is known to activate mammalian target of rapamycin (mTOR) signaling and promotes pancreatic tumor growth in mice ([Liu et al. 2014](#)). Due to the role of leucine in promotion of tumors, it is likely that exposure to levacetylleucine and to leucine as a metabolite may increase carcinogenic risk in humans. Levacetylleucine is intended for lifetime administration beginning in infancy or childhood. Because potential neoplastic effects may not manifest in patients for many years, the risk cannot be evaluated in a timely manner in humans. Therefore, carcinogenicity studies are needed to determine potential carcinogenicity risk to patients.

##### **Conclusion**

Information was described in the carcinogenesis subsection of labeling to indicate that animal carcinogenicity studies have not been conducted with the drug. A 26-week carcinogenicity study in the transgenic rasH2 mouse will be required as a PMR, along with a 2-year rat carcinogenicity study. Alternatively, the Agency may accept a weight-of-evidence evaluation in lieu of conducting the study if the Executive Carcinogenicity Assessment Committee agrees that the study will not add value. However, to date, the Applicant has not submitted a justification for a weight-of-evidence evaluation.

### 7.7.6. Concomitant Miglustat Use

#### Issue

The high degree of concomitant miglustat use in Trial IB1001-301 impacts the determination of risk for levacetylleucine.

#### Background

Miglustat is considered standard of care for patients with NPC by treating clinicians. Miglustat is approved for the progressive neurological symptoms of NPC in other countries and is used off-label in the United States. The percentage of patients with concomitant use of miglustat in Trial IB1001-301 was 87%.

The current labeling for miglustat contains ‘Warnings and Precautions’ for the following: tremor, gastrointestinal events such as diarrhea and weight loss, peripheral neuropathy, and thrombocytopenia. Similar findings, particularly of gastrointestinal symptoms, were identified in IB1001-301, making interpretation of AEs strictly related to levacetylleucine challenging.

#### Assessment

The assessment of the safety of levacetylleucine in patients diagnosed with NPC is based on the comparison to placebo. However, the current standard of care in this multinational trial includes the use of miglustat, which was used by most trial participants in both treatment arms at their baseline dose during the trial. AEs that occurred in at least two subjects or more while on treatment with levacetylleucine in the placebo-controlled parent Trial IB1001-301 include the following: abdominal pain, dysphagia, upper respiratory infections, and vomiting.

Labeling will reflect these AEs. Several of these AEs overlap with those currently listed on the miglustat label, so it is difficult to determine if these events were attributable to levacetylleucine.

#### Conclusion

As the number of enrolled subjects not treated with concomitant miglustat is low, it is difficult to make a comparison of those receiving levacetylleucine with or without miglustat. The data provide an assessment of levacetylleucine, with most subjects on background miglustat. While there are limitations in attributing certain AEs to either miglustat or levacetylleucine (which appeared to have some similarities in safety profile), the data are adequate to support the safety of levacetylleucine with and without background miglustat use.

### 7.7.7. Assessment of Safety in Patients <10 Years Old (**≥15** kg)

#### Issue/Background

Trial IB1001-301, the only placebo-controlled trial in the levacetylleucine development program, enrolled seven (11.7%) subjects who were <10 years old; the youngest subject was 5 years old. There were two (6.1%) subjects <10 years old in the open-label Trial IB1001-201, and six (20%) subjects <10 years old in the open-label study for another indication (GM2 gangliosidosis). The levacetylleucine development program did not include any subjects who were <5 years old for NPC or any other indication. The inclusion criteria for

Trial IB1001-301 specified that subjects should weigh  $\geq 15$  kg; however, there were no subjects who weighed  $< 20$  kg enrolled in the trial.

### **Assessment**

During the review cycle the Applicant provided real world data from 17 subjects who were under the age of 5 years old (ranging from 4 months to 3 years old) and who had received Tanganil (N-acetyl-DL-leucine) as a component of their clinical care as reported to the Applicant by Dr. Michael Strupp, a neurologist in Munich, Germany. Just three of these subjects had a diagnosis of NPC; the remainder had other genetic diagnoses including Tay-Sachs disease, Sandhoff disease (GM2 gangliosidosis), and Ataxia-Telangiectasia. Dosages ranged from 1 gram per day to 2.5 grams per day, divided into BID or TID doses. Treatment durations ranges from 2 to 73 months. The three subjects with NPC were 18 months, 2 years, and 3 years old at the time of treatment initiation. All three were reported to have been on treatment with Tanganil for 12 months or more (range: 12 to 73 months). There were no drug-related AEs reported, although notably these subjects are not being monitored in a clinical trial during which AEs would be systematically reported. No PK values were provided.

Anecdotal reports submitted by subject/caregivers to an online registry were also provided. All these subjects had a diagnosis of GM2 gangliosidosis, were between the ages of 8 months and 4 years old, and the only AEs noted were gastrointestinal upset or potential gastrointestinal reflux; most reported no side effects.

The Applicant is not aware of any real-world data for individuals  $< 5$  years old who have taken levacetylleucine (as opposed to the racemate). (b) (4)

For subjects in the placebo-controlled pivotal Trial IB1001-301, there were no serious safety signals. Subjects  $< 10$  years old did not experience significantly more or different AEs than subjects  $\geq 10$  years old.

Based on the PopPK analyses (see Section 6.3.2), the exposures following the proposed dose in subjects  $< 10$  years old and weighing  $\geq 15$  kg are expected to be similar to the exposures in subjects  $\geq 10$  years.

### **Conclusion**

Levacetylleucine is expected to be well-tolerated at the to-be-marketed doses for individuals  $< 10$  years old and weighing  $\geq 15$  kg. There are limited clinical safety data for subjects  $< 10$  years old, and no data for levacetylleucine in subjects  $< 5$  years old or  $< 20$  kg. However, important considerations are the relatively benign safety profile of levacetylleucine overall in the available clinical trials, anecdotal reports of the to-be-marketed or higher doses in subjects  $< 4$  years old with the related product Tanganil, as well the similar PK profile following the to-be marketed dose in subjects  $> 10$  years old compared to the subjects  $\geq 10$  years old. These data are considered sufficient to support a limited amount of extrapolation of safety to support use in pediatric patients weighing  $\geq 15$  kg. Further considerations included the favorable benefit/risk profile, that NPC is a genetic disease with the same pathophysiology across the age spectrum, that while there can be heterogeneity in manifestations, there was similarity in response to treatment in terms of safety across the studied populations, and that the drug is not anticipated to behave differently in slightly younger children. Thus, it is anticipated that there will be similarity in the safety profile across the studied pediatric subjects who were  $\geq 5$  years old and younger patients weighing

≥15 kg. Routine pharmacovigilance will be adequate to continue assessment of an acceptable risk profile in the approved population.

## 8. Therapeutic Individualization

### 8.1. Intrinsic Factors

The recommended dosage regimen of levacetylleucine in patients with NPC is based on body weight, which is the approach used in the clinical trials of levacetylleucine. Body weight was identified as a significant covariate affecting levacetylleucine PK in the PopPK analyses. The currently available data do not support a need for further therapeutic individualization based on other intrinsic factors.

#### **Body Weight**

Body weight was identified as a significant covariate on apparent clearance and apparent volume of distribution in the PopPK analysis (see Section [14.5](#)). The apparent clearance and apparent volume of distribution of levacetylleucine increases with increasing body weight. These effects on PK of levacetylleucine are minimized by the recommended weight-based dosing regimen.

#### **Sex**

Sex was not identified as a significant covariate in the PopPK analysis, and therefore, not expected to have CS effect on levacetylleucine exposures.

#### **Subjects With NPC vs. Healthy Subjects**

PK data were not available for healthy subjects.

#### **Hepatic Impairment or Renal Impairment**

The effects of renal impairment and hepatic impairment on the PK of levacetylleucine have not been studied. No mass balance study has been conducted with levacetylleucine in humans. The metabolism of levacetylleucine results in the formation of acetate and L-leucine, and both byproducts are used within the body in further catabolic pathways. One study demonstrated that after an intravenous dose of <sup>14</sup>C-L-leucine to rats, 5% of the substrate was excreted in urine as levacetylleucine ([Lee et al. 2015](#)). Thus, the impact of hepatic impairment on PK of levacetylleucine is expected to be low.

Patients with NPC with later onset primarily present with neurological symptoms. While some patients with NPC may exhibit liver organomegaly, significant liver impairment is generally not observed in this disease ([Geberhiwot et al. 2018](#)). Trials IB1001-201 and IB1001-301 did not include specific inclusion/exclusion criteria for liver function. In these trials, the liver function status of subjects (i.e., normal, mild, moderate, or severe) was not explicitly assessed using tools such as the Child-Pugh classification, Mayo risk score, or a comprehensive set of hepatic function markers. However, based on bilirubin levels, which is a key indicator of liver function, as well as other liver blood chemistry parameters (AST, ALT, alkaline phosphatase) monitored throughout the trials, the subjects generally appeared to have normal liver function. This absence of specific liver function assessments limits the ability to correlate liver function status with PK parameters.

## 8.2. Extrinsic Factors

### **Drug-Drug Interaction**

Levacetylleucine was found to not inhibit cytochrome P450 (CYP) enzymes or induce CYP1A2, CYP2B6, or CYP3A4 enzymes via in vitro studies, indicating a low risk for drug-drug interactions through these pathways. Although levacetylleucine is identified as a substrate of organic anion transporter 1 and OAT3, these interactions are not considered clinically relevant due to the established safety profile and minimal renal excretion of levacetylleucine. Breast cancer resistance protein (BCRP) - and P-glycoprotein (P-gp)-mediated levacetylleucine active transport was not detected. In addition, the Applicant assessed the potential for levacetylleucine to inhibit efflux transporters (e.g., P-gp, BCRP, and bile salt export pump; see Section 14). The risk associated with bile salt export pump inhibition is low due to the  $C_{max}/IC_{50}$  of  $<0.1$ . The risk of drug-drug interactions due to BCRP inhibition is also considered low, as the  $I_{gut}/IC_{50}$  is slightly higher than the accepted ratio of 10. However, the potential for P-gp inhibition in vivo cannot be ruled out, given the significantly elevated  $I_{gut}/IC_{50}$ . Consequently, the review team recommends more frequent monitoring for ARs related to P-gp substrates in the label, as well as a PMR trial to further evaluate the potential interactions with P-gp substrates.

### **Food Effect**

The effect of food on PK of the to-be-marketed formulation was not assessed in a dedicated clinical trial. Based on the clinical trial protocols, levacetylleucine was supposed to be administered to subjects with NPC without food (defined as the drug needing to be taken either 30 minutes before a meal or at least 2 hours after a meal). However, approximately 12.5% non-compliance incidents (subjects took the drug within 2 hours after a meal) were reported in the clinical trials. The review team conducted a preliminary PK analysis to compare the drug concentration during the first 2.5 hours postdose under “fasted” (subjects took the drug following the protocols regarding food intake) and fed (subjects took the drug non-compliant with the protocols regarding food intake) conditions (see Section 14). Based on this assessment, similar PK during the absorption phase was observed regardless of food intake. However, due to the small sample size of subjects who had intensive PK data that enabled this analysis and uncontrolled food conditions (i.e., high fat or low fat), these findings cannot support a definitive conclusion. Because patients with NPC often experience feeding difficulties and may require a long time to complete meals, enforcing the administration of the drug without food for a TID dosing regimen would be challenging and burdensome for these patients (i.e., patients will need to fast for 2.5 hours). Therefore, based on the preliminary PK analysis and practical considerations, the review team recommends the drug to be taken with or without food in the label. To address the uncertainty associated with the impact of food on PK, a postmarketing commitment trial has been proposed.

## 8.3. Plans for Pediatric Drug Development

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

Because this drug product for this indication has an orphan drug designation, it is exempt from this requirement.

The currently available data support the approval of this product in patients weighing  $\geq 15$  kg.

### **Nonclinical**

There are no nonclinical data to support the safety of levacetylleucine in children; however, available clinical data suggest that the drug is adequately tolerated. A juvenile animal study will be conducted as a PMR to assess target organ effects and effects on developmental processes including neurocognitive development, growth, and sexual maturation.

### **Clinical**

The safety and effectiveness of levacetylleucine for the treatment of NPC have been established in 23 pediatric subjects weighing  $\geq 15$  kg in Trial IB1001-301. Use of levacetylleucine for this indication is supported by evidence from one adequate and well-controlled trial in adult and pediatric subjects weighing  $\geq 15$  kg with additional pharmacokinetic data from 40 adult and 17 pediatric subjects who participated in two open-label studies. The safety and effectiveness of levacetylleucine have not been established in pediatric subjects weighing  $< 15$  kg. See Section [7.7.7](#) for additional information regarding the safety assessment of pediatric subjects weighing  $\geq 15$  kg.

## **8.4. Pregnancy, Lactation, and Females / Males of Reproductive Potential**

### **Animal Data**

In a dose-ranging rat EFD study, doses of up to 1000 mg/kg/day oral levacetylleucine were administered to pregnant females during organogenesis (gestation day [GD] 6 through GD 17). Increases in the mean number of resorptions, mean post-implantation losses, and skeletal malformations (thoracic arch of the vertebra-fused thoracic arch, misaligned thoracic arch, hemicentric thoracic centrum, and misaligned thoracic centrum; vertebral column-scoliosis, and ribs-absent costal cartilage and short rib) were observed at doses  $\geq 600$  mg/kg/day, which is 1.4-fold the MRHD of IB1001 (levacetylleucine) based on body surface area.

In a dose-ranging rabbit EFD study, doses of up to 2500 mg/kg/day oral levacetylleucine were administered daily to pregnant females during organogenesis (GD 7 through GD 19). Increased embryo-fetal death (post-implantation loss/resorption), decrease in fetal body weight, and increase in external (open or partially open eyes, hyperflexion of limbs) and skeletal malformations (misshapen maxilla and premaxilla, and small interparietal bones) were observed at the  $\geq 1250$  mg/kg/day, which is 6-fold the MRHD of levacetylleucine based on body surface area.

## **9. Product Quality**

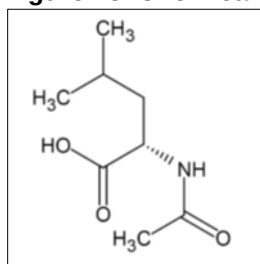
### **Drug Substance**

Levacetylleucine is a modified amino acid; it is acetyl amide of the amino acid L-leucine. Levacetylleucine has not been previously approved or marketed in the United States, and therefore, it is classified as a new molecular entity.

Levacetylleucine is a white crystalline powder with a melting point of 187.6°C and specific optical rotation  $[\alpha]_{D25} = -23^\circ$ . It is slightly hygroscopic (b) (4). Levacetylleucine is slightly soluble in water and free soluble in dimethyl sulfoxide.

Levacetylleucine has the chemical name 2-acetamido-4-methylpentanoic acid, the empirical formula  $C_8H_{15}NO_3$ , a molecular weight of 173.21 g/mol, and the chemical structure is as shown in [Figure 13](#).

**Figure 13. Chemical Structure for Levacetylleucine**



Source: Structural characterization provided in drug substance module 3.2.S.3.1

The chemical structure for this drug substance has been characterized and confirmed by multiple analytical techniques and provided in the module 3.2.S.3.1 of this NDA.

Levacetylleucine for this application is manufactured in accordance with the current good manufacturing practices (cGMP) requirements (b) (4). It is tested and release against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its proposed retest date of (b) (4) months. Sufficient stability data is provided in the application in support of the proposed retest date of (b) (4) months; the retest date is granted.

## **Drug Product**

AQNEURSA® (levacetylleucine) for oral suspension, 1 gram is supplied as white to off-white strawberry flavored granules in a unit-dose packet. It is indicated for the treatment of adult and pediatric patients with neurological symptoms of NPC and who weigh  $\geq 15$  kg.

Each unit-dose packet contains 1.7 grams of white to off-white granules equivalent to 1 gram of levacetylleucine as the active ingredient. The granules also contain hypromellose, isomalt, and strawberry flavor as the inactive ingredients.

AQNEURSA (levacetylleucine) for oral suspension is manufactured (b) (4) for IntraBio, Inc. in accordance with the cGMP requirements. It is tested and release against a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 24 months. Sufficient stability data in support of the proposed expiration date is provided in the application and the expiration dating period of 24 months is granted to this drug product.

AQNEURSA (levacetylleucine) for oral suspension is supplied in a carton containing 28 unit-dose packets. It is also supplied as a multipack containing four cartons providing 112 unit-dose packets. This drug product should be stored at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [see United States Pharmacopeia Controlled Room Temperature].

### **The Office of Pharmaceutical Quality Recommendation**

- The Applicant of this 505(b)(1) NDA has provided sufficient Chemistry, Manufacturing, and Controls information to assure the identity, strength, purity, and quality of the drug substance, levacetylleucine, and the drug product, AQNEURSA (levacetylleucine) for oral suspension, 1 gram.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The Chemistry, Manufacturing, and Controls-recommended revisions and comments regarding prescribing information labeling as well as container and carton labels have been adequately addressed.
- The Applicant's request for categorical exclusion from the preparation of environmental assessment has been found adequate and is granted.

Therefore, this application is recommended for approval from the Office of Pharmaceutical Quality perspective with an expiration dating period of 24 months.

## **9.1. Device or Combination Product Considerations**

Not applicable.

## **10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review**

### **Human Subjects Protections**

As stated by the Applicant, the clinical trials were conducted in substantial conformance with International Council for Harmonisation good clinical practice requirements and with applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and protection of human subjects participating in biomedical research. All studies submitted in this application were conducted according to FDA requirements, under IND 134369.

### **Clinical Site Inspections**

FDA clinical site inspections were performed on-site at three sites in Spain, Switzerland, and Germany (refer to Section [22](#) for details).

### **Financial Disclosure**

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance *Financial Disclosure by Clinical Investigators* ([February 2013](#)) (see Section [25](#)), and by 21 CFR 54.4. None of the investigators of the two trials were employed by the Applicant; none of the investigators disclosed financial interests with the Applicant. In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

## 11. Advisory Committee Summary

An advisory committee was not held for this application. It did not raise challenging efficacy or safety issues that needed external input.

APPEARS THIS WAY ON ORIGINAL

## III. Additional Analyses and Information

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### 12. Summary of Regulatory History

The Applicant, IntraBio Inc, has investigated levacetylleucine, also referred to by the company development code IB1001 and by its chemical name N-acetyl-L-leucine (NALL), for its ability to treat Niemann-Pick disease type C (NPC). The Applicant's development program began with the investigation of commercially available racemic mixture N-acetyl-DL-leucine, a modified amino acid approved in France since 1957 as Tanganil (Pierre Fabre Laboratories) for short term (10 days to 6 weeks) treatment of acute vertigo in adults. The Applicant opened a pre-investigational new drug application (PIND) file (PIND 134369) and submitted a PIND meeting request on February 22, 2017, to discuss their development program for N-acetyl-DL-leucine. The meeting was granted by the Agency; however, the Applicant cancelled the meeting on April 13, 2017 because it determined the program needed additional refinement before any discussions should occur. The Applicant also received an orphan drug designation for N-acetyl-DL-leucine for the treatment of NPC on February 22, 2018.

The Applicant resubmitted a PIND meeting request on February 26, 2018, this time to discuss their nonclinical and clinical plan to develop levacetylleucine, the L-enantiomer and active ingredient of the racemic mixture of N-acetyl-DL-leucine. The Applicant asserted that animal studies suggested that the L-enantiomer had a greater potential clinical benefit over the racemic mixture. The Applicant intended to formulate levacetylleucine as granules for oral suspension for the treatment of NPC (b) (4). In the PIND meeting, held on July 17, 2018, the FDA commented on the Applicant's proposed plan to conduct a phase 2/2b, open-label clinical trial to assess the safety and efficacy of levacetylleucine. The FDA asserted that an open-label trial could be used for proof-of-concept, but that it would be inadequate to generate interpretable efficacy data to support a future marketing application. General comments were also provided, particularly for nonclinical studies, primary endpoints considerations, the statistical analysis approach, and the clinical pharmacology development plan. In addition, the FDA advised the Applicant (b) (4). The meeting minutes were issued on July 26, 2018.

On January 7, 2019, IND 134369 was submitted and included protocol 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." Per the FDA's request, a teleconference took place on January 23, 2019. In the teleconference, the FDA reiterated the concerns regarding the limitations of an open-label trial design versus a randomized, controlled trial and reminded the Applicant that Trial IB1001-201, as designed, would only provide short term safety information. The Sponsor acknowledged the FDA's concerns and stated that Trial IB101-201 was an exploratory study and agreed to revise the protocol per FDA's recommendation to eliminate the open-label extension and limit the trial to 6 weeks in duration. The FDA issued a Study May Proceed letter on February 7, 2019. The FDA recommended the Applicant request a guidance meeting to discuss improving the trial design (e.g., incorporating randomization) and to further discuss some of the trial's key elements (e.g., the clinical outcome assessment endpoints and statistical approach). General

recommendations on the plan for clinical pharmacology studies were also provided in the letter.

In their IND submission received by FDA on January 7, 2019, the Applicant also included a breakthrough therapy designation request for levacetylleucine for the treatment of NPC. Following an evaluation of this request, the FDA issued a breakthrough therapy designation request denied letter on March 5, 2019.

On January 31, 2020, the Applicant submitted a revised protocol for Trial IB1001-201. This resulted in another teleconference at the FDA's request, which was held on February 25, 2020. The teleconference was followed by an advice letter issued by the FDA on February 28, 2020. The FDA informed the Applicant that the revised protocol for Trial IB1001-201 was not sufficient to 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 FDA again advised the Applicant to submit a meeting request to further discuss the program.

On February 3, 2020, the Applicant submitted a request for a fast-track designation. On March 19, 2020, following a review of the request by the FDA, the Applicant was granted a fast-track designation for levacetylleucine for the treatment of NPC.

On September 4, 2020, the Applicant submitted a request for a Type C meeting to discuss the use of their topline data from Trial IB1001-201 to support a marketing application. In the meeting held on November 17, 2020, the FDA repeated its position that Trial IB1001-201 was neither adequate nor well-controlled, and therefore would not be sufficient to provide substantial evidence of effectiveness to support a marketing application. The FDA also cautioned the Applicant on their potential plan to seek accelerated approval for levacetylleucine. Meeting minutes were issued on December 2, 2020.

The Applicant subsequently requested a Type C meeting, which was held on May 27, 2021, to discuss the design and endpoints for a new study, Trial IB1001-301, which was proposed as a phase 3, randomized, double-blind, placebo-controlled, crossover study that the Applicant intended to serve as their pivotal trial to support a marketing application. Although the proposed randomized study design for Trial IB1001-301 appeared acceptable, the FDA reminded the Applicant to address some of its previously communicated concerns, such as the clinical outcome measurement instruments for the endpoints, the statistical approach, and the nonclinical and clinical pharmacology development program. The meeting minutes were issued on June 14, 2021.

On September 8, 2021, the Applicant received an orphan drug designation for NALL for NPC.

On November 5, 2021, the Applicant submitted the protocol for Trial 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." In an advice letter sent on December 20, 2021, as well as in a subsequent advice letter issued on March 21, 2022, the latter of which was in response to the submission of a revised protocol for IB1001-301 received on January 12, 2022, the FDA provided multiple recommendations including on the measurement approach for the primary endpoint.

On January 9, 2023, in response to a revised protocol for Trial IB1001-201 received on October 19, 2022, the FDA issued an advice letter which reiterated its position that Trial IB1001-201 was not adequately designed to generate interpretable efficacy data.

On July 21, 2023, the Applicant requested a premarketing meeting that was granted to discuss the adequacy of their data package to support an NDA for levacetylleucine that was to be submitted via the 505(b)(1) regulatory pathway. A statistical analysis plan was also received on August 7, 2023. During the meeting, which occurred on September 21, 2023, the FDA reminded the Applicant that because they intended their NDA to be supported by a single adequate and well-controlled clinical trial (Trial IB1001-301), additional confirmatory evidence (CE) of the treatment effect would be needed to meet the regulatory standards for a demonstration of substantial evidence of effectiveness; therefore, CE must be provided in their NDA. The FDA recommended that the Applicant request a Type C meeting to further discuss their plan to provide CE. The FDA also noted several missing final reports for nonclinical and clinical pharmacology studies that were needed to support a marketing application. In addition, general guidance was provided for an optimal NDA data package including, but not limited to, clinical outcome assessment evidence, safety, and labeling. Meeting minutes were issued on October 11, 2023.

As a follow-up to the premarketing meeting, the Applicant submitted information regarding their plan to provide CE and nonclinical studies on September 29, 2023. In response, the FDA issued an advice letter on November 24, 2023, providing additional clarifications on CE and nonclinical data.

The Applicant received a rare pediatric disease designation for levacetylleucine for the treatment of NPC on November 18, 2023.

The Applicant submitted NDA 219132 for levacetylleucine, a new molecular entity, for the treatment of NPC via the 505(b)(1) regulatory pathway on January 24, 2024. The Division determined the application would receive a priority review because NPC is a serious condition with no approved treatments.

The proposed proprietary name for levacetylleucine, Aqneursa, was found conditionally acceptable on March 18, 2024. The NDA was filed on March 24, 2024, the midcycle communication with the Applicant was held on May 8, 2024, and the late-cycle meeting with the Applicant was held on August 1, 2024.

## 13. Pharmacology Toxicology

### 13.1. Summary of Review of Studies Submitted With the Investigational New Drug Application

The nonclinical safety profile of IB1001 (also referred as N-acetyl-L-leucine, NALL, and levacetylleucine) supporting this NDA was evaluated in: (1) repeated dose toxicity studies in rats (up to 6 months) and dogs (up to 9 months); (2) a standard battery of in vitro and in vivo genotoxicity studies; and (3) dose-ranging reproductive and developmental toxicity studies including embryo-fetal developmental (EFD) studies in rats and rabbits. Additional nonclinical studies, including fertility studies in male and female rats, peri- and postnatal developmental study in rats, carcinogenicity studies in transgenic mice (6 months) and rats (2-year bioassay). Juvenile toxicology studies in rats were not included in this submission. Given the imminently life-threatening nature of NPC and the high unmet medical need, these studies will be requested as postmarketing requirements (PMRs).

The following study was previously reviewed under the IND:

**Study Number 36243: 6-Week Subchronic Toxicity Study of IB1001 by Repeated Oral Administration to Beagle Dogs**

**Purpose:** Evaluate oral toxicity following daily dosing and reversibility of effects in dogs.

**Design:** Daily oral dosing in Beagle dogs (3M/3F per dose level + 2M/2F in the high dose and control groups) dosed at 0, 225, 750, or 2500 mg/kg/day for 6 weeks followed by a recovery period of 2 weeks. Body weight, feed consumption, electrocardiography (ECG), blood pressure, ophthalmological and auditory examinations, clinical pathology, histopathology, and toxicokinetics (TKs) were evaluated.

**Key Findings:** There were no adverse effects at up to 2500 mg/kg/day. The maximum plasma concentration ( $C_{max}$ ) and area under the concentration-time curve (AUC) levels of levacetylleucine were dose-related after Days 1 and 42 of dosing. The combined male and female  $C_{max}$  was 252.8 µg/mL and  $AUC_{0-\infty}$  was 598 µg.hr/mL at the no-observed-adverse-effect level (NOAEL) on Day 42.

**Conclusion:** The NOAEL for levacetylleucine was 2500 mg/kg/day in a 6-week oral gavage toxicity study in Beagle dogs. The NOAEL dose in dog provides a 19-fold safety margin based on exposures in humans (31.6 µg·hr/mL) at a daily maximum recommended human dose of 4 g/day.

## 13.2. Individual Reviews of Studies Submitted With the New Drug Application

### 13.2.1. Nonclinical Pharmacodynamic Data

Data to support the mechanism of action for levacetylleucine were derived from published literature. The Applicant described data suggesting that in cultured Chinese hamster ovary cells, treatment with levacetylleucine at a concentration of 1mM for 24 hours, was associated with a modest reduction in lysosomal volume, sphingosine, glycosphingolipids (GSLs), and a very modest reduction in stored cholesterol. In NPC patient-derived fibroblasts, treatment with levacetylleucine was also associated with a modest reduction in apparent lysosomal volume when cells were cultured for 7 days with 1mM levacetylleucine ([Mann 2018](#)). These studies suggest that levacetylleucine has the potential to reduce stored intracellular lipid; however, the mechanism of action for this drug, including the molecular targets by which it elicits these effects, is unclear.

The Applicant also provided published data from an animal disease model. In *Npc1*<sup>-/-</sup> mice, pre-symptomatic (from the age of 3 weeks old) treatment with levacetylleucine was also associated with a modest increase in survival and a reduction in markers of neuroinflammation (CD68 staining) in the cerebellum (Section [13.2.2](#); ([Kaya et al. 2021](#))). The above changes were not monitored in the clinical trial to evaluate the association of change in magnitude of levels of GSL and neuroinflammation with the dose of levacetylleucine and efficacy. At the Division's request, the Applicant provided raw data obtained by the publication's authors, and a letter of reference granting them the right to use the raw data (submission dated July 3, 2024) and revised right to use raw data certifying that spreadsheets accurately reflect the data contained in publication by [Kaya et al. 2021](#). The figures in sections below are obtained from [Kaya et al. 2021](#) in sequence #0050 (submission dated July 25, 2024). The figures in sections below are obtained from [Kaya et al. 2021](#) with

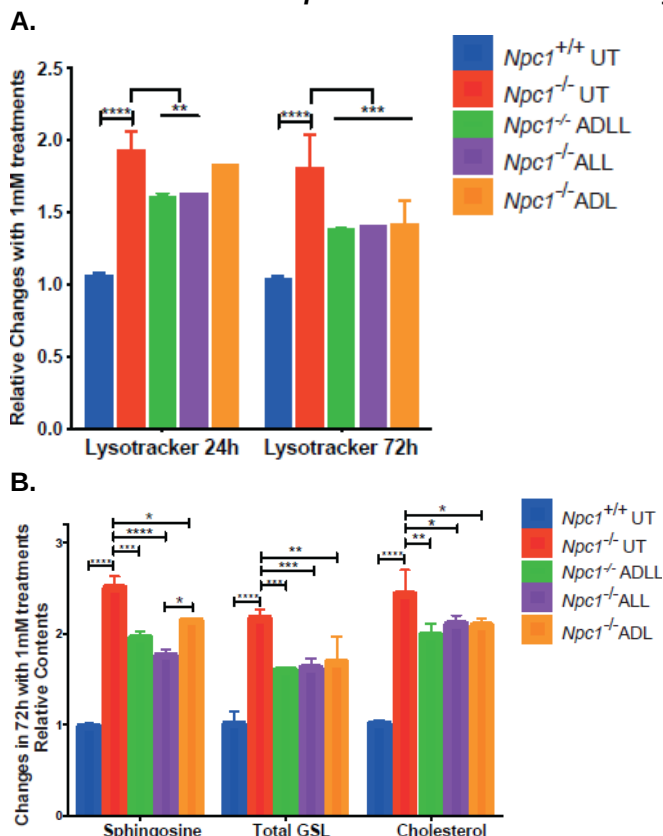
data for racemic and N-acetyl-D-Leucine, however, the data for only NALL in comparison with appropriate controls is described.

## In Vitro Mechanism of Action

### **Study of NALL Treatment on Lysosomal Volume and Accumulation of Sphingosines In Vitro**

The effects of NALL on lysosomal volume and levels of sphingosine, GSLs, and free cholesterol were measured in cultured wildtype and NPC1-deficient (*Npc1*<sup>-/-</sup>) Chinese hamster ovary cells. Treatment of *Npc1*<sup>-/-</sup> Chinese hamster ovary cells with 1mM NALL reduced lysosomal volume compared to untreated cells after 24 hours (16%; *p*=0.0177) and 72 hours of treatment (22.8%; *p*=0.0036) (Figure 14 panel A). Levacetylleucine reduced sphingosine levels by 29% compared to untreated cells (*p*<0.0001). Additionally, NALL significantly reduced cholesterol content by 13% compared to untreated cells (*p*=0.0263) (Figure 14 panel B).

**Figure 14. Effect of NALL on Lysosome Volume and Sphingosine, Total GSL, and Free Cholesterol Levels in *Npc1*<sup>-/-</sup> Chinese Hamster Ovary Cells**



Source: (Kaya et al. 2021)

Wildtype untreated (*Npc1*<sup>+/+</sup> UT - blue), NPC1-null untreated (*Npc1*<sup>-/-</sup> UT - red), and NPC1-null treated with NALL (=ALL) (*Npc1*<sup>-/-</sup> ALL - purple) CHO cells.

A. Effect of NALL on LysoTracker Green in NPC1-null (*Npc1*<sup>-/-</sup>) CHO cells after 24 and 72 hours 1mM NALL compared to untreated *Npc1*<sup>-/-</sup> and *Npc1*<sup>+/+</sup>, mean  $\pm$ SD, \**p*<0.018, \*\**p*<0.005, \*\*\**p*<0.0001 (2-way analysis of variance [ANOVA]).

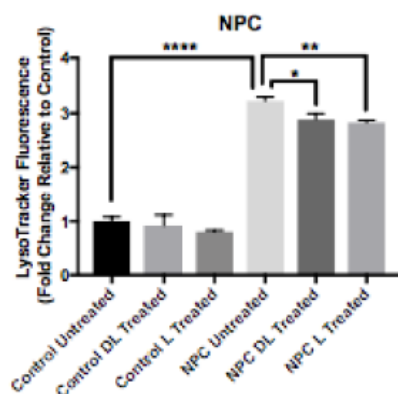
B. Effect of NALL on sphingosine, total GSL, and free cholesterol levels in *Npc1*<sup>-/-</sup> CHO cells after 72 hours 1mM NALL compared to untreated *Npc1*<sup>-/-</sup> and *Npc1*<sup>+/+</sup> CHO cells, mean  $\pm$ SD, \**p*<0.027, \*\*\**p*<0.001, \*\*\*\**p*<0.0001 (2-way ANOVA).

Abbreviations: ADL = acetyl-d-leucine; ADLL = Acetyl-DL-leucine; ALL = acetyl-L-leucine; ANOVA = analysis of variance; CHO = Chinese hamster ovary; GSL = glycosphingolipids; NALL = N-acetyl-L-leucine; SD = standard deviation; UT = untreated

## Study of NALL Treatment on Lysosomal Volume in Fibroblasts From Patients With NPC

The effect of 1mM levacetylleucine on fibroblasts from patients with NPC with severe clinical presentation was evaluated by analyzing change in LysoTracker fluorescence associated with change in lysosomal volume. The treatment of fibroblasts from patients with NPC with levacetylleucine for 7 days modestly reduced the LysoTracker fluorescence, suggesting that the drug reduced lysosomal volume compared to untreated fibroblasts from patients with NPC. There was no numerical difference in the magnitude of the effect when cells were treated with levacetylleucine versus when they were treated with N-acetyl-DL-leucine.

Figure 15. LysoTracker Fluorescence in Control and Disease Fibroblasts



Source: Excerpted from Applicant submission

LysoTracker Fluorescence in Control and Disease fibroblasts. Cells were treated with 1mM N-acetyl-DL-leucine ("DL") or NALL ("L") /0.1% DMSO (as appropriate) for 7 days. LysoTracker fluorescence is expressed as fold change relative to averaged value of untreated control. For NPC, Control Untreated:  $1.00 \pm 0.05$ , Control DL Treated:  $0.92 \pm 0.12$ , Control L Treated:  $0.81 \pm 0.02$ , NPC Untreated:  $3.23 \pm 0.04$ , NPC DL Treated:  $2.89 \pm 0.06$ , and NPC L Treated:  $2.83 \pm 0.02$ . One-way ANOVA was conducted for statistical analysis. \*/\*\*/\*\*\*\* -  $p < 0.05/0.003/0.0001$  versus untreated control (as indicated). IntraBio Ltd in-house data. Abbreviations: ANOVA = analysis of variance; DMSO = dimethyl sulfoxide; GSL = glycosphingolipid; NALL = N-acetyl-L-leucine; NPC = Niemann-Pick disease type C; SEM = standard error of the mean

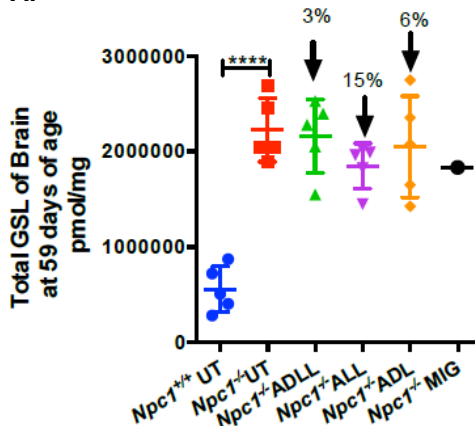
## In Vivo Mechanism of Action

### Study of NALL Treatment on Lipid Storage in Brain in *Npc1*<sup>-/-</sup> Mice

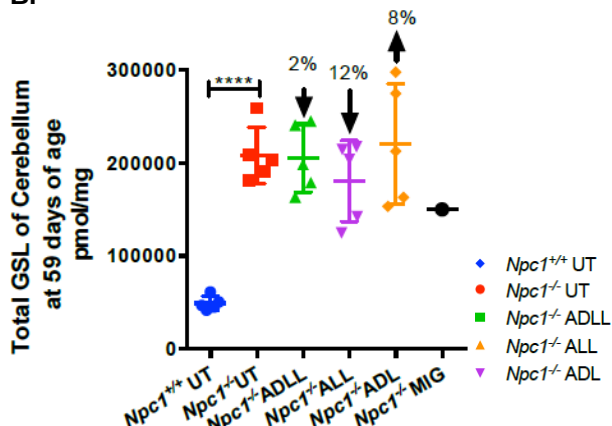
The effect of administering levacetylleucine in pre-symptomatic *Npc1*<sup>-/-</sup> mice beginning at the age of 3 weeks old, was evaluated by measuring lipid storage in brain. The *Npc1*<sup>-/-</sup> mice exhibited an increase in total GSL levels in forebrain and cerebellum compared to wild type mice at 59 days (approximately 8.5 weeks) of age ([Figure 16](#) panels A and B; [Kaya et al. 2021](#)). Treatment of *Npc1*<sup>-/-</sup> mice with levacetylleucine at 0.1 mg/kg/day modestly reduced (not significantly) the total GSL levels compared to untreated *Npc1*<sup>-/-</sup> mice. The reduction in certain GSLs was more pronounced with reduction in GM1a (20.1%;  $p=0.0018$ ) and GM2 (19.6%;  $p=0.0222$ ) in the forebrain and the reduction of GA2 (23.8%;  $p=0.0042$ ) and GA1 (23.5%;  $p=0.0254$ ) in cerebellum.

**Figure 16. Effect of NALL on Total Glycosphingolipids in Forebrain and Cerebellum of *Npc1*<sup>-/-</sup> Mice at the Age of 59 Days**

A.



B.



Source: (Kaya et al. 2021)

Wildtype untreated (*Npc1*<sup>+/+</sup> UT - blue), *NPC1* untreated (*Npc1*<sup>-/-</sup> UT - red), and *NPC1* treated with NALL (*Npc1*<sup>-/-</sup> ALL - purple) mice, n=5 animals per group. NALL (=ALL) was administered to treated *Npc1*<sup>-/-</sup> mice in the diet (0.1 g/kg/day). The effects in mice treated with miglustat are depicted in black.

A. Total GSL in the forebrain. Mean ±SD, \*\*\*\*p=0.0001 (2-way ANOVA)

B. Total GSL in the cerebellum. Mean ±SD, \*\*\*\*p=0.0001 (2-way ANOVA)

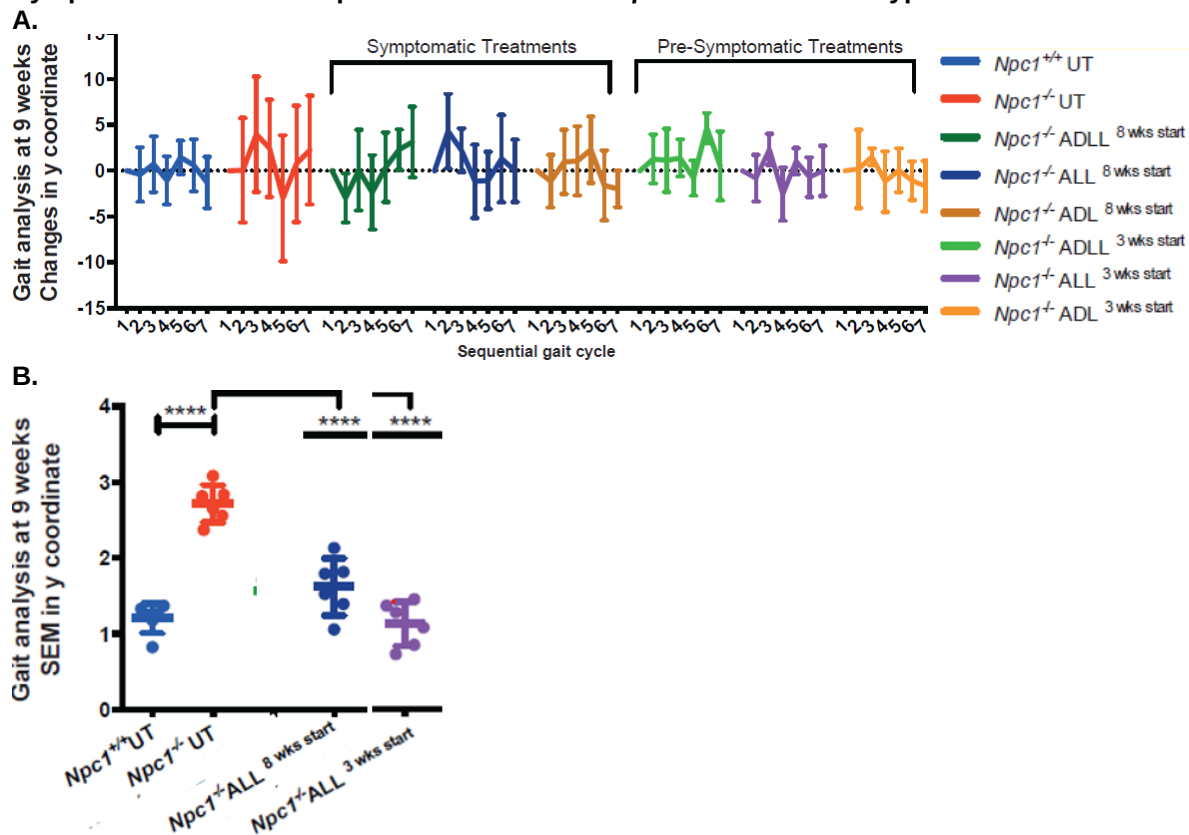
Abbreviations: ADL = acetyl-D-leucine; ADLL = Acetyl-DL-leucine; ALL = acetyl-L-leucine; ANOVA = analysis of variance; GSL = glycosphingolipids; NALL = N-acetyl-L-leucine; NPC = Niemann-Pick disease type C; SD = standard deviation; UT = untreated

### Study of NALL Treatment on Cerebellar Ataxia Motor Skills and Long-Term Neuroprotective Effect in Pre-Symptomatic *Npc1*<sup>-/-</sup> Mice.

The Applicant states that the lifespan of *Npc1*<sup>-/-</sup> mice is about 10 to 12 weeks with onset of symptoms, such as gait abnormalities, tremor, and weight loss beginning at between the ages of 6 and 7 weeks old. The Applicant states that at 9 weeks of age, untreated *Npc1*<sup>-/-</sup> mice show statistically significant ataxia that presents as pronounced sigmoid gait compared to wildtype *Npc1*<sup>-/-</sup> mice (p<0.0001). Ataxia was determined by measuring lateral displacement from a straight trajectory in an automated gait analysis system (Figure 17 panels A and B). Kaya et al. 2021 reported that treatment of *Npc1*<sup>-/-</sup> mice with 100 mg/kg/day of levacetylleucine for 1 week beginning at the age of 8 weeks old showed significant reduction in ataxia (p<0.0001) compared to untreated *Npc1*<sup>-/-</sup> mice. In mice treated pre-symptomatically from weaning (i.e., at the age of 3 weeks old) and assessed at the age of 9 weeks old (i.e., after 6 weeks of treatment), levacetylleucine also significantly reduced the magnitude of ataxia compared to that of the untreated *Npc1*<sup>-/-</sup> mice (p<0.0001). The effect on motor function was more prominent when animals were treated pre-symptomatically than when

treatment was initiated in *Npc1*<sup>-/-</sup> mice after symptoms had started ( $p < 0.003$ ) (Figure 17 panels A and B).

**Figure 17. Gait Analysis of Mice With NALL Treatment Initiated in the Symptomatic or Pre-Symptomatic Period Compared With Untreated *Npc1*<sup>-/-</sup> Mice and Wildtype Controls**



Source: Modified from (Kaya et al. 2021); excerpted from Applicant submission

Gait analysis of wildtype and untreated/N-acetyl-L-leucine treated symptomatically (from 8 weeks of age) *Npc1*<sup>-/-</sup> mice and pre-symptomatically (from the age of 3 weeks) *Npc1*<sup>-/-</sup> mice.  $n = 6$  mice per group. NALL was administered to treated *Npc1*<sup>-/-</sup> mice in the diet (0.1 g/kg/day).

A. Pre-symptomatic and symptomatic N-acetyl-L-leucine (=ALL) treatment. Y coordinates displacement of each consecutive foot from a straight-line trajectory (mean  $\pm$ SD,  $n = 6$ ).

B. Pre-symptomatic and symptomatic N-acetyl-L-leucine (ALL) treatment. Standard error of the means (SEMs) of Y coordinate changes (mean  $\pm$ SD,  $n = 6$ ; \*\* $p < 0.003$ , \*\*\*\* $p < 0.0001$ , one-way ANOVA).

Abbreviations: ADL = acetyl-D-leucine; ADLL = acetyl-DL-leucine; ALL = acetyl-L-leucine; ANOVA = analysis of variance; SEM = standard error of the mean; SD = standard deviation; UT = untreated

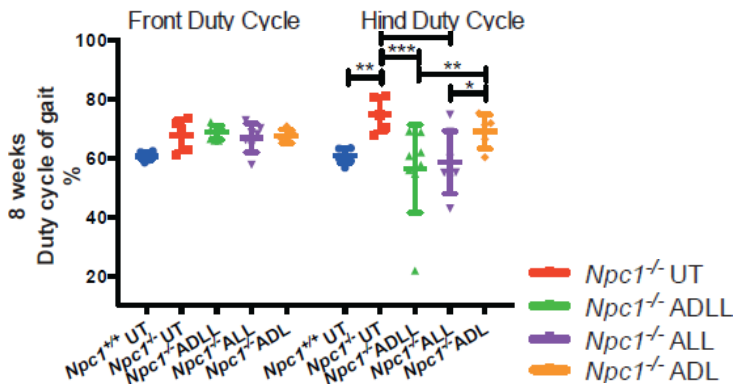
### Study of Pre-Symptomatic Treatment With NALL on Gait Abnormalities, Motor Function, and Lifespan (“Survival”) of *Npc1*<sup>-/-</sup> Mice

The effects of levacetylleucine on motor dysfunction during ambulation were measured in *Npc1*<sup>-/-</sup> mice using the Rotarod, which measures coordination and balance, and using the CatWalk gait analysis, which measures paw placement abnormalities. As shown in Figure 18, treatment of pre-symptomatic *Npc1*<sup>-/-</sup> mice had a significant improvement in hind paw duty cycle (Figure 18 panel A) and hind paw stand mean (Figure 18 panel B) in CatWalk test compared to untreated *Npc1*<sup>-/-</sup> mice (Panel A). Treatment of *Npc1*<sup>-/-</sup> mice with 0.1 g/kg/day levacetylleucine also led to significant functional improvements in hind paw duty cycle (Figure 18 panel A) and hind paw stand mean (Figure 18 panel B) in mice treated after onset of symptoms compared to untreated *Npc1*<sup>-/-</sup> mice. The duty cycle is the percentage of the step cycle spent to the stand phase versus the swing phase (i.e., duty cycle % = stand phase/step cycle) (Haulcomb et al. 2017).

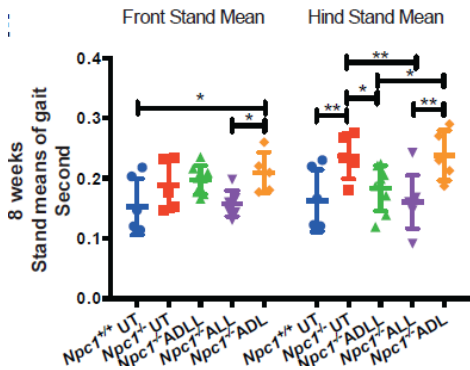
Treatment with levacetylleucine at 0.1 g/kg/day in pre-symptomatic *Npc1*<sup>-/-</sup> mice beginning at the age of 3 weeks old improved motor function as measured as time spent on the accelerating Rotarod (starting from 1 rpm to 10 rpm, accelerating by one rpm every 30 seconds) compared to untreated *Npc1*<sup>-/-</sup> mice (Figure 18 panel C). Additionally, pre-symptomatic treatment (treatment initiated at weaning) with levacetylleucine of *Npc1*<sup>-/-</sup> mice increased lifespan (+9.1%) compared to untreated *Npc1*<sup>-/-</sup> mice (Figure 18 panel D).

**Figure 18. Effect of NALL on Gait Analysis, Motor Function, and Survival of *Npc1*<sup>-/-</sup> Mice Treated Pre-Symptomatically**

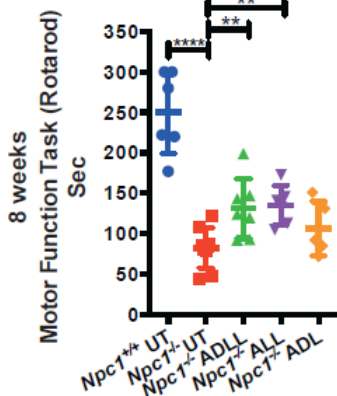
A.

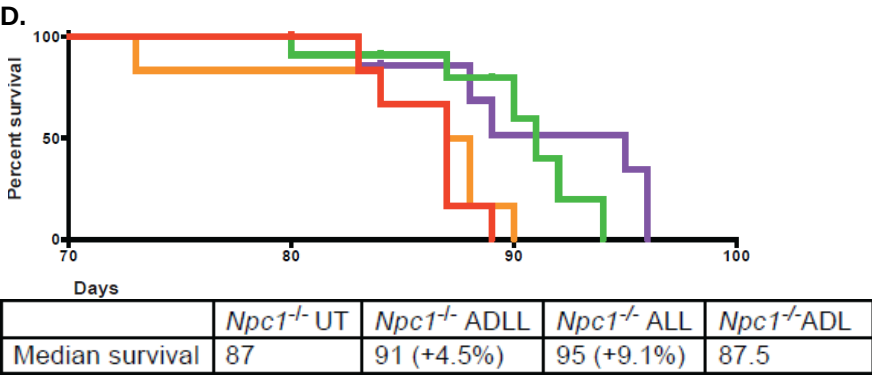


B.



C.





Source: (Kaya et al. 2021)

Wildtype untreated (*Npc1*<sup>+/+</sup> UT – blue), *Npc1* untreated (*Npc1*<sup>-/-</sup> UT – red), and *Npc1* NALL-treated (*Npc1*<sup>-/-</sup> ALL –purple) mice, n≥5 animals per group. N-acetyl-L-leucine was administered to treated *Npc1*<sup>-/-</sup> mice in the diet (0.1 g/kg/day) from the age of 3 weeks.

A. Duty cycle of *Npc1*<sup>-/-</sup> mice treated pre-symptomatically with N-acetyl-L-leucine (ALL) compared with untreated (UT) wildtype and *Npc1*<sup>-/-</sup> controls. Front and hind duty cycle measurements. Mean ±SD, \*\*p<0.032, \*\*\*\*p<0.0001 (2-way ANOVA).

B. Front and hind stand mean measurements of *Npc1*<sup>-/-</sup> mice treated pre-symptomatically with N-acetyl-L-leucine (ALL) compared with untreated (UT) wildtype and *Npc1*<sup>-/-</sup> controls. Mean ±SD, \* p<0.026, \*\*p<0.003 (2-way ANOVA).

C. Early-stage N-acetyl-L-leucine treatment motor performance measurements. Mean ±SD, \*\*p<0.009, \*\*\*\*p<0.0001 (one-way ANOVA).

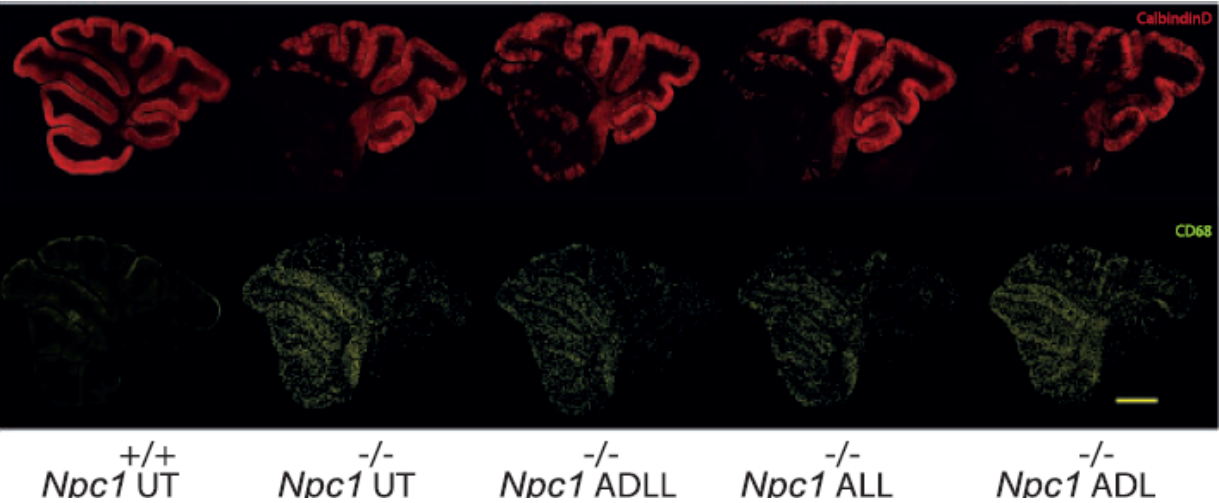
D. Life expectancy percentages of *Npc1*<sup>-/-</sup> mice treated pre-symptomatically with N-acetyl-L-leucine (ALL) compared with untreated (UT) *Npc1*<sup>-/-</sup> mice. Mean ±SD, \* p<0.046 (Gehan-Breslow-Wilcoxon test).

Abbreviations: ADL = acetyl-d-leucine; ADLL = Acetyl-DL-leucine; ALL = acetyl-L-leucine; ANOVA = analysis of variance; SD = standard deviation; UT = untreated

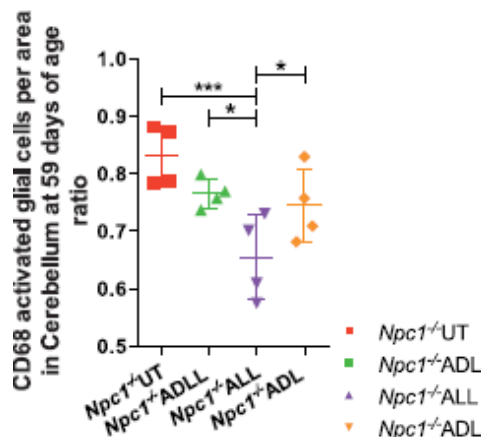
**Study of Neuroinflammation in the Brain of *Npc1*<sup>-/-</sup> Mice**

The Applicant states that neuroinflammation in the brain is a characteristic of NPC, and that this manifests as progressive loss of cerebellar Purkinje cells in *Npc1*<sup>-/-</sup> mice, progressing from the anterior to posterior lobes, and is accompanied by microglial activation. *Npc1*<sup>-/-</sup> mice treated with 0.1 g/kg/day levacetylleucine in the diet from the age of 3 weeks old show a reduction in the frequency of CD68 positive (a marker of microglial activation) cells at 59 days (about 8 weeks) old compared to untreated *Npc1*<sup>-/-</sup> mice (20%; p=0.077). The authors state that this suggests a slowing of disease progression by levacetylleucine (Figure 19 panels A and B).

**Figure 19. Effect of NALL on Activated Microglia in *Npc1*<sup>-/-</sup> Mice at the Age of 59 Days**  
**A.**



B.



Source: (Kaya et al. 2021)

N-acetyl-L-leucine (=ALL) was administered to treated *Npc1*<sup>-/-</sup> mice in the diet (0.1 g/kg/day) from the age of 3 weeks.

A. Cerebellum stained with calbindin-b (Purkinje cells, red) or CD68 (activated microglia, yellow).

B. CD68 cell density in the cerebellum at 59 days of age. n=5 animals per group. Mean ±SD, \*\*\* p<0.0177 (one-way ANOVA). Abbreviations: ADL = acetyl-d-leucine; ADLL = Acetyl-DL-leucine; ALL = acetyl-L-leucine; ANOVA = analysis of variance; SD = standard deviation; UT = untreated

The Applicant cited additional publications that describe other potential modes of action whereby NALL may improve aspects of cellular function in the context of neurodegenerative diseases; however, the data were either not specific to NPC or were of uncertain relevance to the proposed context of use.

### 13.2.2. Safety Pharmacology

The Applicant evaluated safety pharmacology endpoints in good laboratory practice (GLP)-compliant stand-alone studies to evaluate effects on the central nervous system, cardiovascular system, and respiratory system.

#### 13.2.2.1. Central Nervous System

**Study Title:** Neuropharmacological screening in rats according to Irwin following oral administration of IB1001 (Study 38192) (GLP compliant)

**Methods:** Effects of levacetylleucine were evaluated in female rats (8 in each group) following administration of a single oral dose of 250, 800, or 2500 mg/kg (dose volume of 10 mL/kg). Effects were evaluated on the following 40 neuropharmacological parameters at 15-, 30-, 60- and 120-minute postdose timepoints.

**Table 48. Summary of Endpoints Evaluated in the Irwin Functional Observational Battery in Rats**

|                        |                                                                       |                        |                                                                                      |                   |                                                                              |
|------------------------|-----------------------------------------------------------------------|------------------------|--------------------------------------------------------------------------------------|-------------------|------------------------------------------------------------------------------|
| <b>Awareness:</b>      | Alertness<br>Visual Placing<br>Passivity<br>Stereotypy                | <b>CNS Excitation:</b> | Startle Response<br>STRAUB Tail<br>Tremor<br>Twitching<br>Convulsion                 | <b>Reflexes:</b>  | Pinna<br>Corneal<br>Ipsilateral Flexor Reflex<br>Writhing<br>Pupil Size      |
| <b>Mood:</b>           | Grooming<br>Vocalisation<br>Restlessness<br>Aggression                | <b>Posture:</b>        | Body Posture<br>Limb Position<br>Staggering Gait<br>Abnormal Gait<br>Righting Reflex | <b>Autonomic:</b> | Palpebral Opening<br>Exophthalmus<br>Urination<br>Salivation<br>Piloerection |
| <b>Motor Activity:</b> | Reactivity<br>Spontaneous Activity<br>Touch Response<br>Pain Response | <b>Muscle Tone:</b>    | Limb Tone<br>Grip Strength<br>Body Sag<br>Body Tone<br>Abdominal Tone                |                   | Hypothermia<br>Skin Colour<br>Respiration Rate                               |

Source: Compiled from the Applicant's NDA  
Vehicle control was NaCl 0.9 %, w/v, pH 8.0.

**Results:** At oral doses of 250, 800, or 2500 mg/kg, levacetylleucine had no adverse effects on any of the neuropharmacological parameters compared to controls. The oral NOAEL of levacetylleucine on neuropharmacological parameters was 2500 mg/kg; however, the design of the study was not adequately justified (e.g., the use of a single sex (females), the selection of the high dose). Based on the single-dose  $C_{max}$  exposure measured in a 26-week study (Study 36242) in which rats were dosed at 2500 mg/kg, the safety multiple at the NOAEL dose of 2500 mg/kg is 5- to 10-fold when compared to the respective steady-state  $C_{max}$  levels in humans.

#### 13.2.2.2. Cardiovascular System

**Study Title:** IB1001: Telemetric Evaluation of Cardiovascular Effects in the Conscious Beagle Dog (Oral Gavage Administration) (Study 8440125) (GLP compliant)

**Methods:** Effects of single dose of levacetylleucine were evaluated when administered by oral gavage in telemetered beagle dogs at doses of 100, 200 or 600 mg/kg. This study was conducted in four surgically instrumented male Beagle dogs using a Latin Square crossover design, in which each dog received all dose levels in a randomized manner. Doses were separated by a washout period of at least 6 days (which is greater than the 10 half-lives [ $t_{1/2}$ ] of <2 hours). Endpoints evaluated included arterial blood pressure (systolic, diastolic, and derived mean), heart rate, body temperature, ECG lead II intervals (PR interval, QRS interval, QT, and heart rate corrected QT) and waveform morphology. The vehicle was NaCl 0.9%, w/v, pH 8.0. The telemetric data were collected 120 min before dosing through 24 hours post dose. The measured data were averaged at hourly intervals and compared to controls. Clinical and behavioral signs were observed as 1-, 2- and 4-hours post dose. The design of the study was not adequately justified (e.g., the use of a single sex (males), the selection of the high dose).

**Results:** Levacetylleucine, at oral doses of 100, 200 or 600 mg/kg, caused no adverse clinical or behavioral signs, or effects on body temperature and cardiovascular parameters (blood pressure [systolic, diastolic, and mean], heart rate, ECG intervals [PR interval, QRS interval, QT, and heart rate corrected QT], and ECG waveform morphology) compared to vehicle control. The oral NOAEL of levacetylleucine for cardiovascular effect was 600 mg/kg.

Based on the steady state  $C_{max}$  exposure (M 61.1  $\mu\text{g/mL}$ /F 83.9  $\mu\text{g/mL}$ ) measured in a 39-week study (Study 8422660) in which dogs were dosed at 600 mg/kg, the safety multiple at the NOAEL dose is 8- to 12-fold when compared to the respective steady-state  $C_{max}$  (7.4  $\mu\text{g/mL}$ ) in humans. The dose formulation analysis indicated that the formulations met prespecified acceptance criteria, as concentrations ranged between 95.9% and 105.0% of the nominal concentrations and within the acceptable range of 90 to 110%.

**Study Title:** IB1001: Effect on human ether-a-go-go-related gene (hERG) Tail Currents Recorded From Stably Transfected 293 human embryonic kidney (HEK293) Cells (Study A2592) (GLP compliant)

**Methods:** Levacetylleucine was tested for its effects on the hERG outward tail currents recorded in HEK293 cells stably transfected with cDNA encoding this cardiac potassium channel. The test was performed to evaluate the potential for QT-prolongation by levacetylleucine. The concentrations tested were at the close to the limit of solubility (concentration of 1000 $\mu$ M/525  $\mu$ M [nominal/actual concentration determined by analysis of dose formulations after completion of the study]) E-4031 (a methane sulfonanilide class III antiarrhythmic drug) was used as positive control.

**Results:** At the highest feasible concentration of 525 $\mu$ M, levacetylleucine inhibited hERG tail currents by less than 30%, therefore, half-maximal inhibitory concentration (IC<sub>50</sub>) could not be determined, as the concentration response curve was limited by solubility. 525 $\mu$ M (91  $\mu$ g/mL) provide a more than 12-fold safety margin when compared to the mean, steady-state C<sub>max</sub> level in human plasma (7.4  $\mu$ g/mL). The results indicate that levacetylleucine is not likely to inhibit the hERG channel when administered at the intended doses.

#### 13.2.2.3. Respiratory System

**Study Title:** Examination of Respiratory Parameters in Rats Following Oral Administration of IB1001 Employing Whole Body Plethysmography (Study 38191) (GLP)

**Methods:** Levacetylleucine was tested at single oral doses of 250, 800 and 2500 mg/kg, administered by oral gavage at dose volume of 10 mL/kg in female rats (8 in each group). Respiratory endpoints (respiratory rate, tidal volume, minute volume, peak inspiratory flow, peak expiratory flow, inspiratory time, expiratory time, and the airway resistance index) were measured by whole-body plethysmography for 4 hours postdose (baseline was measured predose for 1 hour). The vehicle control was NaCl 0.9 %, w/v, pH 8.0 and Carbamyl- $\beta$ -methylcholine chloride (bethanechol) at 30 mg (subcutaneous) was used as positive control. Respiratory parameters were assessed at intervals of 10 minutes for the first hour (10 minutes to 60 minutes) and intervals of 30 minutes postdose for the remainder of the experiment (1 hour to 4 hours).

**Results:** Levacetylleucine, at oral doses of 250, 800 and 2500 mg/kg, did not affect respiratory parameters (respiratory rate, tidal volume, minute volume, peak inspiratory flow, peak expiratory flow, inspiratory time, expiratory time, and the airway resistance index) in female rats following administration of a single dose. The oral NOAEL of levacetylleucine on respiratory parameters was 2500 mg/kg. Based on the single-dose C<sub>max</sub> exposure measured in a 26-week study (Study 36242) in which rats were dosed at 2500 mg/kg, the safety multiple at the NOAEL dose of 2500 mg/kg is 5- to 10-fold when compared to the respective steady-state C<sub>max</sub> in humans ([Table 62](#)); however, the design of the study was not adequately justified (e.g., the use of a single sex (females), the selection of the high dose).

#### 13.2.3. General Toxicology

Repeat dose oral toxicity 26-week rat and 39-week dog study reviews included below are from PharmTox review by Dr. Miyun Tsai-Turton, dated December 16, 2021, conducted under the IND.

**6.2.1 Study Title: 26-week chronic toxicity study of IB1001 by repeated oral administration to Wistar Han rats (multi-site study)**

|                                     |                                                           |
|-------------------------------------|-----------------------------------------------------------|
| Study no.:                          | 36242                                                     |
| Study report location:              | SN 31 Module 4.2.3.2. – <a href="#">26-week rat study</a> |
| Study initiation date:              | February 19, 2020                                         |
| Conducting laboratory and location: | (b) (4)                                                   |
| Duration:                           | 26                                                        |
| Duration Units:                     | weeks                                                     |
| GLP compliance:                     | Y                                                         |
| Drug, lot #, and % purity:          | LT 50 and 99.9% purity                                    |
| Target Organ*:                      | KIDNEY                                                    |

**Methods**

|                                      |                                                                                 |
|--------------------------------------|---------------------------------------------------------------------------------|
| Doses:                               | 0 (vehicle), 250, 800, and 2500 mg/kg/day                                       |
| Frequency of dosing:                 | Once daily for 182 days                                                         |
| Number/Sex/Group:                    | 20/sex/group                                                                    |
| Dose volume:                         | 10 mL/kg b.w.                                                                   |
| Formulation/Vehicle:                 | NaCl 0.9%, w/v, pH 8.0                                                          |
| Route of administration:             | ORAL GAVAGE                                                                     |
| Species:                             | RAT                                                                             |
| Strain:                              | WISTAR                                                                          |
| Age / Sexual Maturity:               | ~ 60 days of age, sexually matured                                              |
| Comment on Study Design and Conduct: | Recovery (5/sex/group)                                                          |
| Dosing Solution Analysis:            | Dosing solution was correctly prepared (within the range between 96% and 103%). |

**Observations and Results****Mortality**

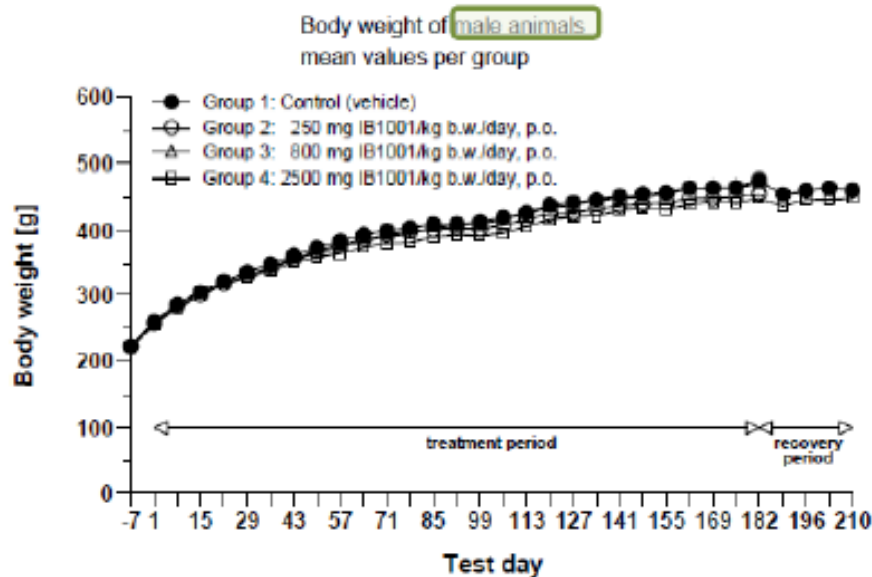
None.

**Clinical Signs**

Salivation and soft feces were observed in both males and females at 2500 mg/kg/day.

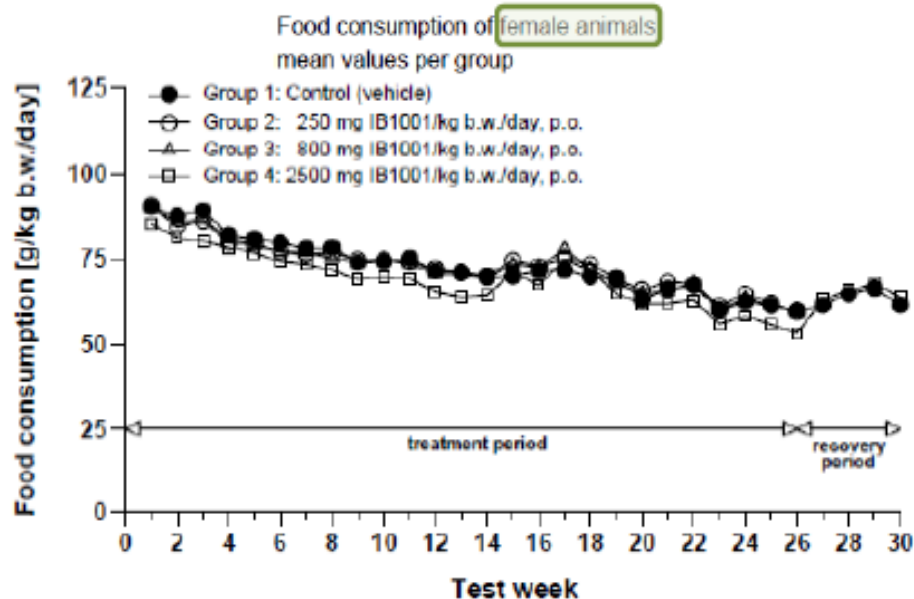
**Body Weights**

Decreased body weight (-6%) was noted in males at 2500 mg/kg/day. This was subsided at the end of the 4-week recovery period. No body weight effect was noted in females.



### Feed Consumption

Decreased food consumption (-11%) was noted in females at 2500 mg/kg/day, without correlation to decreased body weight (not considered adverse). This was subsided at the end of the 4-week recovery period. No effect was noted in males.



In addition, increased drinking water consumption was noted in both males and females. This was also subsided at the end of the 4-week recovery period.

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### Ophthalmoscopy

No effect.

### ECG

Not done.

### Hematology

No effect.

### Clinical Chemistry

Increase in urea and decreases in chloride, potassium, and sodium were noted in both males and females at 2500 mg/kg/day. These changes were subsided at the end of the 4-week recovery period.

Changes in clinical chemistry parameters during and at the end of the treatment period compared to the control group

| Changes in clinical chemistry parameters during and at the end of the treatment period compared to the control group [%] |                        |         |
|--------------------------------------------------------------------------------------------------------------------------|------------------------|---------|
| Parameter                                                                                                                | Group 4:<br>2500 mg/kg |         |
|                                                                                                                          | males                  | females |
| Test day 93                                                                                                              |                        |         |
| Urea                                                                                                                     | +29**                  | +59**   |
| Chloride                                                                                                                 | -2**                   | -6**    |
| Potassium                                                                                                                | none                   | -11**   |
| Sodium                                                                                                                   | -1*                    | -3**    |
| Test day 183                                                                                                             |                        |         |
| Urea                                                                                                                     | +23**                  | +30**   |
| Chloride                                                                                                                 | -4**                   | -5**    |
| Potassium                                                                                                                | -11**                  | -23**   |
| Sodium                                                                                                                   | -2**                   | -2**    |

\*: statistically significant at  $p \leq 0.05$

\*\* : statistically significant at  $p \leq 0.01$

none: no test item-related influence

### Urinalysis

Increased urine pH (16%) was noted in females at 2500 mg/kg/day. No effect was noted in males. This was subsided at the end of the 4-week recovery period.

### Gross Pathology

No effect.

### Organ Weights

Increased kidney weight was noted in both males and females at 2500 mg/kg/day. This was subsided at the end of the 4-week recovery period.

Changes in relative and absolute organ weights at the end of the treatment period compared to the control group

| Changes in relative and absolute organ weights at the end of the treatment period compared to the control group [%] |                        |         |
|---------------------------------------------------------------------------------------------------------------------|------------------------|---------|
| Organ                                                                                                               | Group 4:<br>2500 mg/kg |         |
|                                                                                                                     | males                  | females |
| Kidney, left (relative)                                                                                             | +20**                  | +15**   |
| Kidney, left (absolute)                                                                                             | +12**                  | +15**   |
| Kidney, right (relative)                                                                                            | +21**                  | +15**   |
| Kidney, right (absolute)                                                                                            | +14**                  | +15**   |

\*: statistically significant at  $p \leq 0.05$

\*\*: statistically significant at  $p \leq 0.01$

### Histopathology

Adequate Battery: Yes

Peer Review: Yes

Microscopic findings (increased incidence and severity of tubular basophilia and/or hyaline tubular casts) were noted in males at 800 (not adverse) or 2500 mg/kg/day (adverse). The kidney findings remained (mainly the left kidney in males) at 2500 mg/kg/day at the end of the recovery period. The incidence and severity of these findings did not show a tendency of recovery.

**Figure 20. Summary of Histopathological Findings in 26-Week Chronic Toxicity Study of IB1001**

| Observations: Neo-Plastic and Non Neo-Plastic   |  | ----- MALES ----- |           |           |            | ----- FEMALES ----- |           |           |            |
|-------------------------------------------------|--|-------------------|-----------|-----------|------------|---------------------|-----------|-----------|------------|
| Removal Reasons: Main Study Animals             |  | Group 1:          | Group 2:  | Group 3:  | Group 4:   | Group 1:            | Group 2:  | Group 3:  | Group 4:   |
|                                                 |  | Control           | 250 mg/kg | 800 mg/kg | 2500 mg/kg | Control             | 250 mg/kg | 800 mg/kg | 2500 mg/kg |
| Number of Animals on Study :                    |  | 20                | 20        | 18        | 20         | 20                  | 20        | 20        | 20         |
| Number of Animals Completed:                    |  | (20)              | (20)      | (18)      | (20)       | (20)                | (20)      | (20)      | (20)       |
| <b>KIDNEY, LEFT;</b>                            |  |                   |           |           |            |                     |           |           |            |
| Examined.....                                   |  | (20)              | (20)      | (18)      | (20)       | (20)                | (20)      | (20)      | (20)       |
| Within Normal Limits.....                       |  | 0.0%              | 0.0%      | 0.0%      | 0.0%       | 0.0%                | 0.0%      | 0.0%      | 0.0%       |
| Congestion .....                                |  | 100.0%            | 100.0%    | 100.0%    | 95.0%      | 90.0%               | 95.0%     | 100.0%    | 100.0%     |
| Infiltration, Lymphocytic .....                 |  | 55.0%             | 50.0%     | 55.6%     | 85.0%      | 25.0%               | 15.0%     | 5.0%      | 45.0%      |
| <b>KIDNEY, LEFT; (continued)</b>                |  |                   |           |           |            |                     |           |           |            |
| Basophilia; tubular .....                       |  | 25.0%             | 10.0%     | 44.4%     | 75.0% **   | 0.0%                | 5.0%      | 5.0%      | 10.0%      |
| Cast; hyaline; tubule .....                     |  | 0.0%              | 5.0%      | 5.6%      | 30.0% *    | 10.0%               | 5.0%      | 5.0%      | 5.0%       |
| Cyst .....                                      |  | 5.0%              | 0.0%      | 5.6%      | 0.0%       | 0.0%                | 0.0%      | 0.0%      | 5.0%       |
| Dilation; pelvis .....                          |  | 0.0%              | 0.0%      | 0.0%      | 5.0%       | 0.0%                | 0.0%      | 0.0%      | 0.0%       |
| Dilation; collecting duct .....                 |  | 0.0%              | 0.0%      | 0.0%      | 5.0%       | 0.0%                | 0.0%      | 0.0%      | 0.0%       |
| Dilation; tubular .....                         |  | 0.0%              | 0.0%      | 0.0%      | 0.0%       | 0.0%                | 0.0%      | 0.0%      | 5.0%       |
| Mineralization .....                            |  | 0.0%              | 0.0%      | 0.0%      | 0.0%       | 15.0%               | 5.0%      | 15.0%     | 15.0%      |
| Mineralization; papilla .....                   |  | 0.0%              | 0.0%      | 0.0%      | 5.0%       | 0.0%                | 0.0%      | 0.0%      | 0.0%       |
| Hyperplasia; urothelial; pelvis .....           |  | 0.0%              | 0.0%      | 0.0%      | 5.0%       | 0.0%                | 0.0%      | 0.0%      | 15.0%      |
| Infiltration, Neutrophilic; pelvis .....        |  | 0.0%              | 5.0%      | 0.0%      | 5.0%       | 5.0%                | 0.0%      | 0.0%      | 10.0%      |
| Pigment Laden Macrophages; brown .....          |  | 0.0%              | 5.0%      | 0.0%      | 0.0%       | 0.0%                | 0.0%      | 0.0%      | 5.0%       |
| Pigment Laden Macrophages; brown; pelvis .....  |  | 0.0%              | 5.0%      | 0.0%      | 0.0%       | 0.0%                | 0.0%      | 0.0%      | 0.0%       |
| Pigment Laden Macrophages; brown; papilla ..... |  | 0.0%              | 0.0%      | 0.0%      | 0.0%       | 0.0%                | 0.0%      | 0.0%      | 5.0%       |
| Fibrosis; papilla .....                         |  | 0.0%              | 0.0%      | 0.0%      | 0.0%       | 0.0%                | 0.0%      | 0.0%      | 5.0%       |
| <b>KIDNEY, RIGHT;</b>                           |  |                   |           |           |            |                     |           |           |            |
| Examined.....                                   |  | (20)              | (20)      | (18)      | (20)       | (20)                | (20)      | (20)      | (20)       |
| Within Normal Limits.....                       |  | 0.0%              | 0.0%      | 0.0%      | 0.0%       | 0.0%                | 5.0%      | 0.0%      | 0.0%       |
| Congestion .....                                |  | 100.0%            | 90.0%     | 100.0%    | 100.0%     | 100.0%              | 95.0%     | 100.0%    | 100.0%     |
| Basophilia; tubular .....                       |  | 20.0%             | 20.0%     | 22.2%     | 40.0%      | 10.0%               | 0.0%      | 0.0%      | 0.0%       |
| Infiltration, Lymphocytic .....                 |  | 30.0%             | 35.0%     | 38.9%     | 45.0%      | 20.0%               | 0.0%      | 20.0%     | 25.0%      |
| Cast; hyaline; tubule .....                     |  | 5.0%              | 5.0%      | 11.1%     | 15.0%      | 5.0%                | 0.0%      | 5.0%      | 0.0%       |
| Pigmentation; brown; tubule .....               |  | 5.0%              | 0.0%      | 0.0%      | 0.0%       | 0.0%                | 0.0%      | 0.0%      | 0.0%       |
| Dilation; pelvis .....                          |  | 0.0%              | 0.0%      | 0.0%      | 5.0%       | 0.0%                | 0.0%      | 0.0%      | 0.0%       |
| Dilation; tubular .....                         |  | 0.0%              | 0.0%      | 0.0%      | 0.0%       | 5.0%                | 0.0%      | 0.0%      | 0.0%       |
| Infiltration, Neutrophilic; pelvis .....        |  | 0.0%              | 0.0%      | 0.0%      | 10.0%      | 10.0%               | 0.0%      | 0.0%      | 10.0%      |
| Hyperplasia; urothelial; pelvis .....           |  | 0.0%              | 0.0%      | 0.0%      | 0.0%       | 0.0%                | 0.0%      | 0.0%      | 10.0%      |
| Mineralization .....                            |  | 0.0%              | 0.0%      | 0.0%      | 0.0%       | 5.0%                | 5.0%      | 5.0%      | 20.0%      |
| Cyst .....                                      |  | 0.0%              | 0.0%      | 0.0%      | 0.0%       | 5.0%                | 0.0%      | 0.0%      | 0.0%       |

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Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: Recovery Period Animals

|                                        | ----- MALES -----   |                        | ----- FEMALES ----- |                        |
|----------------------------------------|---------------------|------------------------|---------------------|------------------------|
|                                        | Group 1:<br>Control | Group 4:<br>2500 mg/kg | Group 1:<br>Control | Group 4:<br>2500 mg/kg |
| Number of Animals on Study :           | 5                   | 5                      | 5                   | 5                      |
| Number of Animals Completed:           | (5)                 | (5)                    | (5)                 | (5)                    |
| <hr/>                                  |                     |                        |                     |                        |
| KIDNEY, LEFT;                          |                     |                        |                     |                        |
| Examined.....                          | (5)                 | (5)                    | (5)                 | (5)                    |
| Within Normal Limits.....              | 0.0%                | 0.0%                   | 0.0%                | 0.0%                   |
| Congestion .....                       | 100.0%              | 100.0%                 | 100.0%              | 100.0%                 |
| Infiltration, Lymphocytic .....        | 60.0%               | 100.0%                 | 20.0%               | 0.0%                   |
| Basophilia; tubular .....              | 20.0%               | 100.0% *               | 20.0%               | 0.0%                   |
| Cast; hyaline; tubule .....            | 20.0%               | 80.0%                  | 0.0%                | 0.0%                   |
| Mineralization .....                   | 0.0%                | 20.0%                  | 0.0%                | 20.0%                  |
| KIDNEY, RIGHT;                         |                     |                        |                     |                        |
| Examined.....                          | (5)                 | (5)                    | (5)                 | (5)                    |
| Within Normal Limits.....              | 0.0%                | 0.0%                   | 0.0%                | 0.0%                   |
| Congestion .....                       | 100.0%              | 100.0%                 | 100.0%              | 80.0%                  |
| Basophilia; tubular .....              | 20.0%               | 40.0%                  | 0.0%                | 0.0%                   |
| Infiltration, Lymphocytic .....        | 20.0%               | 60.0%                  | 0.0%                | 40.0%                  |
| Cast; hyaline; tubule .....            | 20.0%               | 20.0%                  | 0.0%                | 0.0%                   |
| Mineralization .....                   | 0.0%                | 0.0%                   | 20.0%               | 20.0%                  |
| Cyst .....                             | 0.0%                | 0.0%                   | 0.0%                | 20.0%                  |
| Pigment Laden Macrophages; brown ..... | 0.0%                | 0.0%                   | 0.0%                | 20.0%                  |

Source: Excerpted from the Applicant's submission.

Fisher's Two-Tailed Exact Test Performed: \* = 5% Significance Level \*\* = 1% Significance Level

### Toxicokinetics

- The  $C_{max}$  and AUC revealed a roughly linear and dose-related exposure of the animals to IB1001 after the oral administration on Day 1 and a non-linear exposure on Days 91 and 176/178.
- The calculated plasma half-lives ( $t_{1/2}$ ) were 0.25 to 4 hours ranged from 0.80 to 4.22 hours in males and from 0.62 to 6.71 hours in females.
- Plateau levels were still observed at 4 hours, in particular for the intermediate dose (800 mg/kg/day) and high dose (2500 mg/kg/day).
- There was no gender difference in exposure at the low and intermediate dose level groups. However, the  $C_{max}$  of the high dosed females on Days 91 and 176 were approx. 2-fold higher than the  $C_{max}$  of the high dosed males.
- The  $C_{max}$  and AUC of the high dose level group were slightly lower on Day 91 (males and females) and on Day 178 (males only) compared to the values of Day 1.
- No accumulation with time was noted.

| Non-compartment analysis of IB1001 |                        |                    |               |                |                             |                            |                                   |      |      |
|------------------------------------|------------------------|--------------------|---------------|----------------|-----------------------------|----------------------------|-----------------------------------|------|------|
| Dose [mg/kg]                       | $C_{max}^{\#}$ [µg/mL] | $t_{max}^{\#}$ [h] | $t_{1/2}$ [h] | $K_{el}$ [1/h] | $AUC_{0-t\ last}$ [µg·h/mL] | $AUC_{0-\infty}$ [µg·h/mL] | $AUC_{0-t\ last}/\ dose$ [g·h/mL] | DPF  | R    |
| <u>Males</u>                       |                        |                    |               |                |                             |                            |                                   |      |      |
| Test day 1                         |                        |                    |               |                |                             |                            |                                   |      |      |
| 250                                | 6.48                   | 0.25               | 1.87          | 0.3716         | 12.79                       | 16.43                      | 0.051                             | N/A  | N/A  |
| 800                                | 13.58                  | 1.00               | 2.77          | 0.2504         | 35.89                       | 59.19                      | 0.045                             | 0.88 | N/A  |
| 2500                               | 53.58                  | 0.25               | 3.74          | 0.1855         | 103.07                      | 187.62                     | 0.041                             | 0.81 | N/A  |
| Test day 91                        |                        |                    |               |                |                             |                            |                                   |      |      |
| 250                                | 8.04                   | 0.50               | 0.80          | 0.8648         | 20.30                       | 21.13                      | 0.081                             | N/A  | 1.59 |
| 800                                | 13.48                  | 2.00               | 1.36          | 0.5103         | 42.14                       | 51.66                      | 0.053                             | 0.65 | 1.17 |
| 2500                               | 25.11                  | 2.00               | 2.57          | 0.2695         | 82.68                       | 137.03                     | 0.033                             | 0.41 | 0.80 |
| Test day 178                       |                        |                    |               |                |                             |                            |                                   |      |      |
| 250                                | 9.76                   | 1.00               | 0.84          | 0.8271         | 22.17                       | 23.28                      | 0.089                             | N/A  | 1.73 |
| 800                                | 17.08                  | 0.25               | 2.56          | 0.2706         | 43.97                       | 66.77                      | 0.055                             | 0.62 | 1.23 |
| 2500                               | 34.98                  | 0.50               | 4.22          | 0.1641         | 86.81                       | 181.81                     | 0.035                             | 0.39 | 0.84 |

| Non-compartment analysis of IB1001 |                                          |                                      |                         |                          |                                      |                                 |                                               |      |      |
|------------------------------------|------------------------------------------|--------------------------------------|-------------------------|--------------------------|--------------------------------------|---------------------------------|-----------------------------------------------|------|------|
| Dose<br>[mg/kg]                    | C <sub>max</sub> <sup>#</sup><br>[µg/mL] | t <sub>max</sub> <sup>#</sup><br>[h] | t <sub>1/2</sub><br>[h] | K <sub>el</sub><br>[1/h] | AUC <sub>0-t last</sub><br>[µg·h/mL] | AUC <sub>0-∞</sub><br>[µg·h/mL] | AUC <sub>0-t last</sub> /<br>dose<br>[g·h/mL] | DPF  | R    |
| <u>Females</u>                     |                                          |                                      |                         |                          |                                      |                                 |                                               |      |      |
| <b>Test day 1</b>                  |                                          |                                      |                         |                          |                                      |                                 |                                               |      |      |
| 250                                | 8.29                                     | 0.50                                 | 1.27                    | 0.5444                   | 18.89                                | 21.59                           | 0.076                                         | N/A  | N/A  |
| 800                                | 17.20                                    | 0.50                                 | 2.06                    | 0.3373                   | 48.53                                | 66.23                           | 0.061                                         | 0.80 | N/A  |
| 2500                               | 72.29                                    | 0.50                                 | 3.80                    | 0.1825                   | 159.06                               | 318.34                          | 0.064                                         | 0.84 | N/A  |
| <b>Test day 91</b>                 |                                          |                                      |                         |                          |                                      |                                 |                                               |      |      |
| 250                                | 11.69                                    | 0.50                                 | 0.62                    | 1.1107                   | 24.43                                | 24.86                           | 0.098                                         | N/A  | 1.29 |
| 800                                | 23.00                                    | 0.50                                 | 1.33                    | 0.5212                   | 59.58                                | 68.34                           | 0.074                                         | 0.76 | 1.23 |
| 2500                               | 52.91                                    | 0.50                                 | 6.71                    | 0.1034                   | 134.36                               | 414.49                          | 0.054                                         | 0.55 | 0.84 |
| <b>Test day 176</b>                |                                          |                                      |                         |                          |                                      |                                 |                                               |      |      |
| 250                                | 16.08                                    | 0.25                                 | 0.75                    | 0.9231                   | 33.29                                | 34.39                           | 0.133                                         | N/A  | 1.76 |
| 800                                | 29.54                                    | 0.25                                 | 1.79                    | 0.3879                   | 62.06                                | 80.12                           | 0.078                                         | 0.58 | 1.28 |
| 2500                               | 76.05                                    | 0.50                                 | 3.54                    | 0.1956                   | 145.47                               | 279.42                          | 0.058                                         | 0.44 | 0.91 |

In the 26-week toxicity study, administration of levacetylleucine (0, 250, 800, and 2500 mg/kg/day) by oral gavage in rats with a 4-week treatment-free recovery period produced no adverse effects at doses of up to 800 mg/kg/day; thus, the NOAEL is 800 mg/kg/day. At 2500 mg/kg/day test article related adverse effects include decreased body weight (males only), changes of clinical chemistry parameters (males and females), changes of urine parameters (females only), increased kidney weights (males and females), histopathological changes in the kidney (males only). Exposure (AUC<sub>0-∞</sub>) in rats dosed at 800 mg/kg provide a safety margin of 2- to 3-fold when compared to the respective steady-state levels in humans (Table 62).

#### 6.2.2 Study Title: IB1001: 39 week oral (gavage) administration toxicity study in the dog followed by a 4 week recovery period

Study no.: 8422660  
Study report location: SN 31 Module 4.2.3.2. – [39-week dog study](#)  
Study initiation date: February 26, 2020  
Conducting laboratory and location: (b) (4)  
Duration: 39  
Duration Units: weeks  
GLP compliance: Y  
Drug, lot #, and % purity: LT 50/15 and LT 60/10 with 99.9% purity  
Target Organ\*: KIDNEY

## Methods

|                                      |                                                                                     |
|--------------------------------------|-------------------------------------------------------------------------------------|
| Doses:                               | 0 (vehicle), 100, 200, and 600 mg/kg/day                                            |
| Frequency of dosing:                 | Once daily for 274 days                                                             |
| Number/Sex/Group:                    | 4/sex/group                                                                         |
| Dose volume:                         | 10 mL/kg b.w.                                                                       |
| Formulation/Vehicle:                 | NaCl 0.9%, w/v, pH 8.0                                                              |
| Route of administration:             | ORAL GAVAGE                                                                         |
| Species:                             | DOG                                                                                 |
| Strain:                              | BEAGLE                                                                              |
| Age / Sexual Maturity:               | 25-33 weeks of age, sexually matured                                                |
| Comment on Study Design and Conduct: | Recovery (2/sex/group)                                                              |
| Dosing Solution Analysis:            | Dosing solution was correctly prepared (within the range between 98.5% and 105.7%). |

## Observations and Results

### Mortality

None.

### Clinical Signs

Liquid feces were observed in both males and females at 600 mg/kg/day.

### Body Weights

No effect.

### Feed Consumption

No effect.

### Ophthalmoscopy

No effect.

### ECG

No effect.

### Hematology

No effect.

### Clinical Chemistry

No effect.

### Urinalysis

No effect.

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### Organ Weights

No effect.

### Histopathology

Adequate Battery: Yes

Peer Review: Yes

No effect.

### Special Evaluation

None.

### Toxicokinetics

- Sex differences in IB1001 mean  $C_{max}$  and  $AUC_{0-24}$  values were less than 2-fold.
- Exposure increased with the increase in dose level from 100 to 600 mg/kg/day. The increases in IB1001 mean  $C_{max}$  and  $AUC_{0-24}$  values were generally dose proportional from 100 to 200 mg/kg/day and less than dose proportional from 200 to 600 mg/kg/day.
- No notable accumulation of IB1001 was observed after multiple doses in dogs.

#### Summary of the Mean IB1001 TK Parameters in Dog Plasma

| Interval | Dose Group | Dose Level (mg/kg/day) | Sex | $C_{max}$ (µg/mL) | $T_{max}$ (h) | $AUC_{0-24}$ (h*µg/mL) | $t_{1/2}$ (h) |
|----------|------------|------------------------|-----|-------------------|---------------|------------------------|---------------|
| Day 1    | 2          | 100                    | M   | 30.0              | 1.00          | 84.2                   | 1.45          |
|          |            |                        | F   | 28.4              | 1.00          | 79.6                   | 1.62          |
|          |            |                        | MF  | 29.2              | 1.00          | 81.9                   | 1.53          |
|          | 3          | 200                    | M   | 50.9              | 1.00          | 145                    | 1.26          |
|          |            |                        | F   | 45.1              | 1.00          | 139                    | 1.34          |
|          |            |                        | MF  | 48.0              | 1.00          | 142                    | 1.29          |
|          | 4          | 600                    | M   | 83.9              | 1.00          | 261                    | 1.07          |
|          |            |                        | F   | 90.8              | 1.00          | 269                    | 1.16          |
|          |            |                        | MF  | 87.3              | 1.00          | 265                    | 1.11          |
| Week 39  | 2          | 100                    | M   | 31.4              | 1.00          | 74.0                   | 1.34          |
|          |            |                        | F   | 37.3              | 1.00          | 118                    | 1.25          |
|          |            |                        | MF  | 34.4              | 1.00          | 96.0                   | 1.28          |
|          | 3          | 200                    | M   | 53.0              | 1.00          | 171                    | 1.39          |
|          |            |                        | F   | 67.2              | 1.00          | 185                    | 1.17          |
|          |            |                        | MF  | 60.1              | 1.00          | 178                    | 1.28          |
|          | 4          | 600                    | M   | 61.1              | 1.09          | 193                    | 1.14          |
|          |            |                        | F   | 83.9              | 1.12          | 272                    | 1.15          |
|          |            |                        | MF  | 72.5              | 1.12          | 232                    | 1.14          |

Note: Median values are presented for  $T_{max}$ .

Levacetylleucine (0, 100, 200, and 600 mg/kg/day) administered by oral gavage in dogs in a 39-week toxicity study followed by a 4-week treatment-free period was without adverse effects with NOAEL of 600 mg/kg/day. Non-adverse findings were limited to liquid feces observed at 600 mg/kg/day. Exposure ( $AUC_{0-24h}$ ) in dogs dosed at 600 mg/kg provides safety margins of 6- to 9-fold when compared to the respective steady-state levels in humans ([Table 62](#)).

### 13.2.4. Genetic Toxicology

Levacetylleucine was non-mutagenic in vitro (in bacterial cells) and non-clastogenic in vitro (in cultured human peripheral lymphocytes) and in vivo (in bone marrow cells of the CD rats).

### 13.2.4.1. In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

#### 13.2.4.1.1. Study Title: Mutagenicity Study of IB1001 in the *Salmonella* Typhimurium Reverse Mutation Assay (In Vitro)

**Table 49. Summary of the Study Design for the Bacterial Mutagenicity Assay**

| Study                               | Findings                                                                            |
|-------------------------------------|-------------------------------------------------------------------------------------|
| Study number                        | Study 38188                                                                         |
| Study report location:              | 0001                                                                                |
| Conducting laboratory and location: | (b) (4)                                                                             |
| GLP compliance:                     | Y (OECD)                                                                            |
| Drug, lot #, and % purity:          | V0251 (IB1001); LT40; 100.4% (b) (4)                                                |
| Strains:                            | <i>Salmonella</i> Typhimurium TA98, TA100, TA102, TA1535, TA1537                    |
| Concentrations in definitive study: | 10, 50, 100, 500, 1000, 2500, 5000 µg/plate                                         |
| Basis of concentration selection:   | Plate incorporation cytotoxicity test, TA100; cytotoxicity at ≥5000-250000 µg/plate |
| Negative control:                   | DMSO                                                                                |
| Positive control:                   |                                                                                     |

**Table 50. Summary of Positive Controls**

| a) without metabolic activation                                             |                     |
|-----------------------------------------------------------------------------|---------------------|
| sodium azide <sup>3</sup> in water for injection <sup>4</sup> (10 µg/plate) | TA1535, TA100       |
| 2-nitrofluorene <sup>5</sup> in DMSO <sup>6</sup> (10 µg/plate)             | TA98                |
| 9-aminoacridine <sup>7</sup> in ethanol, abs. <sup>8</sup> (100 µg/plate)   | TA1537              |
| Mitomycin C <sup>9</sup> in water for injection <sup>4</sup> (10 µg/plate)  | TA102               |
| b) with metabolic activation                                                |                     |
| Benzo[a]pyrene <sup>10</sup> in DMSO <sup>6</sup> (10 µg/plate)             | TA98, TA102, TA1537 |
| 2-aminoanthracene <sup>11</sup> in DMSO <sup>6</sup> (2 µg/plate)           | TA100, TA1535       |

Source: Excerpted from the Applicant's submission

|                             |                                                                                                                                                                                         |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Formulation/Vehicle:        | DMSO                                                                                                                                                                                    |
| Incubation & sampling time: | Plate incorporation and Preincubation (20 min) method with 48 hr incubation                                                                                                             |
| Comment on Study Validity:  | Positive: 2-fold increase in revertant colonies for TA98, TA100, TA1535 and TA1537 and 1.5-fold increase in revertant colonies for TA102 or conc related increase in revertant colonies |

Source:

Abbreviations: DMSO = dimethyl sulfoxide; hr = hour; GLP = good laboratory practice; OECD = Organization for Economic Co-operation and Development

## Results

Levacetylleucine was not mutagenic in *Salmonella* Typhimurium strains TA98, TA100, TA102, TA1535, or TA1537 at exposures between 10 to 5000 µg/plate in presence or absence of S9 when tested by plate incorporation and preincubation methods. The results

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indicate concentrations at or above 2500 µg/plate resulted in reduced background colonies in some or all strains ([Table 51](#)).

Levacetylleucine did not produce greater than 2-fold increase in revertant colonies in *Salmonella* Typhimurium strains TA98, TA100, TA1535 and TA1537 and 1.5-fold increase in revertant colonies for TA102 or concentration-related increase in revertant colonies compared to vehicle control ([Table 51](#)). Positive controls produced greater than 2-fold increases in all strains in the presence or absence of S9 when tested by plate incorporation and preincubation methods.

This study included the levacetylleucine impurities, (b) (4)

**Table 51. Summary of Ames Results of Levacetylleucine by Plate Incorporation and Preincubation Methods**

| TABLE 3<br>Plate incorporation test<br>without metabolic activation                                                       |      |                             |              |              |              |                  | TABLE 5<br>Preincubation test<br>without metabolic activation                                                             |      |                             |              |              |              |                  |
|---------------------------------------------------------------------------------------------------------------------------|------|-----------------------------|--------------|--------------|--------------|------------------|---------------------------------------------------------------------------------------------------------------------------|------|-----------------------------|--------------|--------------|--------------|------------------|
| Test item<br>(µg/plate)                                                                                                   |      | Number of reverted colonies |              |              |              |                  | Test item<br>(µg/plate)                                                                                                   |      | Number of reverted colonies |              |              |              |                  |
|                                                                                                                           |      | TA98                        | TA100        | TA102        | TA1535       | TA1537           |                                                                                                                           |      | TA98                        | TA100        | TA102        | TA1535       | TA1537           |
| mean values ± SD                                                                                                          |      |                             |              |              |              |                  | mean values ± SD                                                                                                          |      |                             |              |              |              |                  |
| IB1001<br>LT40                                                                                                            |      |                             |              |              |              |                  | IB1001<br>LT40                                                                                                            |      |                             |              |              |              |                  |
| 10                                                                                                                        | mean | 26.3                        | 149.7        | 275.3        | 13.7         | 3.7              | 10                                                                                                                        | mean | 45.3                        | 138.0        | 261.3        | 13.3         | 8.7              |
|                                                                                                                           | SD   | 7.5                         | 15.1         | 7.1          | 1.5          | 2.1              |                                                                                                                           | SD   | 16.3                        | 19.3         | 34.6         | 2.9          | 1.5              |
| 50                                                                                                                        | mean | 25.0                        | 133.7        | 306.0        | 9.3          | 3.0              | 50                                                                                                                        | mean | 39.3                        | 139.7        | 250.0        | 15.3         | 7.0              |
|                                                                                                                           | SD   | 6.9                         | 2.1          | 14.9         | 2.5          | 1.0              |                                                                                                                           | SD   | 11.6                        | 6.4          | 9.8          | 1.5          | 2.0              |
| 100                                                                                                                       | mean | 23.0                        | 136.7        | 301.7        | 14.0         | 5.0              | 100                                                                                                                       | mean | 46.3                        | 130.3        | 252.0        | 12.0         | 4.0              |
|                                                                                                                           | SD   | 3.6                         | 3.5          | 7.6          | 5.0          | 3.0              |                                                                                                                           | SD   | 9.1                         | 6.1          | 11.1         | 3.0          | 0.0              |
| 500                                                                                                                       | mean | 23.0                        | 145.0        | 291.7        | 12.7         | 3.0              | 500                                                                                                                       | mean | 46.0                        | 126.3        | 255.0        | 9.0          | 7.0              |
|                                                                                                                           | SD   | 2.0                         | 7.8          | 13.8         | 3.1          | 1.0              |                                                                                                                           | SD   | 6.1                         | 18.0         | 12.2         | 2.0          | 3.6              |
| 1000                                                                                                                      | mean | 29.0                        | 154.0        | 280.3        | 15.7         | 4.7              | 1000                                                                                                                      | mean | 47.0                        | 116.0        | 257.0        | 14.7         | 5.0              |
|                                                                                                                           | SD   | 6.1                         | 13.7         | 30.1         | 7.0          | 1.2              |                                                                                                                           | SD   | 1.0                         | 22.1         | 11.5         | 7.6          | 1.7              |
| 2500                                                                                                                      | mean | 6.0 #                       | 124.0        | 262.3        | 11.7         | 5.3              | 2500                                                                                                                      | mean | 8.0 #                       | 84.3         | 249.7        | 6.3 #        | 6.3              |
|                                                                                                                           | SD   | 2.0                         | 11.5         | 14.0         | 3.1          | 1.2              |                                                                                                                           | SD   | 3.6                         | 8.1          | 16.9         | 2.1          | 0.6              |
| 5000                                                                                                                      | mean | 3.7 #                       | 55.7 #       | 110.3 #      | 4.0 #        | 1.0              | 5000                                                                                                                      | mean | 4.7 #                       | 71.7 #       | 87.7 #       | 1.7 #        | 1.0              |
|                                                                                                                           | SD   | 3.2                         | 16.2         | 34.3         | 2.0          | 0.0              |                                                                                                                           | SD   | 1.5                         | 35.3         | 6.4          | 0.6          | 0.0              |
| Negative reference item<br>100 µL/plate                                                                                   |      |                             |              |              |              |                  | Negative reference item<br>100 µL/plate                                                                                   |      |                             |              |              |              |                  |
|                                                                                                                           |      | mean                        | 34.0         | 152.3        | 298.3        | 13.0             |                                                                                                                           |      | mean                        | 49.7         | 143.0        | 244.7        | 13.3             |
|                                                                                                                           |      | SD                          | 10.6         | 4.0          | 24.6         | 6.0              |                                                                                                                           |      | SD                          | 6.5          | 32.0         | 15.0         | 2.1              |
| Positive reference item                                                                                                   |      | 2-Nitro-fluorene            | Sodium azide | Mito-mycin C | Sodium azide | 9-Amino acridine | Positive reference item                                                                                                   |      | 2-Nitro-fluorene            | Sodium azide | Mito-mycin C | Sodium azide | 9-Amino acridine |
| Concentration µg/plate                                                                                                    |      | 10                          | 10           | 10           | 10           | 100              | Concentration µg/plate                                                                                                    |      | 10                          | 10           | 10           | 10           | 100              |
|                                                                                                                           |      | mean                        | 171.3        | 668.0        | 847.0        | 185.3            |                                                                                                                           |      | mean                        | 103.7        | 753.3        | 740.7        | 152.3            |
|                                                                                                                           |      | SD                          | 14.0         | 73.6         | 75.2         | 37.9             |                                                                                                                           |      | SD                          | 7.6          | 96.9         | 64.5         | 10.7             |
| SD standard deviation<br># scarce background lawn and/or reduction of revertant colonies by more than 50%<br>mean (n = 3) |      |                             |              |              |              |                  | SD standard deviation<br># scarce background lawn and/or reduction of revertant colonies by more than 50%<br>mean (n = 3) |      |                             |              |              |              |                  |

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| TABLE 4<br>Plate incorporation test<br>with metabolic activation                                                          |      |                             |                   |                 |                   |                | TABLE 6<br>Preincubation test<br>with metabolic activation                                                                |      |                             |                   |                 |                   |                |
|---------------------------------------------------------------------------------------------------------------------------|------|-----------------------------|-------------------|-----------------|-------------------|----------------|---------------------------------------------------------------------------------------------------------------------------|------|-----------------------------|-------------------|-----------------|-------------------|----------------|
| Test item<br>(µg/plate)                                                                                                   |      | Number of reverted colonies |                   |                 |                   |                | Test item<br>(µg/plate)                                                                                                   |      | Number of reverted colonies |                   |                 |                   |                |
|                                                                                                                           |      | TA98                        | TA100             | TA102           | TA1535            | TA1537         |                                                                                                                           |      | TA98                        | TA100             | TA102           | TA1535            | TA1537         |
| mean values ± SD                                                                                                          |      |                             |                   |                 |                   |                | mean values ± SD                                                                                                          |      |                             |                   |                 |                   |                |
| I81001<br>LT40                                                                                                            | 10   | mean<br>SD                  | 44.3<br>7.2       | 158.3<br>17.6   | 214.3<br>11.6     | 13.3<br>7.0    | I81001<br>LT40                                                                                                            | 10   | mean<br>SD                  | 60.0<br>8.9       | 153.3<br>11.9   | 235.3<br>7.2      | 13.0<br>6.1    |
|                                                                                                                           | 50   | mean<br>SD                  | 37.0<br>13.5      | 153.0<br>1.7    | 260.0<br>24.2     | 18.0<br>6.1    |                                                                                                                           | 50   | mean<br>SD                  | 49.0<br>9.5       | 150.0<br>9.8    | 254.7<br>16.1     | 15.0<br>4.6    |
|                                                                                                                           | 100  | mean<br>SD                  | 34.0<br>27.2      | 139.0<br>14.0   | 266.3<br>9.7      | 15.0<br>5.3    |                                                                                                                           | 100  | mean<br>SD                  | 52.0<br>13.7      | 136.0<br>5.3    | 273.3<br>26.6     | 15.0<br>3.0    |
|                                                                                                                           | 500  | mean<br>SD                  | 38.7<br>12.7      | 173.7<br>24.8   | 254.3<br>2.5      | 16.0<br>6.6    |                                                                                                                           | 500  | mean<br>SD                  | 35.0<br>6.9       | 135.0<br>12.8   | 270.7<br>4.2      | 16.3<br>2.1    |
|                                                                                                                           | 1000 | mean<br>SD                  | 53.0<br>9.8       | 140.3<br>11.0   | 272.0<br>54.1     | 20.3<br>1.5    |                                                                                                                           | 1000 | mean<br>SD                  | 28.3<br>3.2       | 99.3<br>3.2     | 262.3<br>12.5     | 18.0<br>6.2    |
|                                                                                                                           | 2500 | mean<br>SD                  | 41.3<br>9.1       | 97.0<br>8.2     | 286.3<br>26.6     | 11.3<br>4.2    |                                                                                                                           | 2500 | mean<br>SD                  | 6.7 #<br>3.5      | 70.3 #<br>15.8  | 143.3<br>89.8     | 6.0<br>0.0     |
|                                                                                                                           | 5000 | mean<br>SD                  | 14.3 #<br>6.1     | 88.3 #<br>19.3  | 151.3 #<br>6.4    | 4.3 #<br>0.6   |                                                                                                                           | 5000 | mean<br>SD                  | 8.3 #<br>8.4      | 68.7 #<br>23.2  | 90.7 #<br>15.5    | 2.3 #<br>2.3   |
| Negative reference item<br>100 µL/plate                                                                                   |      |                             |                   |                 |                   |                | Negative reference item<br>100 µL/plate                                                                                   |      |                             |                   |                 |                   |                |
|                                                                                                                           |      | mean<br>SD                  | 50.7<br>4.0       | 159.3<br>18.8   | 274.0<br>34.6     | 12.3<br>6.7    |                                                                                                                           |      | mean<br>SD                  | 46.3<br>3.2       | 157.7<br>21.9   | 222.7<br>76.8     | 11.3<br>1.5    |
| Positive reference item                                                                                                   |      | Benzo[a]pyrene              | 2-Aminoanthracene | Benzo[a]pyrene  | 2-Aminoanthracene | Benzo[a]pyrene | Positive reference item                                                                                                   |      | Benzo[a]pyrene              | 2-Aminoanthracene | Benzo[a]pyrene  | 2-Aminoanthracene | Benzo[a]pyrene |
| Concentration µg/plate                                                                                                    |      | 10                          | 2                 | 10              | 2                 | 10             | Concentration µg/plate                                                                                                    |      | 10                          | 2                 | 10              | 2                 | 10             |
|                                                                                                                           |      | mean<br>SD                  | 232.3<br>44.3     | 1413.7<br>162.8 | 1151.3<br>86.3    | 216.7<br>72.3  |                                                                                                                           |      | mean<br>SD                  | 114.0<br>5.6      | 1359.7<br>239.6 | 856.0<br>22.7     | 115.0<br>3.5   |
| SD standard deviation<br># scarce background lawn and/or reduction of revertant colonies by more than 50%<br>mean (n = 3) |      |                             |                   |                 |                   |                | SD standard deviation<br># scarce background lawn and/or reduction of revertant colonies by more than 50%<br>mean (n = 3) |      |                             |                   |                 |                   |                |

Source: Excerpted from Applicant's report

### 13.2.4.2. In Vitro Assays in Mammalian Cells

#### 13.2.4.2.1. Study Title: In Vitro Assessment of the Clastogenic Activity of IB1001 in Cultured Human Peripheral Lymphocytes

**Table 52. Summary of the Study Design for the in Vitro Chromosomal Aberrations Assay**

| Study                               | Findings                                                                                                                                           |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| Study number                        | 38189                                                                                                                                              |
| Study report location:              | 0001                                                                                                                                               |
| Conducting laboratory and location: | (b) (4)                                                                                                                                            |
| GLP compliance:                     | Y (OECD)                                                                                                                                           |
| Drug, lot #, and % purity:          | V0251 (IB1001); LT40; 100.4% (b) (4)                                                                                                               |
| <b>Methods</b>                      |                                                                                                                                                    |
| Cell line                           | Primary human peripheral blood lymphocytes                                                                                                         |
| Concentrations in definitive study  | 250-2000 µg/mL                                                                                                                                     |
| Basis of concentration selection    | No cytotoxicity or precipitation between 3.16 – 2000 µg/mL; no change in pH or in osmolality with TA versus control in medium                      |
| Negative control                    | DMSO                                                                                                                                               |
| Positive control                    | Mitomycin C (0.2 µg/mL and 0.1 µg/mL)                                                                                                              |
| Formulation/vehicle                 | DMSO                                                                                                                                               |
| Incubation & sampling time          | Without S9, 4 & 24 hr incubation<br>With S9: 4 hr incubation                                                                                       |
| Comment on study validity           | The study met the criteria for a valid test, because the negative and positive control values fell within the facility's historical control range. |

Source: Reviewer's analysis

Abbreviations: DMSO = dimethyl sulfoxide; TA = therapeutic anticoagulation; GLP = good laboratory practice; OECD = Organization for Economic Co-operation and Development

### Results

Levacetylleucine, at up to 2000 µg/mL, was evaluated to be non-genotoxic because it did not produce chromosomal, or chromatid damage in cultured human lymphocytes in the presence (4-hour incubation) or absence (4- and 24-hour incubations) of S9 compared to vehicle control (Table 53). Mitomycin positive control produced significant increases in chromosomal aberrations compared to vehicle control.

This study included the levacetylleucine impurities, (b) (4) due to their reported presence at designated levels.

**Table 53. Summary of Results of Chromosomal Aberration in Human Lymphocytes With Levacetylleucine**

| Table 2Experiments without metabolic activation (S9 mix) - Summarised data                                                                                                                                                                                                        |                             |                             |                                            |                          |                             |                             |                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|-----------------------------|--------------------------------------------|--------------------------|-----------------------------|-----------------------------|--------------------------------------------|
| 4-h exposure                                                                                                                                                                                                                                                                      |                             |                             |                                            | 24-h exposure            |                             |                             |                                            |
| Treatment (µg/mL medium)                                                                                                                                                                                                                                                          | Mitotic index <sup>#1</sup> | Number of metaphases scored | % of cells with aberrations excluding gaps | Treatment (µg/mL medium) | Mitotic index <sup>#1</sup> | Number of metaphases scored | % of cells with aberrations excluding gaps |
| DMSO                                                                                                                                                                                                                                                                              |                             |                             |                                            | DMSO                     |                             |                             |                                            |
| 0                                                                                                                                                                                                                                                                                 | 1.00                        | 300                         | 1.7                                        | 0                        | 1.00                        | 300                         | 1.7                                        |
| IB1001                                                                                                                                                                                                                                                                            |                             |                             |                                            | IB1001                   |                             |                             |                                            |
| 250                                                                                                                                                                                                                                                                               | 1.11                        | 300                         | 1.3                                        | 250                      | 1.12                        | 300                         | 1.0                                        |
| 500                                                                                                                                                                                                                                                                               | 1.03                        | 300                         | 1.7                                        | 500                      | 0.69                        | 300                         | 1.3                                        |
| 1000                                                                                                                                                                                                                                                                              | 0.94                        | 300                         | 1.7                                        | 1000                     | 0.53                        | 300                         | 2.3                                        |
| 2000                                                                                                                                                                                                                                                                              | 1.33                        | 300                         | 2.3                                        | 2000                     | 0.38                        | 183 <sup>#2</sup>           | 2.2                                        |
| Mitomycin C                                                                                                                                                                                                                                                                       |                             |                             |                                            | Mitomycin C              |                             |                             |                                            |
| 0.2                                                                                                                                                                                                                                                                               | 1.00                        | 300                         | 7.7*                                       | 0.1                      | 0.56                        | 300                         | 8.0*                                       |
| <div>* = significantly different from negative control (p ≤ 0.05)</div> <div><sup>#1</sup> = mitotic index: number of metaphases/1000 cells; negative control = 1.00</div> <div><sup>#2</sup> = no more metaphases of sufficient quality for evaluation due to cytotoxicity</div> |                             |                             |                                            |                          |                             |                             |                                            |

| Table 3Experiment with metabolic activation (S9 mix) - Summarised data                                                                                                                                                                                                            |                             |                             |                                            |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|-----------------------------|--------------------------------------------|--|
| 4-h exposure                                                                                                                                                                                                                                                                      |                             |                             |                                            |  |
| Treatment (µg/mL medium)                                                                                                                                                                                                                                                          | Mitotic index <sup>#1</sup> | Number of metaphases scored | % of cells with aberrations excluding gaps |  |
| DMSO                                                                                                                                                                                                                                                                              |                             |                             |                                            |  |
| 0                                                                                                                                                                                                                                                                                 | 1.00                        | 300                         | 1.7                                        |  |
| IB1001                                                                                                                                                                                                                                                                            |                             |                             |                                            |  |
| 250                                                                                                                                                                                                                                                                               | 1.24                        | 300                         | 1.3                                        |  |
| 500                                                                                                                                                                                                                                                                               | 1.05                        | 300                         | 2.0                                        |  |
| 1000                                                                                                                                                                                                                                                                              | 0.92                        | 300                         | 1.7                                        |  |
| 2000                                                                                                                                                                                                                                                                              | 0.54                        | 300                         | 1.7                                        |  |
| Cyclophosphamide                                                                                                                                                                                                                                                                  |                             |                             |                                            |  |
| 20                                                                                                                                                                                                                                                                                | 0.76                        | 300                         | 9.3*                                       |  |
| <div>* = significantly different from negative control (p ≤ 0.05)</div> <div><sup>#1</sup> = mitotic index: number of metaphases/1000 cells; negative control = 1.00</div> <div><sup>#2</sup> = no more metaphases of sufficient quality for evaluation due to cytotoxicity</div> |                             |                             |                                            |  |

Source: Excerpted from Applicant's report

### 13.2.4.3. In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

#### 13.2.4.3.1. Study Title: Micronucleus Test of IB1001 in Bone Marrow Cells of the CD Rat Following Oral Administration

**Table 54. Summary of the Study Design for the in Vivo Rat Micronucleus Assay**

| Study                              | Findings                                                                                                                                                                                                        |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study number                       | 38193                                                                                                                                                                                                           |
| Study report location              | 0001                                                                                                                                                                                                            |
| Conducting laboratory and location | (b) (4)                                                                                                                                                                                                         |
| GLP compliance                     | Y (OECD)                                                                                                                                                                                                        |
| Drug, lot #, and % purity          | V0251 (IB1001); LT40; 100.4% (b) (4)                                                                                                                                                                            |
| <b>Methods</b>                     |                                                                                                                                                                                                                 |
| Doses in definitive study          | 250, 800 and 2500 mg/kg/day                                                                                                                                                                                     |
| Frequency of dosing                | Two doses at 24 hr interval; bone marrow sampled 48 hrs after last dose for TA and 24 hrs after last dose for positive control                                                                                  |
| Route of administration            | Oral                                                                                                                                                                                                            |
| Dose volume                        | 10 mL/kg (levacetylleucine & vehicle); 20 mL/kg (positive control)                                                                                                                                              |
| Formulation/vehicle                | NaCl 0.9%, w/v, pH 8.0                                                                                                                                                                                          |
| Species/strain                     | CD® Rat                                                                                                                                                                                                         |
| Number/sex/group                   | 5 males/group                                                                                                                                                                                                   |
| Satellite groups                   | None                                                                                                                                                                                                            |
| Basis of dose selection            | Toxicological data with levacetylleucine in rats                                                                                                                                                                |
| Negative control                   | NaCl 0.9%, w/v, pH 8.0                                                                                                                                                                                          |
| Positive control                   | Ethyl methane sulfonate (125 mg/kg; Two doses at 24 hr interval)                                                                                                                                                |
| Comment on study validity          | The criteria for study validity were met. The negative and positive control values were within the facility's range of historical control values.                                                               |
| Formulation analysis               | Dose analysis indicated slightly higher concentration than target 25 mg/ml (actual 28.25 & 28.24 mg/mL), 80 mg/mL (actual 87.66 & 85.73 mg/mL) 250 mg/mL (actual 265.59 and 267.24 mg/mL); and were acceptable. |

Source: Reviewer's analysis

Abbreviations: CD® = Sprague Dawley rats; hr = hour; NaCl = sodium chloride; TA = therapeutic anticoagulation; GLP = good laboratory practice; OECD = Organization for Economic Co-operation and Development

### Results

Levacetylleucine was not clastogenic in vivo in rat bone marrow micronucleus assay tested at 0, 250, 800 and 2500 mg/kg/day (Table 55). The positive control produced significant cytogenetic damage compared to vehicle control.

This study also included impurities, (b) (4) due to their reported presence at designated levels.

**Table 55. Summary of Results of Micronucleus Test of Levacetylleucine in Bone Marrow Cells of the CD® Rat Following Oral Administration**

of the CD-1 Rat Following Oral Administration

Table 1

Summarised data of the bone marrow micronucleus test in rats

| IB1001<br>[mg/kg b.w./day, p.o.] | Sampling<br>time (h) <sup>*</sup> | Number of polychromatic<br>erythrocytes scored<br>per group | Ratio<br>PCE/NCE <sup>#</sup> | Micronucleated polychromatic<br>erythrocytes |               | Significances |
|----------------------------------|-----------------------------------|-------------------------------------------------------------|-------------------------------|----------------------------------------------|---------------|---------------|
|                                  |                                   |                                                             |                               | mean frequency                               |               |               |
|                                  |                                   |                                                             |                               | per 4 000 PCE                                | per 1 000 PCE |               |
|                                  |                                   |                                                             | mean (n = 5)                  | mean (n = 5)                                 | mean (n = 5)  |               |
| 0                                | 24                                | 20000                                                       | 0.72                          | 3.0                                          | 0.8           | -             |
| 250                              | 24                                | 20000                                                       | 0.64                          | 4.2                                          | 1.1           | n.s.          |
| 800                              | 24                                | 20000                                                       | 0.77                          | 3.4                                          | 0.9           | n.s.          |
| 2500                             | 24                                | 20000                                                       | 0.73                          | 3.8                                          | 1.0           | n.s.          |
| <u>Ethyl methane sulfonate</u>   |                                   |                                                             |                               |                                              |               |               |
| 125 mg/kg<br>b.w., o.p.          | 24                                | 20000                                                       | 0.66                          | 31.2                                         | 7.8           | s.            |

s.  
n.s.  
p.o.

significant at  $p \leq 0.05$  for increases compared to the control  
not significant at  $p \leq 0.05$  for increases compared to the control  
per oral

PCE polychromatic erythrocytes  
NCE normochromatic erythrocytes  
\* after the last administration  
# per 500 counted cells

Source: Excerpted from Applicant's report

### 13.2.5. Carcinogenicity

Rodent carcinogenicity studies have not been conducted with levacetylleucine. PMRs for carcinogenicity will be issued because levacetylleucine is likely to be administered for a lifetime beginning in infancy or early childhood.

### 13.2.6. Reproductive and Developmental Toxicology

#### 13.2.6.1. Fertility and Early Embryonic Development

A fertility and early embryonic development study in rats has not been conducted with levacetylleucine. PMRs for evaluating effects of levacetylleucine on fertility and early embryonic development will be issued because there are adult-onset forms of NPC, and treatment with levacetylleucine for early onset NPC may continue into reproductive age; therefore, some patients of reproductive age are likely to be exposed. Additionally, levacetylleucine is a modified amino acid and appears to have widespread distribution; therefore, placental and lactational transfer are expected.

#### 13.2.6.2. Embryonic and Fetal Development

Dose-ranging embryonic and fetal development studies in rats and rabbits have been conducted with levacetylleucine. The data from the Applicant's dose-ranging studies indicate levacetylleucine is potentially fetotoxic and causes effects on embryofetal development in rats and rabbits, as described below.

The Applicant conducted a 10-day oral dose-range finding study in non-pregnant rabbits at 1250 or 2500 mg/kg/day in two groups of three female rabbits New Zealand White (HsdHra:(NZW)SPF) to determine tolerability of levacetylleucine. A decrease in food

consumption and macroscopic observations of brown fluid in the cecum and urinary bladder (single female) were observed at 2500 mg/kg/day. The results of the dose-range finding study in non-pregnant rabbits were used to select doses of 675, 1250 and 2500 mg/kg/day for the main study.

### 13.2.6.2.1. Study Title: Embryonic and Fetal Development Study in Rats (Terminal Sacrifice; Study 8519317)

**Table 56. Summary of the Study Design for the Dose-Ranging Rat Embryofetal Development Study**

| Study                               | Findings                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study number                        | 8519317                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Study report location               | 0001                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Conducting laboratory and location: | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| GLP compliance                      | Yes (report not audited)                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Drug, lot #, and % purity           | IB1001; 501; 99.9% (COA not provided)                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Methods</b>                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Doses                               | Phase 1 & 2: 0, 300, 600, 1000 mg/kg/day                                                                                                                                                                                                                                                                                                                                                                                                          |
| Frequency of dosing                 | Once daily GD 6 to 17; Sacrificed GD 21                                                                                                                                                                                                                                                                                                                                                                                                           |
| Number/sex/group                    | Phase 1: six GD 6 pregnant females/group<br>Phase 2: Fourteen GD 6 pregnant females/group                                                                                                                                                                                                                                                                                                                                                         |
| Dose volume                         | 4 mL/kg                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Formulation/vehicle                 | NaCl 0.9%, w/v, in RO water, pH to 8.0 ±0.5                                                                                                                                                                                                                                                                                                                                                                                                       |
| Route of administration             | ORAL GAVAGE                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Species                             | Rats                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Strain                              | Wistar Han (CrI:WI[Han])                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Comment on study design and conduct | Doses were selected based on a 6-month chronic toxicity in nonpregnant rats, with NOAEL of 800 mg/kg/day. A DRF in pregnant rats was not conducted, instead this study was conducted in two phases, and Phase 1 was considered the dose-ranging phase. The reports contain data from terminal sacrifice of Phase 1 animals. Several parameters are not reported including dose analysis, TK, GLP compliance, and results of Phase 2 of the study. |
| Dosing solution analysis            | Not reported                                                                                                                                                                                                                                                                                                                                                                                                                                      |

Source: Reviewer generated

Abbreviations: DRF = dose-range finding; GD = gestation day; GLP = good laboratory practice; NaCl = sodium chloride; NOAEL = no-observed-adverse-effect level; RO = reverse osmosis; TK = toxicokinetics

Data from terminal sacrifice of six animals/group in Phase 1 from dose range-finding study is reported.

### **Observations and Results**

#### **F0 Dams**

#### Mortality

All phase 1 dams survived to schedule sacrifice.

#### Clinical Signs

No test article related dose-dependent clinical signs were observed.

NDA 219132  
Aqneursa (levacetylleucine)

#### Body Weight

No test article related dose-dependent effects on body weight were observed.

#### Feed Consumption

No test article related dose-dependent effects on feed consumption were observed.

#### Necropsy/Histopathology

No test article related dose-dependent macroscopic observations were noted in phase 1 animals.

#### Toxicokinetics

These data are pending.

#### Cesarean Section Data

#### *Reproductive Assessment*

At scheduled necropsy on gestation day (GD) 21, five of six control animals, and six of six, four of six, and six of six females administered 300, 600, or 1000 mg/kg/day, respectively, were pregnant with live fetuses ([Table 57](#)).

The mean number of resorptions and mean post-implantation loss appeared higher in the 1000 mg/kg/day than controls ([Table 57](#)).

### **F1 Offspring**

#### Terminal Observations

#### *Fetal Weights*

No test article related dose-dependent effects were observed on mean fetal weight.

#### *Fetal Malformations/Variations (External, Visceral, Skeletal)*

No test article related dose-dependent fetal external and visceral malformations were observed.

Fetal skeletal malformations were observed in a single 600 mg/kg/day fetus (R0206-R8). The following malformations were observed: fused thoracic arch, misaligned thoracic arch, hemicentric thoracic centrum, and misaligned thoracic centrum; and in a 1000 mg/kg/day fetus (R0306-L3) in the vertebral column (scoliosis), and ribs (absent costal cartilage and short rib). The findings of absent costal cartilage and the observations in the lumbar arch were reported in the report to be not present in the laboratory's historical control data.

**Table 57. Reproductive and Fetal Effects in Rats in Embryo-Fetal Development Study, Phase 1**

| Daily Dose (mg/kg)                         | 0 (Control)         | 300 mg/kg (Low) | 600 mg/kg (Mid) | 1000 mg/kg (High) |
|--------------------------------------------|---------------------|-----------------|-----------------|-------------------|
| <b>Dams/Does (phase 1):</b>                | <b>6</b>            | <b>6</b>        | <b>6</b>        | <b>6</b>          |
| Food Consumption GD 6-21 (% <sup>a</sup> ) | 19 + 1.85 g/rat/day | 6               | 6               | 12                |
| Mean No. Corpora Lutea                     | 10.2 + 4.71         | 9.2 + 2.04      | 10.0 + 1.41     | 11.3 + 1.37       |
| Mean No. Implantations                     | 7.2 + 4.82          | 7.5 + 2.39      | 9.5 + 1.29      | 10.3 + 2.07       |
| Mean Pre-implantation Loss (%)             | 35.25 + 32.32       | 22.27 + 30.42   | 4.55 + 9.09     | 8.84 + 14.09      |
| <b>Litters:</b>                            |                     |                 |                 |                   |
| No. Litters Evaluated                      | 5                   | 6               | 4               | 6                 |
| Mean No. Live Fetuses                      | 7.0 + 5.05          | 7.0 + 3.35      | 9.0 + 1.83      | 9.0 + 2.19        |
| Mean No. Resorptions per animal (%)        | 6.7 + 14.91         | 6.1 + 9.75      | 5.6 + 11.11     | 12.5 + 12.35      |
| No. of Litters with Dead Fetuses           | 0.0                 | 0.0             | 0.0             | 0.0               |
| Mean Post-implantation Loss (%)            | 6.67 + 14.91        | 6.08 + 9.76     | 5.56 + 11.11    | 12.46 + 12.35     |
| Mean Adjusted Fetal Body Weight (g)        | 5.393 + 0.878       | 5.196 + 0.467   | 5.553 + 0.668   | 5.330 + 0.395     |
| Fetal Sex Ratios (% Male Fetuses)          | 43.6 + 25.02        | 45.2 + 28.80    | 65.9 + 17.12    | 39.6 + 13.01      |
| Fetal Anomalies (Fetuses /Litters)         |                     |                 |                 |                   |
| Gross External                             | -                   | -               | -               | -                 |
| Visceral Malformations                     | 0/0                 | 0/0             | 0/0             | 0/0               |
| Skeletal Malformations                     | 0/0                 | 0/0             | 1/1             | 1/1               |
| Total Affected Fetuses (Litters)           | 0/0                 | 0/0             | 1/1             | 1/1               |

Source: Excerpted from Applicant's submission

<sup>a</sup> At end of dosing period; for controls, group means are shown; for treated groups, percent differences from controls are shown.

- indicates no noteworthy findings; + indicates mild; ++ indicates moderate; +++ indicates marked.

Abbreviation: GD = gestation day

**Conclusion**

In conclusion, in phase 1, daily oral administration via gavage from GD 6 to 17, IB1001 at up to 1000 mg/kg/day was maternally tolerated in rats. Levacetylleucine appeared to be fetotoxic at doses 600 mg/kg/day and greater with increase in resorptions and post-implantation loss. Levacetylleucine is considered to cause effects on embryofetal development at doses 600 mg/kg/day and greater due to observation of visceral and skeletal malformation in thoracic arch of the vertebra (fused thoracic arch, misaligned thoracic arch, hemicentric thoracic centrum, and misaligned thoracic centrum), vertebral column (scoliosis), and ribs (absent costal cartilage and short rib).

### 13.2.6.2.2. Study Title: Embryonic and Fetal Development Study in Rabbits (Terminal Sacrifice; Study 8519173)

**Table 58. Summary of the Study Design for the Rabbit Embryofetal Development Study**

| Study                               | Findings                                                                                  |
|-------------------------------------|-------------------------------------------------------------------------------------------|
| Study number                        | 8519173                                                                                   |
| Study report location               | 0001                                                                                      |
| Conducting laboratory and location  | (b) (4)                                                                                   |
| GLP compliance                      | Yes (report not audited)                                                                  |
| Drug, lot #, and % purity           | IB1001; 501; 99.9% (COA not provided)                                                     |
| <b>Methods</b>                      |                                                                                           |
| Doses                               | Phase 1: 0, 675, 1250, 2500 mg/kg/day<br>Phase 2: 0, 675, 1250, 1925 mg/kg/day            |
| Frequency of dosing                 | Once daily GD 6 to 19; Sacrificed GD 29                                                   |
| Number/sex/group                    | Phase 1: six GD 6 pregnant females/group<br>Phase 2: Fourteen GD 6 pregnant females/group |
| Dose volume                         | 10 mL/kg                                                                                  |
| Formulation/vehicle                 | NaCl 0.9%, w/v, in RO water, pH to 8.0 ±0.5                                               |
| Route of administration             | ORAL GAVAGE                                                                               |
| Species                             | Rabbit                                                                                    |
| Strain                              | New Zealand White (HsdHra:[NZW]SPF)                                                       |
| Comment on study design and conduct | Phase 1 consists of the DRF for Phase 2.                                                  |
| Dosing solution analysis            | Not reported                                                                              |

Source: Reviewer generated

Abbreviations: COA = certificate of analysis; DRF dose-range finding; GD = gestation day; GLP = good laboratory practices; NaCl = sodium chloride; RO = reverse osmosis

This study was conducted in two phases: an initial dose-ranging tolerability phase at doses of up to 2500 mg/kg/day, and a definitive dosing phase at doses of up to 1925 mg/kg/day.

### **Observations and Results**

#### **F0 Dams**

#### Mortality

There was no treatment-related mortality in phase 1. A single 1250 mg/kg/day female (Animal R0201) died following dosing on GD 13. The death was considered a gavage error based on the observed presence of red discoloration and perforation of the lung lobes and red/tan contents in the trachea.

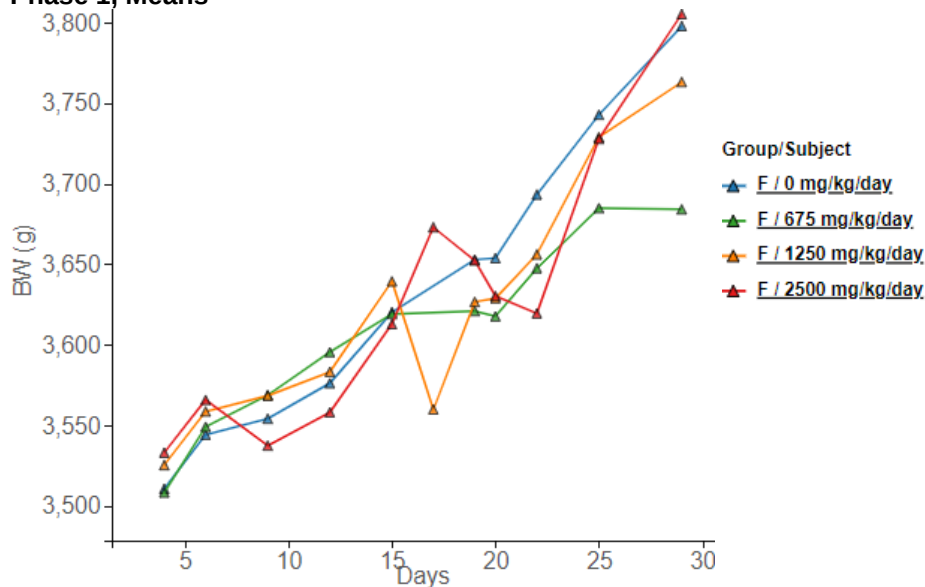
#### Clinical Signs

Four of six rabbits administered 2500 mg/kg/day appeared thin at one or two instances and this was considered incidental. No dose related clinical signs were observed.

#### Body Weight

Body weight loss and decreased body weight gain were observed primarily around GD 22; however, the effect was not dose dependent ([Figure 21](#)).

**Figure 21. Summary of Mean Body Weights of Rabbits in Embryo-Fetal Development Study, Phase 1, Means**

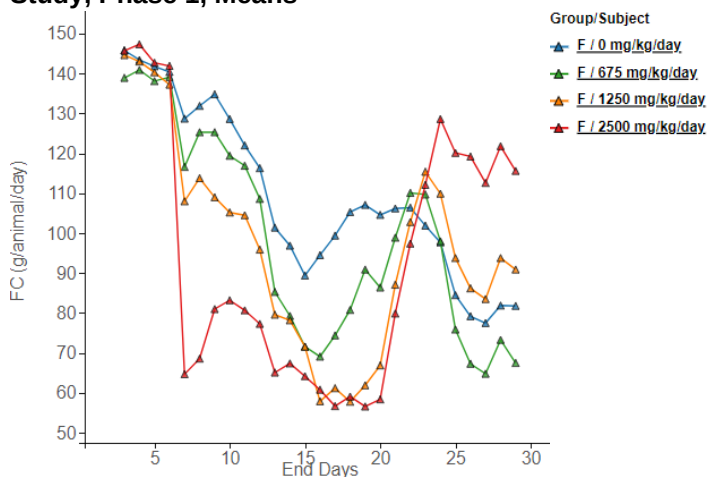


Source: Reviewer generated from SEND  
Abbreviation: BW = body weight

### Feed Consumption

Mean food consumption was lower than controls for the overall dosing period, GD 6 to GD 20, -13.8%, -21.8%, or -54.0%, respectively, in the groups administered 675, 1250, or 2500 mg/kg/day and considered test article related (Figure 22). Significant decreases in food consumption were noted in the group administered 2500 mg/kg/day over GD 6 to 10 (as low as -56.6% compared to controls).

**Figure 22. Summary of Mean Food Consumption in Rabbits in Embryo-Fetal Development Study, Phase 1, Means**



Source: Reviewer generated from SEND  
Abbreviation: FC = food consumption

**Table 59. Body Weight and Food Consumption in Rabbits in Embryo-Fetal Development Study, Phase 1**

| Daily Dose (mg/kg)                         | 0 (Control)    | 675 mg/kg (Low) | 1250 mg/kg (Mid) | 2500 mg/kg (High)   |
|--------------------------------------------|----------------|-----------------|------------------|---------------------|
| <b>Dams/Does (phase 1):</b>                | <b>6</b>       | <b>6</b>        | <b>6</b>         | <b>6</b>            |
| Body Weight GD 22 (% <sup>a</sup> )        | 3630 + 444.4 g | -2.26           | -3.88            | -6.72               |
| Food Consumption GD 6-20 (% <sup>a</sup> ) | 1635 + 432.1 g | -13.76          | -21.83           | -54.01 <sup>b</sup> |

Source: Excerpted from Applicant's submission

- No noteworthy findings; +- Mild; ++- Moderate; +++- Marked; Statistically significance: +f Wilcoxon Rank Sum Test Significant at 0.01 level

<sup>b</sup> At end of dosing period; for controls, group means are shown; for treated groups, percent differences from controls are shown. Abbreviation: GD = gestation day

### Necropsy/Histopathology

No test article related dose dependent macroscopic observation were noted in Phase 1 animals.

### Toxicokinetics

The TK data are pending.

### Cesarean Section Data

#### *Reproductive Assessment*

All phase 1 females were pregnant. On GD 13, one 1250 mg/kg/day female (Animal R0201) died following dosing but was considered due to gavage error and not related to test article effect.

In all levacetylleucine-treated groups, mean number of live fetuses per litter was lower and reached statistical significance in 675 mg/kg/day and 2500 mg/kg/day groups. However, reduction in live fetuses in low dose group is likely due to fewer implantations and not test article-related effects. The mean number of early resorptions, mean number of total resorptions, mean resorption rate, and mean post-implantation loss were higher in 2500 mg/kg/day than controls ([Table 60](#)).

Mean gravid uterine weight was lower than control in all levacetylleucine-treated groups and reached statistical significance in the 2500 mg/kg/day (-39.9%). The decrease in gravid uterine weight correlated with increase in post-implantation loss in this group.

### F1 Offspring

#### **Terminal Observations**

#### Fetal Weights

Mean fetal weights (males, females, and the sexes combined) were lower than controls, although not statistically significant, in a dose-responsive manner in mid (1250 mg/kg/day) and high (2500 mg/kg/day) dose groups ([Table 60](#)).

#### Fetal Malformations/Variations (External, Visceral, Skeletal)

Fetal external malformations observed in 2500 mg/kg/day group included open eyes (two of six litters), partially open eyes (three of six litters), and hyperflexion of the limbs (two of six litters). Other external malformations were of low occurrence or lacked dose responsiveness ([Table 60](#)).

The fetal visceral developmental variation of absent accessory lung lobe was observed in four of six litters (67%) at the 2500 mg/kg/day dose level (Table 60).

Fetal skeletal malformations observed in 2500 mg/kg/day included misshapen maxilla (two of six litters), misshapen premaxilla (two of six litters, 33%), and small interparietal bone (one of six litters, 17%). Skeletal developmental variations indicative of delayed ossification (e.g., incomplete ossification of frontal bone, palatine, and sternebrae) were observed in the 1250 or 2500 mg/kg/day. The above findings in the 2500 mg/kg/day correlated with lower fetal body weights (Table 60).

**Table 60. Reproductive and Fetal Effects in Rabbits in Embryo-Fetal Development Study, Phase 1**

| Daily Dose (mg/kg)                                  | 0 (Control)                 | 675 mg/kg (Low)         | 1250 mg/kg (Mid)        | 2500 mg/kg (High)         |
|-----------------------------------------------------|-----------------------------|-------------------------|-------------------------|---------------------------|
| <b>Dams/Does (phase 1):</b>                         | 6                           | 6                       | 6                       | 6                         |
| Mean No. Corpora Lutea                              | 11.3 + 1.51                 | 9.8 + 1.47              | 10.2 + 1.30             | 9.7 + 1.86                |
| Mean No. Implantations                              | 10.7 + 1.51                 | 8.3 + 0.82 <sup>±</sup> | 9.8 + 1.48              | 9.3 + 2.07                |
| Mean Pre-implantation Loss (%)                      | 5.56 + 8.61                 | 13.28 + 17.18           | 4.04 + 5.58             | 3.75 + 5.86               |
| Daily Dose (mg/kg)                                  | 0 (Control)                 | 675 mg/kg (Low)         | 1250 mg/kg (Mid)        | 2500 mg/kg (High)         |
| <b>Litters:</b>                                     |                             |                         |                         |                           |
| No. Litters Evaluated                               | 6                           | 6                       | 5                       | 6                         |
| Mean No. Live Fetuses                               | 10.7 + 1.51                 | 8.2 + 0.75 <sup>±</sup> | 9.0 + 1.22              | 7.0 + 2.68 <sup>±</sup>   |
| Mean No. Resorptions per animal (resorption rate %) | 0.0 (0)                     | 0.2 + 0.41 (1.9 + 4.54) | 0.6 + 0.89 (5.7 + 8.79) | 2.3 + 4.27 (20.0 + 32.21) |
| No. of Litters with Dead Fetuses                    | 0                           | 0                       | 1                       | 0                         |
| Mean Post-implantation Loss (%)                     | 0.00                        | 1.85 + 4.54             | 7.76 + 8.30             | 20.0 + 32.21              |
| Mean Adjusted Fetal Body Weight (g)                 | 36.61 + 3.49                | 38.13 + 6.06            | 34.11 + 5.22            | 30.24 + 8.19              |
| Fetal Sex Ratios (% Male Fetuses)                   | 45.2 + 14.75                | 51.1 + 23.04            | 49.4 + 7.69             | 62.7 + 23.51              |
| <b>Fetal Anomalies</b>                              |                             |                         |                         |                           |
| <b>Gross External</b>                               |                             |                         |                         |                           |
| Open eyes                                           | fetuses/litter<br>% fetuses | 0/0<br>0.0              | 0/0<br>0.0              | 2/6 (33%)<br>18.52        |
| Partially open eyes                                 | fetuses/litter<br>% fetuses | 0/0<br>0.0              | 0/0<br>0.0              | 3/6 (50%)<br>11.34        |
| Hyperflexion of limbs                               | fetuses/litter<br>% fetuses | 0/0<br>0.0              | 0/0<br>0.0              | 2/6 (33%)<br>21.53        |
| <b>Visceral Malformations</b>                       |                             |                         |                         |                           |
| <b>Visceral Variants</b>                            |                             |                         |                         |                           |
| Accessory lung lobe absent                          | fetuses/litter<br>% fetuses | 1/6 (17%)<br>6.94       | 1/6 (17%)<br>2.08       | 4/6 (67%)<br>18.06        |
| <b>Skeletal Malformations</b>                       |                             |                         |                         |                           |
| Misshapen maxilla                                   | fetuses/litter<br>% fetuses | 0/0<br>0.0              | 0/0<br>0.0              | 2/6 (33%)<br>12.04        |
| Misshapen premaxilla                                | fetuses/litter<br>% fetuses | 0/0<br>0.0              | 0/0<br>0.0              | 2/6 (33%)<br>12.04        |
| Small interparietal bone                            | fetuses/litter<br>% fetuses | 0/0<br>0.0              | 0/0<br>0.0              | 1/6 (17%)<br>1.85         |
| <b>Skeletal Variants</b>                            |                             |                         |                         |                           |
| Skull frontal incomplete ossification               | fetuses/litter<br>% fetuses | 0/0<br>0.0              | 0/0<br>0.0              | 2/5 (40%)<br>20.28        |
| Skull palatine incomplete ossification              | fetuses/litter<br>% fetuses | 0/0<br>0.0              | 0/0<br>0.0              | 2/6 (33%)<br>5.79         |
| Sternebra incomplete ossification                   | fetuses/litter<br>% fetuses | 2/6 (33%)<br>4.26       | 0/0<br>0.0              | 3/5 (60%)<br>8.36         |
| Sternebra unossified                                | fetuses/litter<br>% fetuses | 4/6 (67%)<br>11.90      | 4/6 (67%)<br>10.48      | 2/5 (40%)<br>16.59        |
| Vertebra cervical centrum incomplete ossification   | fetuses/litter<br>% fetuses | 1/6 (17%)<br>1.85       | 1/6 (17%)<br>1.85       | 3/5 (60%)<br>10.18        |
| Vertebra cervical centrum isolated ossification     | fetuses/litter<br>% fetuses | 0/0<br>0.0              | 0/0<br>0.0              | 2/6 (33%)<br>2.08         |

Source: Excerpted from Applicant's submission

- No noteworthy findings; +- Mild; ++ Moderate; +++ Marked; Statistical significance: +f Wilcoxon Rank Sum Test Significant at 0.01 level

\*\* -p.01 (Kruskal Wallis and Wilcoxon)

<sup>b</sup> At end of dosing period; for controls, group means are shown; for treated groups, percent differences from controls are shown.

<sup>c</sup> Not statistically significant for the period GD 6 to 20; statistically significant increase after dosing period from GD 24 to GD 29

Abbreviation: GD = gestation day

### **Conclusion**

In conclusion, in phase 1 animals, daily oral administration of IB1001 via gavage from GD 6 to 19 at up to 2500 mg/kg/day was maternally tolerated with decreases in food consumption at the highest dose. Levacetylleucine appeared to be fetotoxic at doses of  $\geq 1250$  mg/kg/day with a dose-related increase in resorptions and post-implantation loss that corresponded with a decrease in mean maternal weight, and a slight decrease in the mean number of live fetuses at doses greater than 675 mg/kg/day. There was also a decrease in mean fetal body weight.

Levacetylleucine induced fetal malformations in dams treated at doses of  $\geq 1250$  mg/kg/day. Findings included fetal external malformations of open/partially open eyes and hyperflexion of the limbs, fetal skeletal malformations of small interparietal bone and misshapen maxilla and/or premaxilla. The adverse embryofetal findings observed at doses  $\geq 1250$  mg/kg/day occurred in the absence of overt toxicity to the dam; therefore, N-acetyl-L-leucine is considered a selective developmental toxicant.

#### **13.2.6.3. Prenatal and Postnatal Development**

The prenatal and postnatal development study in rats has not been conducted with levacetylleucine. PMRs for evaluating effects of levacetylleucine on pre- and postnatal development will be issued because onset of NPC ranges from infancy into adulthood, and treatment with levacetylleucine may range from infancy into late adulthood. Levacetylleucine was found to cause increases in post-implantation loss and malformation in skeletal bones in a dose-range finding (DRF) EFD study in rabbits. Leucine, a metabolite of levacetylleucine, injection as a single 0.2 mL of a 1% solution in the amnionic sac of a 9-day-old embryo of chicken is reported to cause morphological anomalies of the legs (including inward flexion of the toes, leg extension or flexion at hip joint), defects in ossification of the skull, torsion of the neck and depression of the brain waves ([Bergstrom et al. 1967](#)). Therefore, exposure to levacetylleucine has potential to cause adverse effects on growth and development (neurological, physical, and sexual) from prenatal and into postnatal stage of life and requires investigation. Additionally, levacetylleucine is a modified amino acid and appears to have widespread distribution; therefore, placental and lactational transfer are expected.

#### **13.2.6.4. Juvenile Animal Studies**

A DRF juvenile toxicity study was conducted in postnatal day (PND) 7-PND 28 Wistar Han rats (six animals/sex/group) with levacetylleucine at doses 300, 600, 1000 mg/kg administered once daily (QD) by oral gavage. The animal was observed for survival, clinical and post dose observations, body weights and food consumption. At termination animals were observed for macroscopic changes. A dose of 1000 mg/kg/day was found to be tolerated without significant toxicological findings in any of the above parameters.

(b) (4)

PMRs for evaluating toxicity of levacetylleucine on juvenile animals will be issued because onset of NPC ranges from infancy into adulthood, and treatment with levacetylleucine may range from infancy into adulthood. In addition, nonclinical studies available at the times of NDA submission used doses that lacked an adequate justification, as they were not clearly based on achieving a maximum tolerated dose, maximum feasible dose, or saturation of exposure with dose, nor did they achieve a sufficient safety margin relative to the clinical dose. Further, the rat and rabbit EFD studies indicate levacetylleucine crossed placenta and modulated growth of bones, and it is uncertain if levacetylleucine will modulate the growth of bones in juvenile animals. Considering leucine causes defects in ossification of the skull, torsion of the neck and depression of the brain waves ([Bergstrom et al. 1967](#)), levacetylleucine has potential to influence growth, neurological development (learning and memory), sexual development, and general health. Hence, there is need for a juvenile toxicity study to determine the toxic effects of levacetylleucine on juvenile animals and inform patients of potential risks of medication.

### 13.2.7. Impurities

(b) (4) were reported as impurities with potential for exposure to (b) (4) in the body. The (b) (4) exposure at (b) (4) mg/kg/day in a 39-week dog study was (b) (4) times higher than exposure to (b) (4) mg/kg/day in the drug product to subjects. The (b) (4) exposure at (b) (4) mg/kg/day in a 39-week dog study was (b) (4) times higher exposure to (b) (4) mg/kg/day by the drug product to subjects. The above impurities were reported to be negative for genotoxicity in Derek and Sarah computational quantitative and qualitative structure analysis for genotoxicity. The Applicant justified the exposure to small level (b) (4) based on dietary reference values for adult dietary intake of (b) (4) milligrams of (b) (4) per kilogram body weight and (b) (4) milligrams of (b) (4) per kg body weight by American Food and Nutrition Board. Daily intake in diet is estimated at (b) (4) milligrams (b) (4) and (b) (4) milligrams (b) (4) for a 70 kg patient. The safety margins (b) (4) are estimated at (b) (4)-fold and (b) (4)-fold respectively.

**Table 61. Summary of Toxicological Qualification for Drug-Related Impurities**

| Impurity | Exposure at MDD<br>mg/kg/day <sup>1</sup> (limit) | Exposure at NOAEL<br>(mg/kg/day) | Margin of Exposure<br>(b) (4) |
|----------|---------------------------------------------------|----------------------------------|-------------------------------|
| (b) (4)  |                                                   |                                  |                               |

Source: Reviewer's analyses

<sup>1</sup> Exposure in humans estimated considering 50 kg adult body weight.

<sup>2</sup> Exposure based on dietary reference values for 50 kg adult daily dietary intake by American Food and Nutrition Board considering 70 kg.

<sup>3</sup> (b) (4) exposure is assumed from (b) (4) in the body.

<sup>4</sup> Exposure based on assumption (b) (4)

Abbreviations: MDD = maximum daily dose; NMT = not more than; NOAEL = no-observed-adverse-effect level

### 13.2.8. Excipients

#### Isomalt (b) (4)

Isomalt (b) (4) at maximum daily exposure (MDE) (b) (4) mg/day exceeds levels documented in the FDA Inactive Ingredients Database (IID) of MDE of (b) (4) mg/day. The Applicant

provided safety justification stating isomalt is regarded as a nontoxic, nonallergenic, and non-irritant with no known mutagenic or carcinogenic potential and no effects on reproduction or embryofetal development; and tolerated at 10% in diet for long term in several toxicological species. The Applicant provided published information indicating that daily exposure in rats that weigh 0.25 to 0.5 kg that consumed a diet containing isomalt at a dose of (b) (4) g/kg/day supported a human equivalent dose up to (b) (4) g/day for 50 kg person, which is (b) (4)-fold higher than MDE of isomalt ((b) (4) mg/day) in patients, which is considered acceptable.

### **Hypromellose** (b) (4)

Hypromellose (b) (4) is not listed in IID, but Center for Drug Evaluation and Research/Office of Pharmaceutical Quality considers this same as (b) (4). Hypromellose is in the IID at MDE of (b) (4) mg/day and qualifies the exposure from drug at MDE of (b) (4) mg/day.

### **Strawberry Flavor**

The Applicant describes the Strawberry Flavor as being composed of several sub-ingredients, and justifies the levels based on a statement provided by (b) (4) to suggest this flavor is in use in powdered medication at a flavor concentration of (b) (4) % with MDE of (b) (4) mg/day in patients aged 6 to 12 years, and at (b) (4) mg/day in patients >13 years of age. They state that the levels are much lower in levacetylleucine ((b) (4) mg/day). Further, the Applicant describes this flavor is composed of (b) (4)

Overall, the ingredients in this flavoring appear acceptable based on available safety data.

### 13.2.9. Human Exposure Margins From Nonclinical Studies

**Table 62. Human Exposure Margins Calculated From Nonclinical Studies**

| Species<br>(Duration)                                   | Dose<br>(mg/kg/day) | HED<br>(mg/kg) | Sex | C <sub>max</sub><br>(µg/mL) |           | AUC <sub>0-24h or Inf</sub><br>(µg.hr/mL) |           | MOS<br>(Animal to<br>Human C <sub>max</sub><br>Ratio) | MOS<br>(Animal to<br>Human<br>AUC Ratio) |
|---------------------------------------------------------|---------------------|----------------|-----|-----------------------------|-----------|-------------------------------------------|-----------|-------------------------------------------------------|------------------------------------------|
|                                                         |                     |                |     | Day 1                       | Study End | Day 1                                     | Study End |                                                       |                                          |
| Rat (26-weeks oral)                                     | 800 (NOAEL)         | 129            | M   | 13.6                        | 17.1      | 59.2                                      | 66.8      | 2.3                                                   | 2.1                                      |
|                                                         |                     |                | F   | 17.2                        | 29.5      | 66.2                                      | 80.1      | 4                                                     | 2.5                                      |
|                                                         | 2500 >NOAEL         | 404            | M   | 53.6                        | 35        | 188                                       | 182       | 4.7                                                   | 5.8                                      |
|                                                         |                     |                | F   | 72.3                        | 76.1      | 318                                       | 279       | 10.3                                                  | 8.8                                      |
| Dog (39 weeks, oral)                                    | 600 (NOAEL)         | 333            | M   | 83.9                        | 61.1      | 261                                       | 193       | 8.3                                                   | 6.1                                      |
|                                                         |                     |                | F   | 90.8                        | 83.9      | 269                                       | 272       | 11.7                                                  | 8.6                                      |
| Human Dosing<br>(po, 4 g/day, given 2,1,1) <sup>1</sup> | 67                  | 67             | M/F |                             | 7.4       |                                           | 31.6      | 1                                                     | 1                                        |

Source: Reviewer's analyses

<sup>1</sup> Human PK data based on the oral daily dose of 4 g, administered at 2 g in the morning and 1 g at noon and 1 g in the evening. C<sub>max</sub> and AUC values are obtained from the IB1001-201 study internal review.

Abbreviations: AUC = area under curve; AUC<sub>0-24h or Inf</sub> = area under the plasma concentration-time curve from time zero to 24 hours or zero to infinity; C<sub>max</sub> = maximum plasma concentration; F = female; HED = human equivalent dose; M = male; MOS = margin of safety at steady state; NOAEL = no-observed-adverse-effect level

## 14. Clinical Pharmacology

### 14.1. In Vitro Studies

#### **Protein Binding**

The plasma protein binding of levacetylleucine was assessed in plasma from CD1 mice, Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs, and humans at concentrations of 1 µg/mL, 10 µg/mL, and 100 µg/mL using rapid equilibrium dialysis (Study No. ADM-20-2970b, 2020). The analysis was performed using a specially developed liquid chromatography with tandem mass spectrometry method, with all samples compared against a calibration curve prepared in a corresponding matrix. The results showed that the free fractions of levacetylleucine were approximately 100% across all species and concentrations, indicating minimal binding to plasma proteins.

#### **Metabolism**

##### **Study No. ADM-20-2970a, 2020**

In this study, a deuterated N-acetyl-DL-leucine was used to compare metabolism across various species (human, mouse, rat, rabbit, dog) at concentrations of 40 µM, 2mM, and 1, 10, and 100µM. The study found that only one metabolite, L-leucine, was produced during a 1-hour incubation period, regardless of the species. The highest metabolic turnover of N-acetyl-DL-leucine-D10 was observed in rabbit liver S9, with 39 to 51% of the initial concentration remaining after 60 minutes. In comparison, mouse, rat, and human liver S9 showed a remaining concentration range of 47 to 72%. The lowest disappearance rate was seen in dog liver S9, where 85% or more of the parent molecule remained after 60 minutes. The disappearance of N-acetyl-DL-leucine-D10 was not cofactor-dependent, indicating it was not mediated by cytochrome P450 (CYP), uridine diphosphate glucuronosyltransferase, or sulfotransferase enzymes.

No qualitative differences in metabolism were observed between the two doses across any species, indicating consistent metabolic capacity across species. The measured concentrations of L-leucine-D10 correlated well with the disappearance of N-acetyl-DL-leucine-D10, suggesting that the observed disappearance is primarily due to the formation of L-leucine-D10.

#### **Excretion**

No specific excretion studies have been conducted for levacetylleucine. However, since its metabolism produces only acetate and L-leucine, both of which are further processed in the body through catabolic pathways, dedicated excretion studies were deemed unnecessary. [Lee et al. 2015](#) showed that after administering an intravenous dose of <sup>14</sup>C-L-leucine to rats, 5% of the parent compound was excreted in urine as levacetylleucine.

#### **Cytochrome P450 Induction**

##### **Study No. ADM-18-2066a, 2018**

The induction potential of levacetylleucine on human CYP enzymes 1A2, 2B6, and 3A4 at the mRNA level was evaluated using cryopreserved hepatocytes from three human donors at concentrations ranging from 6 to 2000 µg/mL [Study No. ADM-18-2066a, 2018]. The total

exposure duration was 48 hours, with the cell culture media containing the test compound being refreshed after 24 hours. Cytotoxicity was assessed visually and by measuring lactate dehydrogenase leakage after 24 hours of incubation.

The mRNA levels of CYP1A2, CYP2B6, and CYP3A4 following incubation with levacetylleucine at concentrations of 6 to 2000 µg/mL remained within 0.5- to 1.7-fold of the solvent control and below 3% of the corresponding positive control inducer. These results indicate that N-acetyl-L-leucine did not induce these genes. Additionally, no signs of cytotoxicity or morphological changes were observed due to the test compound.

### **Transporter Inhibition**

#### **P-gp, BCRP, and BSEP**

##### Study No. ADM-18-2106a, 2018

Efflux transporter inhibition was assessed by measuring the vesicular uptake of a probe substrate into inside-out membrane vesicles expressing individual human adenosine triphosphate (ATP) binding cassette transporters (P-glycoprotein [P-gp], breast cancer resistance protein [BCRP], and bile salt export pump [BSEP]) in the presence and absence of levacetylleucine (MW=173.21 g/mol) at six concentrations ranging from 6 µg/mL to 2000 µg/mL, both with and without ATP [Study No. ADM-18-2106a, 2018]. Inhibition of the transporters was indicated by a reduced level of vesicular uptake of the probe substrate in the presence of ATP.

The Applicant demonstrated that levacetylleucine inhibited the efflux transporters P-gp, BCRP, and BSEP, with IC<sub>50</sub> values of 227 µg/mL (1.31mM) for P-gp, 491 µg/mL (2.83mM) for BCRP, and 408 µg/mL (2.36mM) for BSEP.

Based on the molecular weight of levacetylleucine (173.21 g/mol) and its IC<sub>50</sub> values for key efflux transporters, potential drug interactions have been assessed. With a maximum dose of 2 grams, the calculated I<sub>gut</sub>/IC<sub>50</sub> ratio is close to 10 for BCRP, but a very high ratio of 35.2 for P-gp was observed. This ratio suggests a potential for interaction with substrates of P-gp. The FDA has recommended a PMR study to further investigate these potential interactions.

#### **OATP1B1\*1, OATP1B3, OAT1, OAT3, and OCT2**

##### Study No. ADM-18-2106c, 2018

Human solute carrier transporter inhibition was evaluated by measuring the cellular uptake of probe substrates into HEK293 cells (Corning® TransportoCells™) overexpressing a single human solute carrier transporter (organic anion transporter [OAT]P1B1\*1, OATP1B3, OAT1, OAT3, or organic cation transporter [OCT]2) in the absence and presence of levacetylleucine (MW=173.21 g/mol) at concentrations ranging from 30 to 900 µg/mL [Study No. ADM-18-2106c, 2018]. Inhibition of OATP1B1 and OATP1B3 was evaluated both with and without a 30-minute pre-incubation of the cells with the test compound. Inhibition of active transport was indicated by decreased cellular uptake of the probe substrate in the presence of the inhibitor. Positive control inhibitors for each transporter were incubated in parallel to confirm active cellular uptake of the probe substrate.

Inhibition of OAT1 and OAT3 by levacetylleucine was observed, with IC<sub>50</sub> values of 1030 µg/mL (5.9mM) for OAT1 and 103 µg/mL (0.59mM) for OAT3. Additionally, minor inhibition of OCT2 was observed, with 61% activity remaining at 900 µg/mL

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levacetylleucine (extrapolated  $IC_{50}$  of 1700  $\mu\text{g/mL}$ ). Levacetylleucine was not an inhibitor of OATP1B1\*1 or OATP1B3.

Based on these results, inhibition of the human solute carrier transporters OATP1B1\*1, OATP1B3, OAT1, OAT3, or OCT2 by levacetylleucine is considered unlikely.

### **Transporter Substrate**

#### **P-gp and BCRP**

The apparent permeability of levacetylleucine was measured bidirectionally (pH 7.4; apical to basolateral [A>B] and basolateral to apical [B>A]) at a concentration of 10  $\mu\text{g/mL}$  through Madin-Darby canine kidney (MDCK)-wild type, MDCK-BCRP, and MDCK-P-gp cell monolayers. Incubations with MDCK-BCRP and MDCK-P-gp cells were conducted both in the presence and absence of specific chemical inhibitors for BCRP and P-gp, respectively [Study No. ADM-18-2106d, 2018]. Appropriate positive and negative controls were included. Transporter inhibition was indicated by a reduced level of vesicular uptake of the probe substrate in the presence of ATP.

The efflux ratio for levacetylleucine was 1.6 with MDCK-wild type cells (consistent across both plates), 0.7 with MDCK-BCRP without inhibitor and 1.3 with the inhibitor (2  $\mu\text{M}$  Ko143), and 1.6 with MDCK-P-gp without inhibitor and 2.6 with the inhibitor (50  $\mu\text{M}$  verapamil). Therefore, no BCRP- or P-gp-mediated active transport of N-acetyl-L-leucine was detected in this study.

#### **OAT1, OAT3, and OCT2**

The cellular uptake of levacetylleucine was measured in human cells transfected with single transporters at two concentrations (10 and 100  $\mu\text{g/mL}$ ) both in the presence and absence of chemical transporter inhibitors, as well as in control cells without transfected transporters and without inhibitors [Study No. ADM-18-2106e, 2018]. Transporter-mediated uptake was identified by comparing the cellular uptake in transporter overexpressing cells to that in vector-transfected control cells and by observing the inhibition of uptake in transporter overexpressing cells when control inhibitors were used. Positive control substrates at a single concentration were tested in parallel.

Levacetylleucine was found to be a substrate for OAT1 and OAT3, but not OCT2, in vitro. Uptake into OAT1-expressing cells was approximately 5-fold higher, and into OAT3-expressing cells approximately 9-fold higher, after 3 minutes of incubation compared to control cells. This uptake was completely inhibited by the addition of diclofenac.

The clinical relevance of this finding is unknown. However, due to the overall safety profile of levacetylleucine, no significant drug interactions with inhibitors of OAT1 or OAT3 transporters are expected.

## **14.2. In Vivo Studies**

### **Trial IB1001-201**

Pharmacokinetic (PK) analysis for Trial IB1001-201 was conducted on the PK set, which included all subjects who received at least one dose of levacetylleucine in the extension phase (EP) and had at least one PK plasma concentration measurement after oral administration. Intensive PK samples were collected at Visit 7B, following the first administration of the drug, and again after 1 year of treatment (Visit 9B). The Applicant conducted non-

compartment analysis using the intensive PK data. Sparse PK sampling from the parent study was not included in this context but was instead used for the population PK (PopPK) analysis.

At Visit 7B, the highest mean plasma concentration of the drug was observed 1 hour after administration, with a mean ( $\pm$ standard deviation [SD])  $C_{\max}$  value of 6.69 ( $\pm$ 1.85)  $\mu\text{g/mL}$ , and a  $C_{\max}$  value of 10.04  $\mu\text{g/mL}$  (Table 63). At Visit 9B, the highest mean plasma concentration was again reached 1-hour post-treatment, with a mean ( $\pm$ SD)  $C_{\max}$  value of 8.32 ( $\pm$ 3.3 SD)  $\mu\text{g/mL}$  and a  $C_{\max}$  value of 15.85  $\mu\text{g/mL}$  (Table 64). However, geometric coefficient of variation values at all time points exceeded 40%, indicating substantial variability in plasma concentrations among subjects.

When administered orally, levacetylleucine was rapidly absorbed, with time to maximum concentration values ranging from 0.5 to 2.5 hours and a median value of 1 hour. The half-life ( $t_{1/2}$ ) was approximately 1 hour. Likely metabolites include L-leucine and acetic acid. Elimination of levacetylleucine from plasma was rapid after a single dose. The apparent volume of distribution was 200 L, and the apparent clearance was 144 L/h. Similar values were observed at steady state. A large inter-individual variability (coefficient of variation: 40 to 50%) was observed at both Visit 7B and Visit 9B. No relevant sex differences were observed in any of the PK parameters. PK parameters for visit 7B are summarized descriptively in (Table 63) and PK parameters for visit 9B are summarized descriptively in (Table 64).

**Table 63. Descriptive Statistics of PK Parameters for Visit 7B, IB1001-201**

| Descriptive Statistics | $C_{\max}$<br>( $\mu\text{g/mL}$ ) | $t_{1/2}$<br>(h) | $t_{\max}$<br>(h) | $AUC_{0-24}$<br>(h· $\mu\text{g/mL}$ ) | CL/F<br>(L/h)  | $V_z/F$<br>(L) |
|------------------------|------------------------------------|------------------|-------------------|----------------------------------------|----------------|----------------|
| N                      | 19                                 | 19               | 19                | 19                                     | 19             | 19             |
| Mean                   | <b>6.695</b>                       | <b>0.992</b>     |                   | <b>14.636</b>                          | <b>144.311</b> | <b>200.502</b> |
| SD                     | 1.852                              | 0.328            |                   | 4.720                                  | 63.914         | 82.518         |
| Min                    | 3.36                               | 0.63             | 0.50              | 5.56                                   | 66.71          | 64.75          |
| Median                 | 6.61                               | 0.91             | <b>1.00</b>       | 13.50                                  | 138.71         | 185.05         |
| Max                    | 10.04                              | 1.94             | 2.50              | 22.57                                  | 359.91         | 353.49         |
| Geom Mean              | 6.433                              | 0.948            |                   | 13.866                                 | 134.060        | 183.305        |
| Geom SD                | 1.349                              | 1.355            |                   | 1.419                                  | 1.463          | 1.573          |
| Geom %CV               | 30.62                              | 31.06            |                   | 36.11                                  | 39.47          | 47.71          |

Source: Summary of clinical pharmacology, Table 5

Abbreviations:  $AUC_{0-24}$  = area under the curve from 0 to 24 hours; CL/F = apparent clearance;  $C_{\max}$  = maximum observed concentration; %CV = coefficient of variation; geom = geometric; max = maximum; min = minimum; N = number of valid observations for the variable; SD = standard deviation;  $t_{1/2}$  = terminal half-life in hours;  $t_{\max}$  = time of the maximum observed concentration;  $V_z/F$  = apparent volume of distribution

**Table 64. Descriptive Statistics of PK Parameters for Visit 9B, IB1001-201**

| Descriptive Statistics | $C_{\max}$<br>( $\mu\text{g/mL}$ ) | $t_{1/2}$<br>(h) | $t_{\max}$<br>(h) | $AUC_{0-24}$<br>(h· $\mu\text{g/mL}$ ) | CL <sub>ss</sub> /F<br>(L/h) | $V_{ss}/F$<br>(L) |
|------------------------|------------------------------------|------------------|-------------------|----------------------------------------|------------------------------|-------------------|
| N                      | 17                                 | 17               | 17                | 17                                     | 17                           | 17                |
| Mean                   | <b>8.324</b>                       | <b>0.958</b>     |                   | <b>16.614</b>                          | <b>138.857</b>               | <b>252.917</b>    |
| SD                     | 3.309                              | 0.183            |                   | 6.252                                  | 58.683                       | 125.193           |
| Min                    | 2.57                               | 0.61             | 0.50              | 8.69                                   | 62.22                        | 87.48             |
| Median                 | 8.87                               | 0.93             | <b>1.00</b>       | 16.76                                  | 119.18                       | 211.83            |
| Max                    | 15.84                              | 1.28             | 1.50              | 32.71                                  | 248.48                       | 573.82            |
| Geom Mean              | 7.647                              | 0.941            |                   | 15.549                                 | 127.720                      | 227.227           |
| Geom SD                | 1.563                              | 1.217            |                   | 1.460                                  | 1.528                        | 1.610             |
| Geom %CV               | 46.99                              | 19.82            |                   | 39.24                                  | 44.35                        | 50.49             |

Source: Summary of clinical pharmacology, Table 6

Abbreviations:  $AUC_{0-24}$  = area under the curve from 0 to 24 hours; CL<sub>ss</sub>/F = difference in clearance;  $C_{\max}$  = maximum observed concentration; %CV = coefficient of variation; geom = geometric; max = maximum; min = minimum; N = number of valid observations for the variable; SD = standard deviation;  $t_{1/2}$  = terminal half-life in hours;  $t_{\max}$  = time of the maximum observed concentration;  $V_{ss}/F$  = volume of distribution

### **Trial IB1001-202**

Similar to Trial IB1001-201, a PK analysis was conducted for Trial IB1001-202 that included all subjects who received at least one dose of levacetylleucine during the EP and had at least one PK plasma concentration measurement following oral administration. Detailed PK profiles were obtained at Visit 7B, following the initial drug administration, and again after 1 year of treatment at Visit 9B (Table 65 and [Table 66](#))

**Table 65. Descriptive Statistics of PK Parameters for Visit 7B, IB1001-202**

| <b>Descriptive Statistics</b> | <b>C<sub>max</sub><br/>(µg/mL)</b> | <b>t<sub>1/2</sub><br/>(h)</b> | <b>T<sub>max</sub><br/>(h)</b> | <b>AUC<sub>0-24</sub><br/>(h·µg/mL)</b> | <b>V<sub>z</sub>/F<br/>(L)</b> | <b>CL/F<br/>(L/h)</b> |
|-------------------------------|------------------------------------|--------------------------------|--------------------------------|-----------------------------------------|--------------------------------|-----------------------|
| N                             | 13                                 | 12                             | 13                             | 13                                      | 13                             | 13                    |
| Mean                          | 6.440                              | 0.908                          |                                | 15.393                                  | 181.906                        | 130.833               |
| SD                            | 2.534                              | 0.370                          |                                | 9.954                                   | 102.127                        | 83.167                |
| Min                           | 2.08                               | 0.49                           | 0.50                           | 3.21                                    | 60.96                          | 45.71                 |
| Median                        | 6.14                               | 0.76                           | 1.00                           | 13.89                                   | 171.70                         | 101.43                |
| Max                           | 12.14                              | 1.70                           | 2.00                           | 44.07                                   | 347.03                         | 311.60                |
| Geom Mean                     | 5.927                              | 0.852                          |                                | 13.021                                  | 153.663                        | 111.600               |
| Geom SD                       | 1.570                              | 1.436                          |                                | 1.853                                   | 1.881                          | 1.774                 |
| Geom %CV                      | 47.52                              | 37.39                          |                                | 68.03                                   | 70.04                          | 62.34                 |

Source: Summary of clinical pharmacology, Table 9

Abbreviations: AUC<sub>0-24</sub> = area under the curve from 0 to 24 hours; CL/F = apparent clearance; C<sub>max</sub> = maximum observed concentration; %CV = coefficient of variation; geom = geometric; max = maximum; min = minimum; N = number of valid observations for the variable; SD = standard deviation; t<sub>1/2</sub> = terminal half-life in hours; T<sub>max</sub> = time of the maximum observed concentration; V<sub>z</sub>/F = apparent volume of distribution

**Table 66. Descriptive Statistics of PK Parameters for Visit 9B, IB1001-202**

| <b>Descriptive Statistics</b> | <b>C<sub>max</sub><br/>(µg/mL)</b> | <b>t<sub>1/2</sub><br/>(h)</b> | <b>T<sub>max</sub><br/>(h)</b> | <b>AUC<sub>0-24</sub><br/>(h·µg/mL)</b> | <b>V<sub>ss</sub>/F<br/>(L)</b> | <b>CL<sub>ss</sub>/F<br/>(L/h)</b> |
|-------------------------------|------------------------------------|--------------------------------|--------------------------------|-----------------------------------------|---------------------------------|------------------------------------|
| N                             | 11                                 | 9                              | 11                             | 9                                       | 9                               | 9                                  |
| Mean                          | 6.877                              | 1.105                          |                                | 13.828                                  | 176.53                          | 115.669                            |
| SD                            | 2.554                              | 0.236                          |                                | 4.583                                   | 69.968                          | 52.978                             |
| Min                           | 3.08                               | 0.79                           | 0.5                            | 9.2                                     | 106.54                          | 54.46                              |
| Median                        | 6.61                               | 1.02                           | 1.00                           | 13.16                                   | 167.42                          | 94.82                              |
| Max                           | 11.74                              | 1.41                           | 2.00                           | 23.01                                   | 336.56                          | 229.81                             |
| Geom Mean                     | 6.421                              | 1.083                          |                                | 13.236                                  | 166.209                         | 106.374                            |
| Geom SD                       | 1.493                              | 1.24                           |                                | 1.358                                   | 1.431                           | 1.533                              |
| Geom %CV                      | 41.76                              | 21.76                          |                                | 31.35                                   | 36.99                           | 44.73                              |

Source: Summary of clinical pharmacology, Table 9

Abbreviations: AUC<sub>0-24</sub> = area under the curve from 0 to 24 hours; CL<sub>ss</sub>/F = difference in clearance; C<sub>max</sub> = maximum observed concentration; %CV = coefficient of variation; geom = geometric; max = maximum; min = minimum; N = number of valid observations for the variable; SD = standard deviation; t<sub>1/2</sub> = terminal half-life in hours; t<sub>max</sub> = time of the maximum observed concentration; V<sub>ss</sub>/F = volume of distribution

### **Trial IB1001-301 – PK Results**

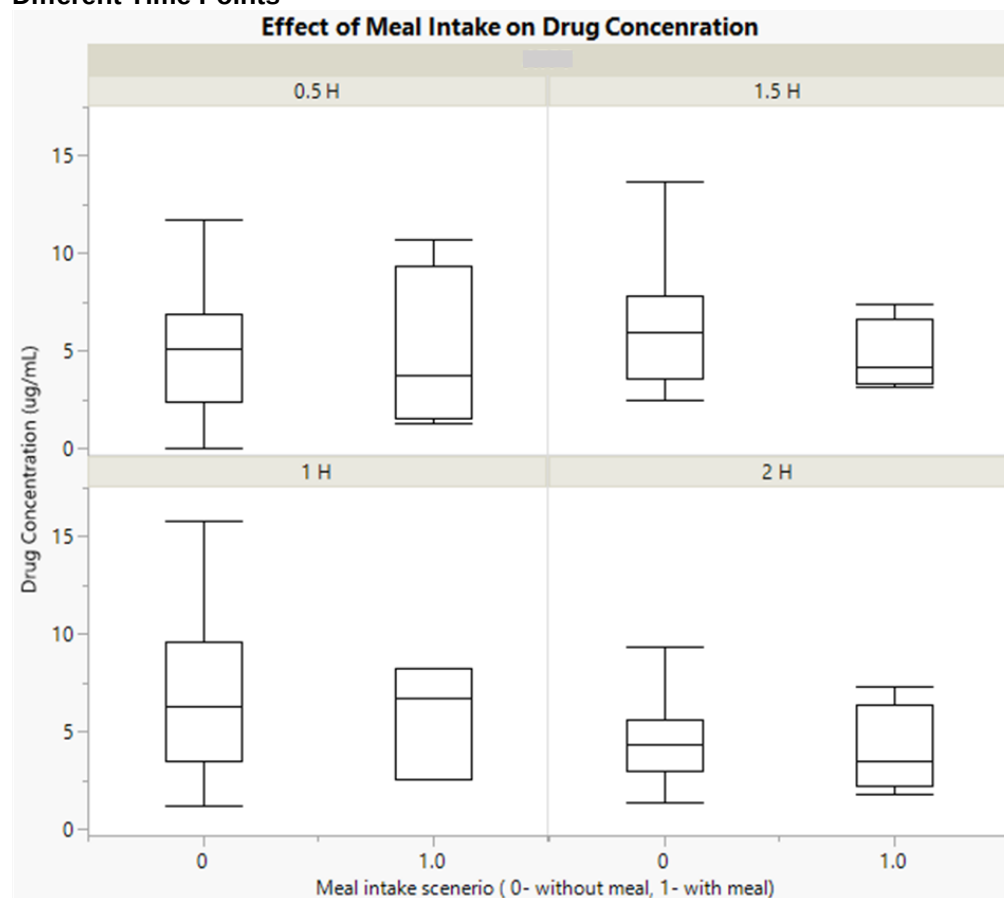
At the time when action was taken on initial NDA submission, the IB1001-301 EP is still ongoing, and therefore data from the rich PK sampling are not yet available. No noncompartmental PK analysis was performed on data from the sparse PK sampling from the parent study (Trial IB1001-301 PK report); instead, these samples were utilized in the PopPK analysis.

### **Impact of Food Effect on Pharmacokinetics**

The Applicant did not conduct dedicated food effect study using the to-be-marketed formulation. In Trial IB1001-301, drug administration was proposed to be under fasted conditions (at least 30 minutes before meal or at least 2 hours after meal). However, approximately 12.5% non-compliance with fasting was reported. The food components (high

fat versus low fat) were unknown. The review team conducted preliminary PK analyses to compare the drug concentration at various time points (0.5-, 1-, 1.5-, and 2-hour) following drug administrations under two scenarios: with and without meal intake. The results ([Figure 23](#) and [Table 67](#)) show that the drug concentrations are similar between the groups that consumed a meal and those that did not across all time points. While there is some variability within each group, the overall pattern indicates that meal intake did not significantly affect drug concentration during the first 2 hours postdose. These data suggest that given the current available information, the drug's absorption and subsequent concentrations remain similar regardless of meal intake.

**Figure 23. Drug Concentration of Levacetylleucine Under Fasted and Fed Condition at Different Time Points**



Source: Reviewer's analyses

**Table 67. Comparison of Drug Concentration at Different Time Points**

| Time Points | Mean (SD), N  |              |
|-------------|---------------|--------------|
|             | Without Meal  | With Meal    |
| 0.5 h       | 5.3 (3), 29   | 4.9 (4.2), 4 |
| 1 h         | 6.6 (3.7), 29 | 5.8 (2.9), 3 |
| 1.5 h       | 6 (2.6), 30   | 4.4 (1.8), 4 |
| 2 h         | 4.2 (1.7), 30 | 4 (2.3), 4   |

Source: Reviewer's analyses

Abbreviations: h = hour; SD = standard deviation

### 14.3. Bioanalytical Method Validation and Performance

A high-performance liquid chromatography method with tandem mass spectrometric was developed [REDACTED] <sup>(b) (4)</sup> for quantifying N-acetyl-L-leucine in human plasma. This method was used to analyze plasma samples from clinical Trials IB1001-202 (phase II), IB1001-203 (phase II), and IB1001-301 (phase III).

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**Table 68. Summary of Life Cycle Information on Bioanalytical Method Determination of N-Acetyl-L-Leucine and N-Acetyl-D-Leucine in Human Plasma Samples (for Completed Clinical Trials)**

|                                                                                                         | <b>Method Validation Study<br/>Val 18_015</b>                                                                                                                                              | <b>Sample Analysis in<br/>Clinical Trial IB1001-<br/>201</b> | <b>Sample Analysis in<br/>Clinical Trial IB1001-<br/>202</b> | <b>Sample Analysis in Clinical Trial<br/>IB1001-301</b>                                                                           |
|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Analyte(s)                                                                                              | Levacetylleucine                                                                                                                                                                           | Levacetylleucine                                             | Levacetylleucine                                             | Levacetylleucine                                                                                                                  |
| Validation type                                                                                         | Full                                                                                                                                                                                       | In-trial (Sample analysis phase of Trial IB1001-201)         | In-trial (Sample analysis phase of Trial IB1001-202)         | In-trial (Sample analysis phase of Trial IB1001-301)                                                                              |
| eCTD reference number                                                                                   | [Module 5.3.1.4]                                                                                                                                                                           | [Module 5.3.5.2]                                             | [Module 5.3.5.2]                                             | [Module 5.3.5.1]                                                                                                                  |
| Method ID                                                                                               | PV 335-01                                                                                                                                                                                  | PV 335-01                                                    | PV 335-01                                                    | PV 335-01                                                                                                                         |
| Duration of method in use                                                                               | Oct 9 to 15, 2018 (period of validation)                                                                                                                                                   | Sep 14, 2020 to Dec 22, 2021                                 | Sep 14, 2020 to Dec 22, 2021                                 | Parent phase: 15-Jun- 2023 to Sep 19, 2023 extension phase: no sample analysis has been performed for the ongoing extension phase |
| Bioanalytical site                                                                                      | (b) (4)                                                                                                                                                                                    |                                                              |                                                              |                                                                                                                                   |
| Matrix                                                                                                  | Human plasma                                                                                                                                                                               | Human plasma                                                 | Human plasma                                                 | Human plasma                                                                                                                      |
| Platform                                                                                                | High-performance liquid chromatography (HPLC) method with tandem mass spectrometric (MS/MS) detection                                                                                      |                                                              |                                                              |                                                                                                                                   |
| Format                                                                                                  | Internally standardized HPLC method using reverse-phase chromatography with a CHIRALPAK® QD-AX column and tandem mass spectrometric detection with Sciex API 4000 Qtrap mass spectrometer. |                                                              |                                                              |                                                                                                                                   |
| Stock reference, lot number expiration date                                                             | Levacetylleucine, Lot LT 40, Exp. Date: Apr 2, 2021                                                                                                                                        | Levacetylleucine, Lot LT 40, Retest Date: Apr- 2021          | Levacetylleucine, Lot LT 40, Retest. Date: Apr- 2021         | Levacetylleucine, Lot LT 40, Retest Date: Apr-21                                                                                  |
| Calibration range from the lower limit of quantitation (LLOQ) to the upper limit of quantitation (ULOQ) | 0.100 to 100.000 µg/mL                                                                                                                                                                     | 0.100 to 100.000 µg/mL                                       | 0.100 to 100.000 µg/mL                                       | 0.100 to 100.000 µg/mL                                                                                                            |
| Matrix/trial population                                                                                 | Normal                                                                                                                                                                                     | Diseased (NPC)                                               | Diseased (GM2 Gangliosidosis)                                | Diseased (NPC)                                                                                                                    |

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Aqneursa (levacetylleucine)

|                                           | <b>Method Validation Study<br/>Val 18_015</b>                                                                       | <b>Sample Analysis in<br/>Clinical Trial IB1001-<br/>201</b> | <b>Sample Analysis in<br/>Clinical Trial IB1001-<br/>202</b> | <b>Sample Analysis in Clinical Trial<br/>IB1001-301</b> |
|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|---------------------------------------------------------|
| Link to reports and applicable Amendments | Report [Val 18_015],<br>[Amendment 1 to Val 18_015],<br>[Amendment 2 to Val 18_015],<br>[Amendment 3 to Val 18_015] | Pharmacokinetic report [IB1001-201]                          | Pharmacokinetic report [IB1001-202]                          | Pharmacokinetic report [IB1001-301]                     |
| Amendment history                         | Long-term storage stability (Amendment 1, Amendment 2 and Amendment 3).                                             | Not applicable                                               | Not applicable                                               | Not applicable                                          |

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods

Abbreviations: eCTD = electronic common technical document; HPLC = high-performance liquid chromatography; LLOQ = lower limit of quantitation; MS/MS = tandem mass spectrometric; ULOQ = upper limit of quantitation

**Table 69. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 1)**

| Method Information                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks | Method Validation Report Titled "Validation of a HPLC-MS/MS Method for the Quantitative Determination of N-Acetyl-L-Leucine in Human Plasma", Report [Val 18_015]                                                                                                                                                                                                                                                                                                                        |
| Analyte                                                                 | N-acetyl-L-leucine                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Validation type                                                         | Full validation                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Method number                                                           | PV 335-01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Period of validation                                                    | Oct 9 to Oct 15, 2018                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Study period                                                            | Following the main validation, additional experiments were conducted to determine the long-term stability of levacetylleucine in human plasma. Results of long-term stability for 363 days at < -70°C (in plasma) and for 271 days at 5°C (in solution) are reported in [Amendment 1 to Val 18_015], long-term stability for 581 days at < -70°C is reported in [Amendment 2 to Val 18_015] and long-term stability for 1125 days at < -70°C is reported in [Amendment 3 to Val 18_015]. |
| Bioanalytical site                                                      | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Matrix                                                                  | Human plasma                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Platform                                                                | High-performance liquid chromatography (HPLC) method with tandem mass spectrometric (MS/MS) detection                                                                                                                                                                                                                                                                                                                                                                                    |
| Format                                                                  | Internally standardized HPLC method using reverse-phase chromatography with a CHIRALPAK QD-AX column and tandem mass spectrometric detection with Sciex API 4000 Qtrap mass spectrometer.                                                                                                                                                                                                                                                                                                |
| Stock reference                                                         | N-acetyl-L-leucine, Lot LT40, Retest date: Apr-2021                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Calibration range                                                       | LLOQ=0.100 µg/mL, ULOQ=100.000 µg/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Matrix study population                                                 | Normal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Source: Summary of Biopharmaceutical Studies and Associated Analytical Methods

Abbreviations: HPLC = high-performance liquid chromatography; LLOQ = lower limit of quantitation; MS/MS = tandem mass spectrometric; ULOQ = upper limit of quantitation

**Table 70. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 2)**

| Method Summary                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Method description                                              | Internally standardized HPLC method using reverse-phase chromatography with a CHIRALPAK QD-AX column and tandem mass spectrometric detection using a Sciex API 4000 Qtrap mass spectrometer. Plasma samples spiked with the internal standard (N-acetyl-DL-leucine- d10) and acetonitrile are enriched with methanol and analyzed by HPLC-MS/MS. Run time (time between injections) was approximately 8.0 minutes.                                                                                                                                                                                                                                                                                                                |
| Materials used for standard calibration curve and concentration | N-acetyl-L-leucine stock solution (10000.000 µg/mL) was prepared in methanol. Stock solution was further diluted to spiking solutions with 50:50 methanol:water (2.000-2000.000 µg/mL)<br>Spiking solutions were spiked in pooled human plasma to prepare the calibration standards.<br>Concentration of calibration standards: 0.100, 0.200, 0.500, 1.000, 10.000, 50.000, 80.000 and 100.000 µg/mL                                                                                                                                                                                                                                                                                                                              |
| Validated assay range                                           | 0.100 to 100.000 µg/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Material used for quality controls (QCs) and concentration      | A separate N-acetyl-L-leucine stock solution (10000.000 µg/mL) was prepared in methanol. Stock solution was further diluted to spiking solutions with 50:50 methanol:water (2.000-1500.000 µg/mL)<br>Spiking solutions were spiked in pooled human plasma to prepare quality controls.<br>Concentration of quality controls (QCs): 0.100 (QC lower limit), 0.300 (QC low), 30.000 (QC medium), 75.000 (QC high) and 1000.000 (QC upper limit) µg/mL                                                                                                                                                                                                                                                                               |
| Minimum required dilution (MRD)                                 | Not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Source and lot of reagents                                      | Calibrator standard: N-acetyl-L-leucine, lot number LT 40, used for preparation of calibration, validation and QC samples, provided by (b) (4)<br>(b) (4)<br>Internal standard: N-acetyl-DL-leucine-d <sub>10</sub> , Lot number AZB 4572 a36 IV, used as internal standard, provided by (b) (4)<br>Biological Matrix: Blank human, fresh frozen lithium heparin plasma, provided by (b) (4), was used for QC samples and calibrators (Lot number: BRH 1565746-55), for measuring matrix effect (Lots number: BRH 1565747 – BRH 1565752), for measuring lipemic effect (Lot number: BRH 1565744), for measuring hemolytic effect (Lot number: BRH 1565745) and for measuring selectivity (Lots number: BRH 1565746 – BRH 1565755) |
| Regression model and weighting                                  | Sample concentrations were determined mathematically comparing the peak area ratios in the sample to the weighted (1/x) regression equation obtained from the standards data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods  
Abbreviations: HPLC = high-performance liquid chromatography; QC = quality controls

**Table 71. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 3)**

| Validation Parameters                                                                            | Method Validation Summary                        |              |
|--------------------------------------------------------------------------------------------------|--------------------------------------------------|--------------|
| Standard calibration curve performance during accuracy and precision runs in part 1 <sup>1</sup> | Number of standard calibrators from LLOQ to ULOQ | 8            |
|                                                                                                  | Cumulative accuracy (%bias) from LLOQ to ULOQ    | -3.1 to 8.4% |
|                                                                                                  | Cumulative precision (%CV) from LLOQ to ULOQ     | ≤5.3%        |

| Validation Parameters                                                                            | Method Validation Summary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Standard calibration curve performance during accuracy and precision runs in part 2 <sup>1</sup> | Number of standard calibrators from LLOQ to ULOQ 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                  | Cumulative accuracy (%bias) from LLOQ to ULOQ -2.3 to 0.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                  | Cumulative precision (%CV) from LLOQ to ULOQ ≤2.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Performance of QCs during accuracy and precision runs                                            | Cumulative accuracy (%bias) in 3 QCs -4.0 to 2.4%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                  | Inter-batch %CV ≤8.6%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                  | Total Error (TE) Not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Selectivity & matrix effect                                                                      | <u>Selectivity</u> of the method was tested using 10 different human plasma lots. Ten out of ten processed blank samples without internal standard (IS) and with IS showed negligible interfering signal with N-acetyl-L-leucine. The method is selective for N-acetyl-L-leucine analytes.<br><u>Matrix effect</u> of the method was tested using 6 different human plasma lots. The CV of the IS- normalized matrix factor (MF) at QC low, QC medium and QC high level is <15 % and therefore in good accordance with the acceptance criteria |
| Recovery*                                                                                        | <u>Recovery</u> values of the analyte calculated comparing the detector response of N-acetyl-L-leucine and internal standard to the response of the analyte in spiked blank extracts are very consistent for the matrix samples                                                                                                                                                                                                                                                                                                                |
| Interference & specificity                                                                       | <u>Interference</u> between N-acetyl-L-leucine and N-acetyl-DL-leucine-d10 were tested using three ULOQ without IS samples and three blanks with IS samples with one lot of plasma. No interference from N-acetyl-DL-leucine-d10 to N-acetyl-L-leucine, as well as from N-acetyl-L-leucine to N-acetyl-DL-leucine-d10 were detected.                                                                                                                                                                                                           |
| Hemolysis effect                                                                                 | <u>Hemolysis effect</u> in three lots were tested, the bias for all hemolytic plasma samples was within acceptance criteria                                                                                                                                                                                                                                                                                                                                                                                                                    |

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods

<sup>1</sup> Due to the size of the study the results were divided over two tables (i.e., part 1 and part 2)

Abbreviations: CV = coefficient of variation; HPLC = high-performance liquid chromatography; IS = internal standard; LLOQ = lower limit of quantitation; MF = matrix factor; TE = total error; ULOQ = upper limit of quantitation; QC = quality control

**Table 72. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 4)**

| Validation Parameters            | Method Validation Summary                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lipemic effect                   | Lipemic effect in 3 lots were tested, the bias for all lipemic serum samples was within acceptance criteria.                                                                                                                                                                                                                                                                                                                              |
| Dilution linearity & hook effect | Dilution linearity within acceptance criteria.<br>Samples containing the analyte at concentration >ULOQ (100.000 µg/mL) were diluted with blank plasma, dilution factor of 20 (1:20). The observed individual absolute bias was 1.9% of the nominal value for samples within validated range and overall CV was 3.2% meeting the acceptance criteria and demonstrated the plasma samples can be diluted with a factor of at least twenty. |
| Integrity of dilution            | No prozone (hook effect) was tested.<br>Samples of the analyte in plasma can be diluted at least 20-fold at concentration >ULOQ (100.000 µg/mL). Accuracy 101.9%, Precision 3.2%                                                                                                                                                                                                                                                          |

| Validation Parameters         | Method Validation Summary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bench-top/process stability   | Demonstrated for 24 hours at room temperature. Observed change between -6.3% and 2.5%.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Freeze-thaw stability         | Demonstrated for at least 3 cycles in plasma at <-70°C. Observed change between -6.8 and 7.5%.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Long-term storage / stability | Demonstrated for 48 hours, when stored in the automatic sampler at 10°C.<br>Demonstrated stable at 5°C ±3°C for 32 days in working solution or 63 days in stock solution. Demonstrated stable for at least 3 freeze-thaw cycles in working solution at <-70°C.<br><br>Assessment for 363 days at <-70°C (in plasma) and for 271 days at 5°C ±3°C (in solution) was ongoing at the time the main validation report was finalized and results are reported in [Amendment 1 to Val 18_015]. Long-term stability for 581 and 1125 days at <-70°C (in plasma) are reported in [Amendment 2 to Val 18_015] and [Amendment 3 to Val 18_015] respectively. |
| Parallelism                   | Not done.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Carryover                     | Carryover was observed in 3 runs when a blank sample was analyzed directly after two injections of the highest calibrator (100.000 µg/mL). Two blank samples will be injected after higher concentration samples and the clinical sample will not be randomized injected, so there will be no impact on the preclinical study.                                                                                                                                                                                                                                                                                                                     |

Source: Summary of Biopharmaceutical Studies and Associated Analytical Methods

Abbreviations: CV = coefficient of variation; ULOQ = upper limit of quantitation; Val = validation

**Table 73. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 5)**

|                                                             | Method Information                                                                                                                                                                                 |
|-------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bioanalytical method validation report name, and amendments | Amendment 1 to the method validation report titled "Validation of a HPLC-MS/MS Method for the quantitative determination of N-Acetyl-L-Leucine in human plasma" Report [Amendment 1 to Val 18_015] |
| Analyte                                                     | Levacetylleucine                                                                                                                                                                                   |
| Validation type                                             | Full validation                                                                                                                                                                                    |
| Method number                                               | PV 335-01                                                                                                                                                                                          |
| Study period                                                | Experimental start date: Nov 9, 2018, completion date: Oct 9, 2019                                                                                                                                 |
| Bioanalytical site                                          | (b) (4)                                                                                                                                                                                            |
| Matrix                                                      | Human plasma                                                                                                                                                                                       |
| Platform                                                    | High-performance liquid chromatography (HPLC) method with tandem mass spectrometric (MS/MS) detection                                                                                              |
| Format                                                      | Internally standardized HPLC method using reverse-phase chromatography with a CHIRALPAK QD-AX column and tandem mass spectrometric detection with Sciex API 4000 Qtrap mass spectrometer.          |
| Stock reference                                             | N-acetyl-L-leucine, Lot LT40, Retest date: Apr-2021                                                                                                                                                |
| Calibration range                                           | LLOQ=0.100 µg/mL, ULOQ=100.000 µg/mL                                                                                                                                                               |
| Matrix study population                                     | Normal                                                                                                                                                                                             |
| Synopsis of amendment history                               | Additional long-term stabilities of the analyte: for 363 days at < -70°C (in plasma) and for 271 days at 5°C (in solution) are described in Amendment 1.                                           |

Source: Summary of Biopharmaceutical Studies and Associated Analytical Methods

Abbreviations: HPLC = high-performance liquid chromatography; LLOQ = lower limit of quantitation; MS/MS = tandem mass spectrometric; ULOQ = upper limit of quantitation

**Table 74. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 6)**

| <b>Method Summary</b>                                                                                                                                                                                                                 |                                                                                                                                                        |                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Refer to the "method summary" section for the main method validation report, as described above in this table. (Information on batch numbers for materials might have differed between the main validation report and the amendment.) |                                                                                                                                                        |                |
| <b>Validation Parameters</b>                                                                                                                                                                                                          | <b>Method Validation Summary</b>                                                                                                                       |                |
| Standard calibration curve performance in part 1                                                                                                                                                                                      | Number of standard calibrators from LLOQ to ULOQ                                                                                                       | 8              |
|                                                                                                                                                                                                                                       | Cumulative accuracy (%bias) from LLOQ to ULOQ                                                                                                          | 2.0 to 7.6%    |
|                                                                                                                                                                                                                                       | Cumulative precision (%CV) from LLOQ to ULOQ                                                                                                           | ≤0.020%        |
| Standard calibration curve performance in part 2                                                                                                                                                                                      | Number of standard calibrators from LLOQ to ULOQ                                                                                                       | 8              |
|                                                                                                                                                                                                                                       | Cumulative accuracy (%bias) from LLOQ to ULOQ                                                                                                          | -0.5 to 0.6%   |
|                                                                                                                                                                                                                                       | Cumulative precision (%CV) from LLOQ to ULOQ                                                                                                           | ≤4.7%          |
| Performance of QCs during accuracy and precision runs                                                                                                                                                                                 | Cumulative accuracy (%bias) in 4 QCs                                                                                                                   | -1.4 to 4.2%   |
|                                                                                                                                                                                                                                       | Inter-batch %CV                                                                                                                                        | ≤12.9%         |
|                                                                                                                                                                                                                                       | Total Error (TE)                                                                                                                                       | Not applicable |
| Long-term storage/ stability                                                                                                                                                                                                          | Demonstrated for 363 days when stored at <-70°C and at 271 days when stored in the refrigerator at 5°C ±3°C Assessment for 581 days at <-70°C ongoing. |                |

Source: Summary of Biopharmaceutical Studies and Associated Analytical Methods

Abbreviations: CV = coefficient of variation; HPLC = high-performance liquid chromatography; LLOQ = lower limit of quantitation; MF = matrix factor; TE = total error; ULOQ = upper limit of quantitation; QC = quality control

**Table 75. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 7)**

| <b>Method Information</b>                                               |                                                                                                                                                                                                    |
|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bioanalytical method validation report name, amendments, and hyperlinks | Amendment 1 to the method validation report titled "Validation of a HPLC-MS/MS Method for the quantitative determination of N-Acetyl-L-Leucine in human plasma" Report [Amendment 2 to Val 18_015] |
| Analyte                                                                 | N-acetyl-L-leucine                                                                                                                                                                                 |
| Validation type                                                         | Full validation                                                                                                                                                                                    |
| Method number                                                           | PV 335-01                                                                                                                                                                                          |
| Study period                                                            | Experimental start and completion date: May 13, 2020                                                                                                                                               |
| Bioanalytical site                                                      | (b) (4)                                                                                                                                                                                            |
| Matrix                                                                  | Human plasma                                                                                                                                                                                       |
| Platform                                                                | High-performance liquid chromatography (HPLC) method with tandem mass spectrometric (MS/MS) detection                                                                                              |
| Format                                                                  | Internally standardized HPLC method using reverse-phase chromatography with a CHIRALPAK QD-AX column and tandem mass spectrometric detection with Sciex API 4000 Qtrap mass spectrometer.          |

| Method Information            |                                                                                                                |
|-------------------------------|----------------------------------------------------------------------------------------------------------------|
| Stock reference               | N-acetyl-L-leucine, Lot LT40, Retest date: Apr-20. 21                                                          |
| Calibration range             | LLOQ=0.100 µg/mL, ULOQ=100.000 µg/mL                                                                           |
| Matrix study population       | Normal                                                                                                         |
| Synopsis of amendment history | Additional long-term stability of the analyte for 581 days at < -70°C (in plasma) is described in Amendment 2. |

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods

Abbreviations: HPLC = high-performance liquid chromatography; LLOQ = lower limit of quantitation; MS/MS = tandem mass spectrometric; ULOQ = upper limit of quantitation

**Table 76. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 8)**

| Method Summary                                                                                                                                                                                                                               |                                                                                            |                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------|
| Please refer to the "method summary" section for the main method validation report, as described above in this table. (Information on batch numbers for materials might have differed between the main validation report and the amendment.) |                                                                                            |                |
| Validation Parameters                                                                                                                                                                                                                        | Method Validation Summary                                                                  |                |
| Standard calibration curve performance in part 1                                                                                                                                                                                             | Number of standard calibrators from LLOQ to ULOQ                                           | 8              |
|                                                                                                                                                                                                                                              | Cumulative accuracy (%bias) from LLOQ to ULOQ                                              | Not applicable |
|                                                                                                                                                                                                                                              | Cumulative precision (%CV) from LLOQ to ULOQ                                               | Not applicable |
|                                                                                                                                                                                                                                              |                                                                                            |                |
| Standard calibration curve performance in part 2                                                                                                                                                                                             | Number of standard calibrators from LLOQ to ULOQ                                           | 8              |
|                                                                                                                                                                                                                                              | Cumulative accuracy (%bias) from LLOQ to ULOQ                                              | Not applicable |
|                                                                                                                                                                                                                                              | Cumulative precision (%CV) from LLOQ to ULOQ                                               | Not applicable |
|                                                                                                                                                                                                                                              |                                                                                            |                |
| Performance of QCs during accuracy and precision runs                                                                                                                                                                                        | Cumulative accuracy (%bias) in 4 QCs                                                       | -4.4 to 8.2%   |
|                                                                                                                                                                                                                                              | Inter-batch %CV                                                                            | ≤12.4%         |
|                                                                                                                                                                                                                                              | Total Error (TE)                                                                           | Not applicable |
| Long-term storage / stability                                                                                                                                                                                                                | Demonstrated for 581 days when stored at -70°C. Assessment for 1125 days at -70°C ongoing. |                |

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods

Abbreviations: CV = coefficient of variation; LLOQ = lower limit of quantitation; TE = total error; ULOQ = upper limit of quantitation; QC = quality control

**Table 77. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 9)**

| Method Information                                                      |                                                                                                                                                                                                    |
|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bioanalytical method validation report name, amendments, and hyperlinks | Amendment 1 to the method validation report titled "Validation of a HPLC-MS/MS Method for the quantitative determination of N-Acetyl-L-Leucine in human plasma" Report [Amendment 3 to Val 18_015] |
| Analyte                                                                 | N-acetyl-L-leucine                                                                                                                                                                                 |
| Validation type                                                         | Full validation                                                                                                                                                                                    |
| Method number                                                           | PV 335-01                                                                                                                                                                                          |
| Study period                                                            | Experimental start and completion date: Nov 8, 2021                                                                                                                                                |
| Bioanalytical site                                                      | (b) (4)                                                                                                                                                                                            |
| Matrix                                                                  | Human plasma                                                                                                                                                                                       |
| Platform                                                                | High-performance liquid chromatography (HPLC) method with tandem mass spectrometric (MS/MS) detection                                                                                              |

| Method Information            |                                                                                                                                                                                           |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Format                        | Internally standardized HPLC method using reverse-phase chromatography with a CHIRALPAK QD-AX column and tandem mass spectrometric detection with Sciex API 4000 Qtrap mass spectrometer. |
| Stock reference               | N-acetyl-L-leucine, Lot LT40, Retest date: Apr-2021                                                                                                                                       |
| Calibration range             | LLOQ=0.100 µg/mL, ULOQ=100.000 µg/mL                                                                                                                                                      |
| Matrix study population       | Normal                                                                                                                                                                                    |
| Synopsis of amendment history | Additional long-term stability of the analyte for 1125 days at < -70°C (in plasma) is reported in Amendment 3.                                                                            |

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods

Abbreviations: HPLC = high-performance liquid chromatography; LLOQ = lower limit of quantitation; MS/MS = tandem mass spectrometric; ULOQ = upper limit of quantitation

**Table 78. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 10)**

| Method Summary                                                                                                                                                                                                                        |                                                  |                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|----------------|
| Refer to the "method summary" section for the main method validation report, as described above in this table. (Information on batch numbers for materials might have differed between the main validation report and the amendment.) |                                                  |                |
| Method Validation Summary                                                                                                                                                                                                             |                                                  |                |
| Standard calibration curve performance in part 1                                                                                                                                                                                      | Number of standard calibrators from LLOQ to ULOQ | 8              |
|                                                                                                                                                                                                                                       | Cumulative accuracy (%bias) from LLOQ to ULOQ    | Not applicable |
|                                                                                                                                                                                                                                       | Cumulative precision (%CV) from LLOQ to ULOQ     | Not applicable |
|                                                                                                                                                                                                                                       |                                                  |                |
| Standard calibration curve performance in part 2                                                                                                                                                                                      | Number of standard calibrators from LLOQ to ULOQ | 8              |
|                                                                                                                                                                                                                                       | Cumulative accuracy (%bias) from LLOQ to ULOQ    | Not applicable |
|                                                                                                                                                                                                                                       | Cumulative precision (%CV) from LLOQ to ULOQ     | Not applicable |
|                                                                                                                                                                                                                                       |                                                  |                |
| Performance of QCs during accuracy and precision runs                                                                                                                                                                                 | Cumulative accuracy (%bias) in 3 QCs             | -7.1 to -0.8%  |
|                                                                                                                                                                                                                                       | Inter-batch %CV                                  | Not applicable |
|                                                                                                                                                                                                                                       | Total Error (TE)                                 | Not applicable |
| Long-term storage/ stability                                                                                                                                                                                                          | Demonstrated for 1125 days when stored at -70°C. |                |

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods

Abbreviations: CV = coefficient of variation; LLOQ = lower limit of quantitation; TE = total error; ULOQ = upper limit of quantitation; QC = quality control

**Table 79. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 11)**

| <b>Method Performance in Study IB1001-201</b>                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pharmacokinetic report titled “Effects o N-Acetyl-L-Leucine on Niemann-Pick disease type C: A multinational, multicenter, open-label, rater-blinded Phase II study” Report [Pharmacokinetic report of IB1001-201] |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Assay passing rate                                                                                                                                                                                                | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                                                                                                                                             |
| Standard curve performance                                                                                                                                                                                        | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                                                                                                                                             |
| QC performance                                                                                                                                                                                                    | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                                                                                                                                             |
| Method reproducibility                                                                                                                                                                                            | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                                                                                                                                             |
| Study sample analysis/ stability                                                                                                                                                                                  | In the parent phase (Visit 1 to 6) sparse PK samplings of 33 subjects were collected to establish the baseline, administrate the treatment and perform the washout. A total of 19 subjects continued into Extension Phase I (Visit 7B and 9B), in which the individual plasma concentration profiles were collected. The concentrations of N-acetyl-L-leucine in human plasma of 19 subjects (in Extension Phase I) were successfully analyzed. |
| Standard calibration curve performance during accuracy and precision runs                                                                                                                                         | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                                                                                                                                             |
| Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Abbreviations: ISR = incurred sample reanalysis; PK = pharmacokinetics                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

**Table 80. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 12)**

| <b>Method Performance in Trial IB1001-202</b>                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pharmacokinetic report titled “Effects of N-Acetyl-L-Leucine on GM2 Gangliosidosis (Tay-Sachs and Sandhoff Disease): A multinational, multicenter, open-label, rater- blinded Phase II study” Report [Pharmacokinetic report of IB1001-202] |                                                                                                                                                                                                                                                                                                                      |
| Assay passing rate                                                                                                                                                                                                                          | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                  |
| Standard curve performance                                                                                                                                                                                                                  | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                  |
| QC performance                                                                                                                                                                                                                              | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                  |
| Method reproducibility                                                                                                                                                                                                                      | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                  |
| Study sample analysis/ stability                                                                                                                                                                                                            | In the parent phase (Visit 1 to 6) sparse PK samplings of 30 subjects were collected to establish the baseline, administrate the treatment and perform the washout. A total of 14 subjects continued into Extension Phase I (Visit 7B and 9B), in which the individual plasma concentration profiles were collected. |
| Standard calibration curve performance during accuracy and precision runs                                                                                                                                                                   | Not applicable. No ISR was performed in this study                                                                                                                                                                                                                                                                   |
| Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                      |
| Abbreviations: ISR = incurred sample reanalysis; PK = pharmacokinetics                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                      |

**Table 81. Summary of Method Performance of a Bioanalytical Method Determination of N-Acetyl-L-Leucine in Human Plasma (Part 13)**

| <b>Method Performance in Study IB1001-301</b>                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pharmacokinetic report titled “Effects of N-Acetyl-L-Leucine on Niemann-Pick disease type C (NPC): A Phase III, randomized, placebo-controlled, double-blind, crossover study” Report [Pharmacokinetic report of IB1001-301] |                                                                                                                                                                                                                                                                                                                        |
| Assay passing rate                                                                                                                                                                                                           | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                    |
| Standard curve performance                                                                                                                                                                                                   | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                    |
| QC performance                                                                                                                                                                                                               | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                    |
| Method reproducibility                                                                                                                                                                                                       | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                    |
| Study sample analysis/ stability                                                                                                                                                                                             | In the parent phase (Visits 2, 4 and 6) sparse PK samplings of 60 subjects were collected at baseline, during treatment and washout. The extension phase will enroll subjects who have completed Visit 6 (ongoing). In Extension Phase I (Visit 7B and 9B) individual plasma concentration profiles will be collected. |
| Standard calibration curve performance during accuracy and precision runs                                                                                                                                                    | Not applicable. No ISR was performed in this study.                                                                                                                                                                                                                                                                    |

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods  
Abbreviations: ISR = incurred sample reanalysis; PK = pharmacokinetics

## 14.4. Immunogenicity Assessment–Impact of PK/PD, Efficacy, and Safety

No studies of immunogenicity and its impact on PK/PD, efficacy and safety were conducted.

## 14.5. Pharmacometrics Assessment

### Population PK Analysis

#### **Applicant’s Population PK Analysis**

The PopPK analysis for levacetylleucine was conducted based on the PK data collected from three trials: IB1001-201 (n=32), IB1001-202 (n=25), and IB1001-301 (n=38). Sparse PK sampling was collected in Trials IB1001-201, IB1001-202 and IB1001-301 and rich PK sampling was conducted in the EPs of Trials IB1001-201 and IB1001-202. A total of 567 levacetylleucine concentrations from 95 subjects were used in PopPK analysis. In the PopPK population, majority of subjects were White (94%) and male (51%). The median (range) age was 26 (6, 67) years old, and the median (range) body weight was 59.2 (20.5, 98.4) kg. Dosing regimen used in IB1001-201 is same as the proposed dosing regimen with minor deviations in the age categories for dosing in IB1001-201 and IB1001-202.

Phoenix WinNonlin™ nonlinear mixed effect using estimation method of First Order Conditional Estimation-Extended Least Squares (FOCE ELS) was used for PopPK analysis. To investigate the source of between-subject variability, intrinsic factors and extrinsic factors were tested for inclusion in the base model using forward stepwise covariate search to test the addition or deletion of covariates effects by adding one at a time. Visual predictive check and bootstrap test were used to validate the final covariate model.

The base model is a one-compartment model with the error model combining additive and multiplicative method. The base model also includes a 5-minute lag time ( $T_{lag}$ ) and covariance between clearance (CL) and volume of distribution (V). Between-subject variability coefficient of variation were 39% for CL and 74% for V. The examined covariates were age, sex, weight, body mass index, body surface area, disease (NPC or GM2 gangliosidosis), race (White, Asian or other), dose (1 gram or 2 grams), miglustat as comedication, and meal consumption (no meal, meal consumed during the 2 hours before drug administration, meal consumed during the 2 hours after drug administration, meal consumed during the 2 hours both before and after the drug administration). The final PopPK model includes the effect of body weight with power model on CL and V, and the effect of dose (1 gram versus 2 grams) on the absorption rate constant ( $K_a$ ). The final model estimates are presented in [Table 82](#). Goodness-of-fit plots and visual predictive check are presented in [Figure 24](#) and [Figure 25](#). Between-subject variability coefficient of variation were 29% for CL, 80% for V, and 19% for  $K_a$ . Eta shrinkages were 20%, 44%, and 48% for CL, V, and  $K_a$ .

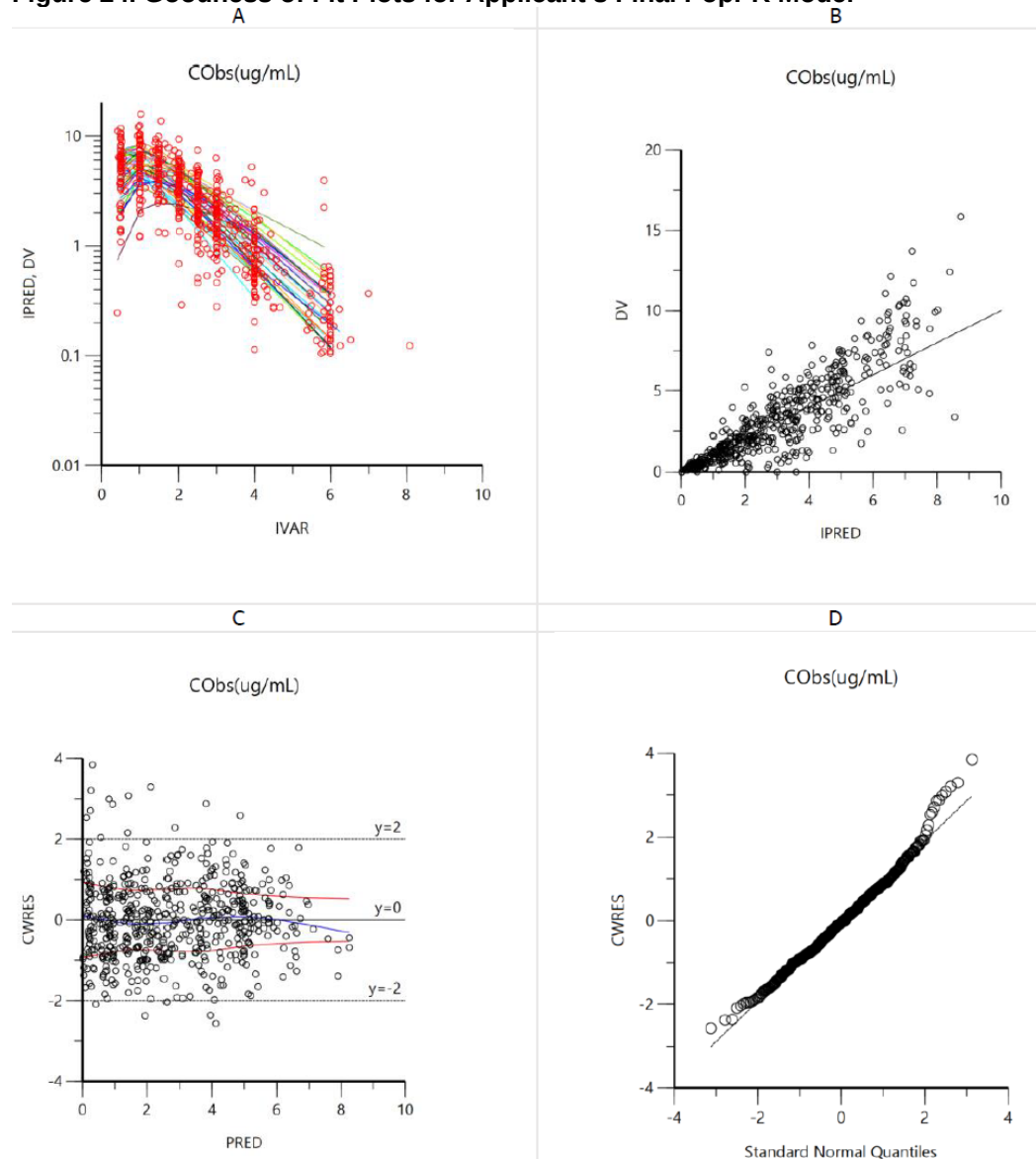
**Table 82. Parameter Estimates for Applicant's Final PopPK Model**

| Parameter    | Estimate | Units | Stderr | CV%      | 2.5% CI  | 97.5% CI |
|--------------|----------|-------|--------|----------|----------|----------|
| tvKa         | 0.8184   | 1/h   | 0.0544 | 6.6488   | 0.7116   | 0.9253   |
| tvV          | 43.3537  | L     | 6.9098 | 15.9381  | 29.7813  | 56.9261  |
| tvCl         | 145.5156 | L/h   | 7.4643 | 5.1295   | 130.8540 | 160.1771 |
| tvTlag       | 0.2426   | h     | 0.0439 | 18.0798  | 0.1564   | 0.3287   |
| tvCMultStdev | 0.4451   |       | 0.0294 | 6.5984   | 0.3874   | 0.5027   |
| dVdWEIGHT    | 0.1790   |       | 0.0323 | 18.0361  | 0.1156   | 0.2424   |
| dKadDOSECOV2 | -0.1783  |       | 0.0587 | -32.9560 | -0.2937  | -0.0629  |
| dCldWEIGHT   | 0.5829   |       | 0.0822 | 14.0970  | 0.4215   | 0.7443   |
| stdev0       | 0.0153   |       | 0.0041 | 26.8390  | 0.0072   | 0.0234   |

Source: PopPK report, Table 17 on page 34

Abbreviations: CI = confidence interval; dVdWEIGHT = effect of the covariate weight on the volume of distribution in the model; dKadDOSECOV2 = effect of the dose on the absorption rate; dCldWEIGHT = weight covariate on CL; PopPK = population pharmacokinetic; stdev0 = standard deviation in additive residual error model; tvKa = a population typical value for the absorption rate constant  $K_a$ ; tvV = a population typical value for the volume of distribution V; tvCl = a population typical value for the clearance CL; tvTlag = a population typical value of lag time of first-order absorption; tvCMultStdev = a population typical value for the multiplicative component of the residual error model

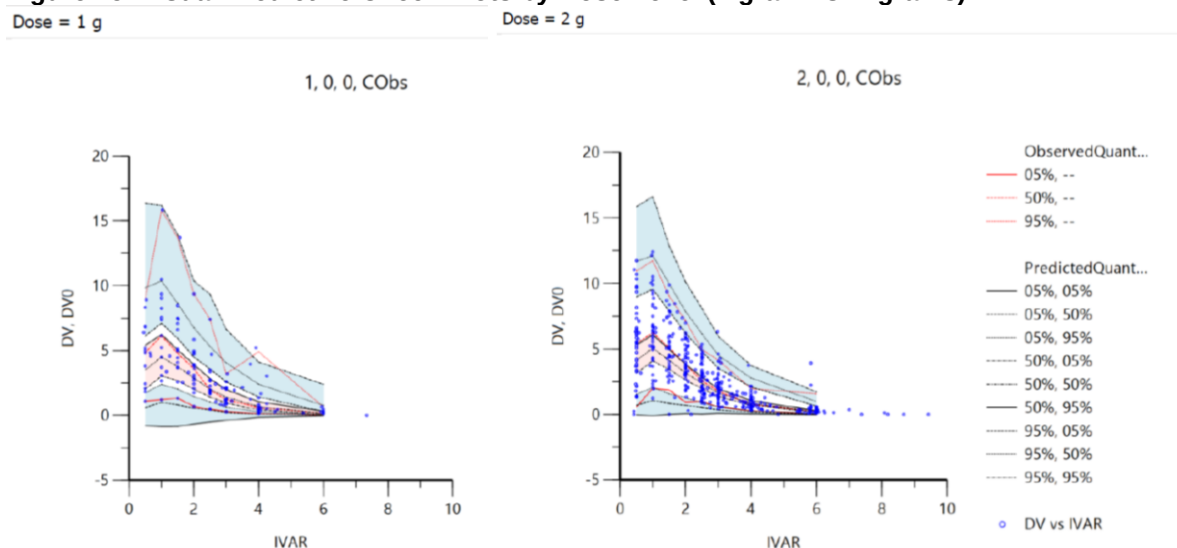
**Figure 24. Goodness of Fit Plots for Applicant's Final PopPK Model**



Source: PopPK report (updated), Figure 3 on page 35

Abbreviations: CWRES = conditional weighted residuals; C<sub>Obs</sub> = observed concentration; IPRED = individual predicted concentration; IVAR = independent variable; PRED = predicted concentration

**Figure 25. Visual Predictive Check Plots by Dose Level (1 gram vs. 2 grams)**



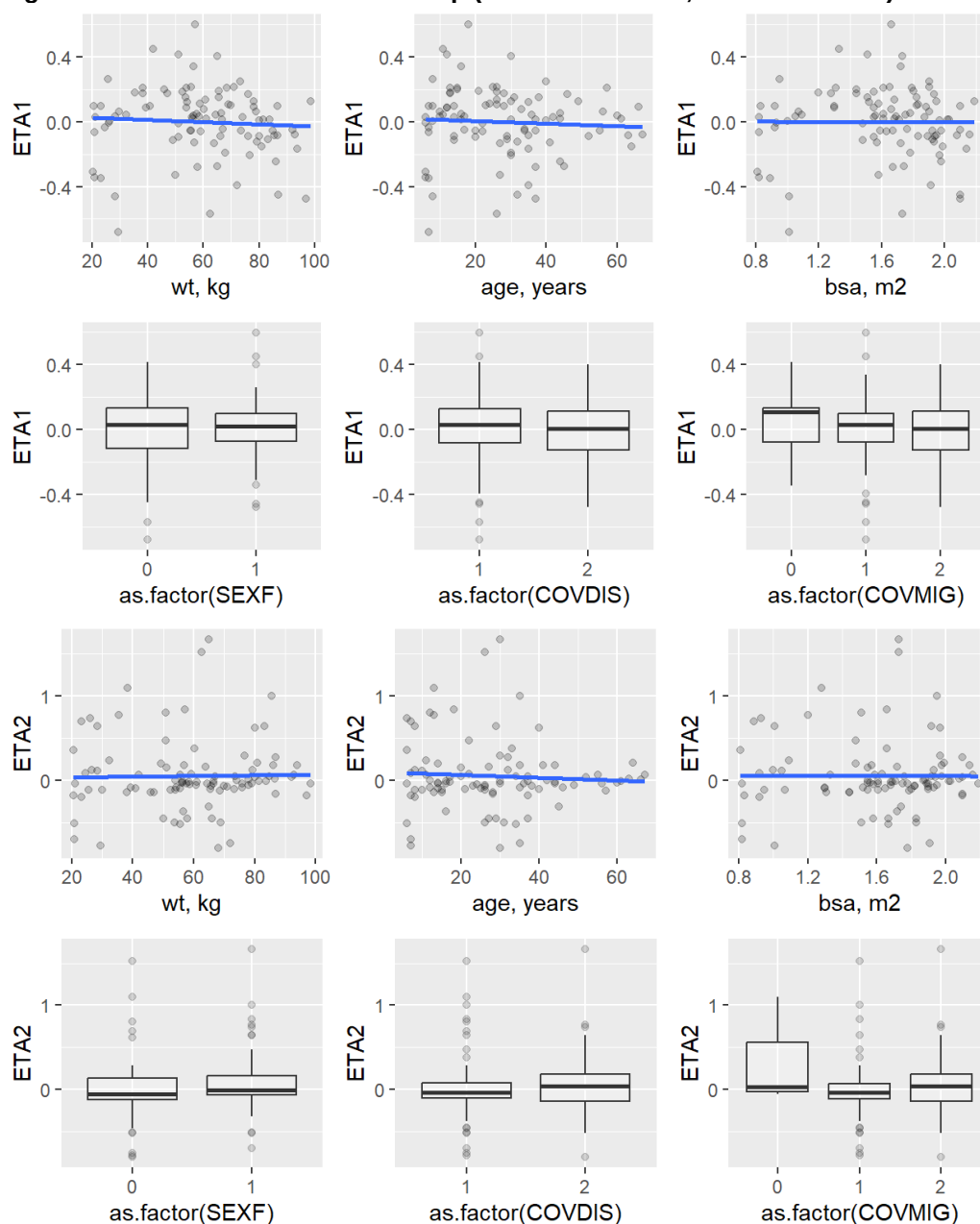
Source: PopPK analysis report, Figure 4 on page 39

Abbreviations:  $C_{Obs}$  = observed concentration; DV = dependent variable, observed concentrations; DV0 = dependent variable 0, concentrations predicted by the model; IVAR = independent variable

### Reviewer's Assessment

Data handling of exclusions and correction of missing values and unplausible values were adequately documented. The final PopPK model reasonably describes the observed PK data. The reviewer's independent analysis shows similar parameter estimates as Applicant's. The structural parameters were estimated with acceptable precision (relative standard error <20%). The goodness-of-fit plots does not show obvious model misspecification, and the visual predictive check plots shows that the model generally captures the central tendency and variability of the observed data. No systemic trends were observed in ETA-covariate plots (Figure 26). Age was not identified as significant covariate once body weight is included in the model. Eta shrinkage for CL less than 20% supports use of empiric Bayes estimates to derive individual CL and exposure metrics of AUC. Given the fast absorption with a short half-life and the moderately high eta shrinkage for V, the model derived  $C_{max}$  was only used for the purpose of comparisons with the model derived  $C_{max}$  values predicted for different body weight groups when evaluating dosing regimens.

**Figure 26. ETA-Covariate Relationship (ETA1: Eta for CL, ETA2: Eta for V)**



Source: Reviewer's analysis

Abbreviations: 0 = Yes, 1 = No; 2 = NA; BSA = body surface area; SEXF = sex, 0-male and 1-female; COVDIS = disease as covariate, 1-NPC and 2-GM2; CL = clearance; COVMIG = comedication with miglustat; V = volume of distribution

Applicant's PopPK analysis assumed that levacetylleucine follows dose-linear PK. There is no dose-proportionality information provided by Applicant. The available PK data used for PopPK analysis are limited to evaluate relative oral bioavailability (1 gram versus 2 grams). The subjects younger than 13 years old and weighing <35 kg received 1 gram at the time of PK sampling and the remaining subjects ( $\geq 13$  years old or  $\geq 35$  kg) received 2 grams at the time of PK sampling. Since PK samples were collected only after the morning dose, there are no data where two dose strengths (1 gram and 2 grams) were tested within a subject or in similar subjects in terms of body size (e.g., weight) at the time of PK sampling. This exclusive correlation between body

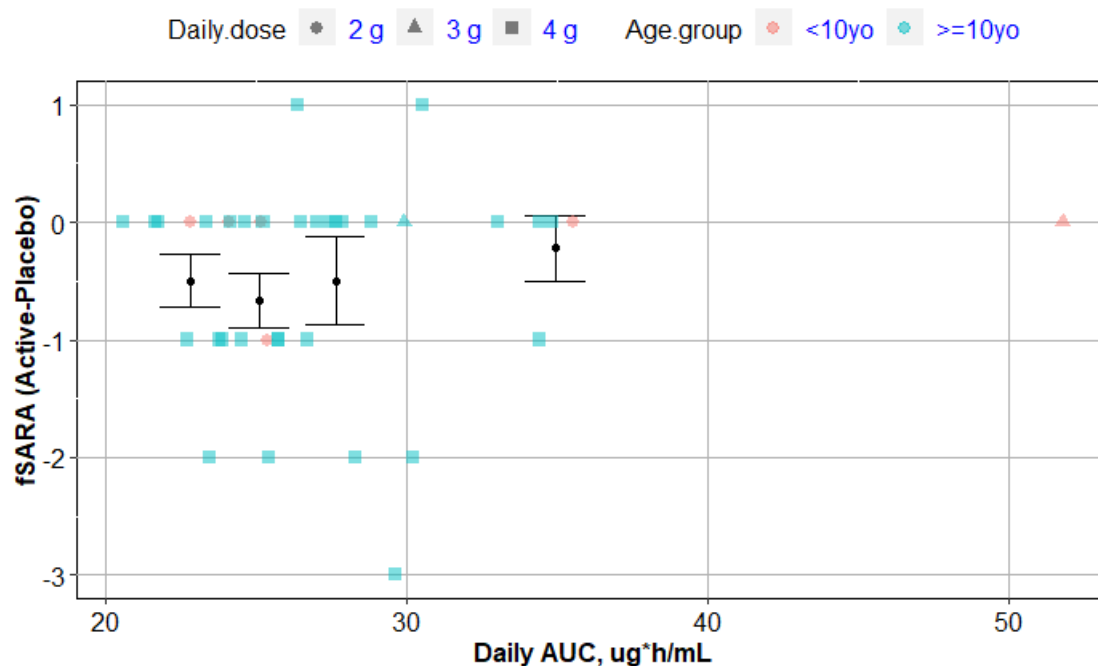
weight and dose levels does not allow covariate analysis to assess independent impacts of body size (e.g., weight) and dose level (1 gram versus 2 grams) on PK parameters, such as apparent clearance and relative bioavailability. If dose-proportionality data become available in the future, the PopPK model should be re-assessed accordingly.

(b) (4)

### Exposure-Response Analysis

Reviewer conducted E-R analysis for Agency-recommended rescored scale for the assessment and rating of ataxia (SARA) (functional SARA) based on the data from 38 subjects who had both efficacy evaluation and evaluable PK data in Trial IB1001-301. The exposure metric used for E-R analysis was daily AUC at steady state derived based on the individual predicted PK parameters (empirical bayes estimates) following the dosing regimen received during phase 3 study. No apparent E-R relationship for efficacy endpoint was observed ([Figure 27](#)). Due to the limited event rate for each treatment-emergent adverse event (Section 7.6), E-R analysis for safety was not performed.

**Figure 27. Exposure-Response for fSARA**



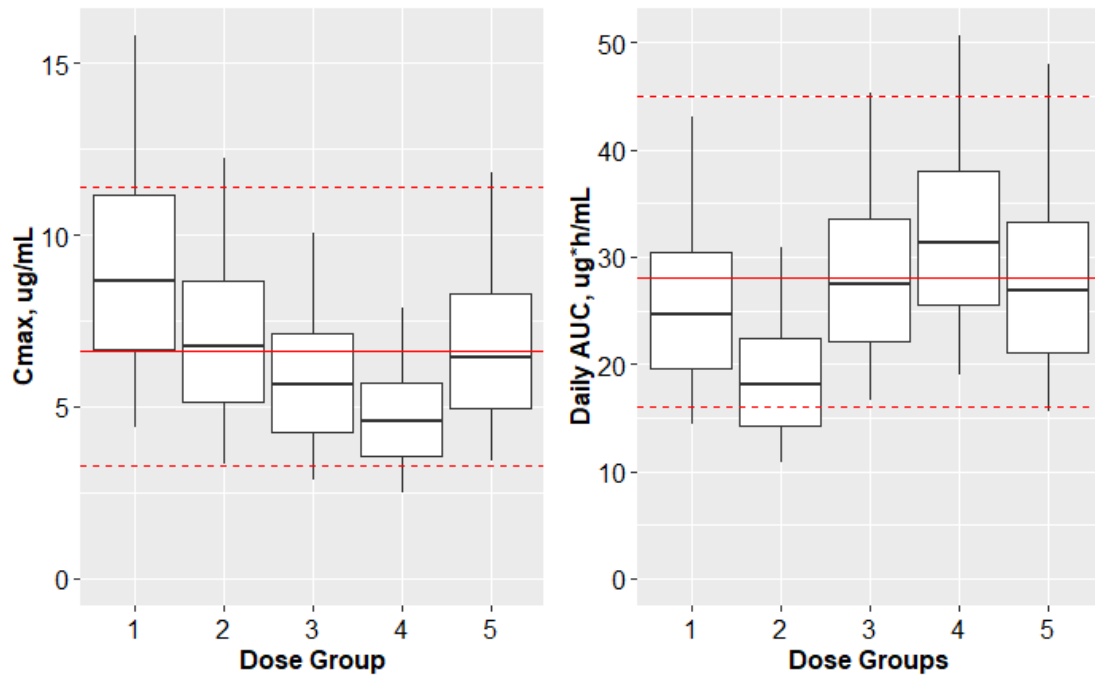
**Evaluation of Dosing Regimen**

The Applicant's proposed dosing regimen is based on (b) (4) body weight. (b) (4)

To estimate steady state PK profiles of levacetylleucine following the proposed dosing regimen, PopPK simulations were conducted using the reviewer's PopPK model, which is similar to the Applicant's. As body weight was the only significant covariate included in the PopPK model, simulations were conducted in virtual populations, each of which includes 1000 subjects whose body weight was sampled from uniformly distributed values within each body weight group. To generate the reference range for comparison, PopPK simulation was conducted based on a virtual NPC population (n=1000) sampled from the subjects with NPC from Trials IB1001-201 and IB1001-301. The red lines in [Figure 28](#) to [Figure 30](#) present 5<sup>th</sup>, mean, and 95<sup>th</sup> percentiles of the reference PK exposures ( $C_{max}$  and daily AUC).

The simulations show that PK exposure metrics ( $C_{max}$ , and daily AUC) are generally similar across body weight groups 15 to <25 kg (dose group 3), 25 to <35 kg (dose group 4), and  $\geq 35$  kg (dose group 5). The proposed dosing regimens for patients weighing  $\geq 15$  kg are deemed adequate and supported by the efficacy and safety findings from Trial IB1001-301, and the similar PK exposures across body weight groups.

**Figure 28. Applicant's Proposed Dosing and the Simulated PK Exposures by Weight Group**



Source: Reviewer's Analysis

For each boxplot, the whisker presents 5<sup>th</sup>-95<sup>th</sup> percentiles, and the box presents 25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentiles of the simulated exposure metrics. The red lines present 5<sup>th</sup>, mean, and 95<sup>th</sup> percentiles of the reference PK exposure.

Abbreviations: AUC = area under the concentration-time curve;  $C_{max}$  = maximum plasma concentration; PK = pharmacokinetic

(b) (4)

## 14.6. Pharmacogenetics

No pharmacogenetics assessment was conducted.

## 15. Study/Trial Design

Not applicable.

## 16. Efficacy

### 16.1. Trial IB1001-201

#### 16.1.1. Criteria To Select Primary Anchor Test for CI-CS

The procedures for selecting the primary anchor test were defined in an administration and scoring manual for clinical impression of change in severity (CI-CS) Version 3, dated January 21, 2020. At Visit 1, the Investigating Physician selected either the 8-meter walk test (8MWT) or the 9-Hole Peg Test of the dominant hand (9HPT-D) for each subject based on the subject's performance at Visit 1 on the 8MWT, the Gait subtest of the SARA, the 9HPT-D, and a cognitive assessment. Examples of standard cognitive assessments include the Montreal Cognitive Assessment or the Mini-Mental State Examination.

The default selection of the 8MWT or 9HPT-D was based on the following criteria:

The 8MWT was selected as the default anchor test if the subject's:

- Score on the SARA Gait subtest was 2 to 7, or
- Time on the 9HPT-D was <20 seconds or >150 seconds.

The 9HPT-D was selected as the default anchor test if the subject's:

- Score on the SARA Gait subtest was 0, 1, or 8, or
- Time on the 9HPT-D was  $\geq 20$  seconds and  $\leq 150$  seconds.

If the subject's score on the SARA Gait subtest was 2 to 7, and the time on the 9HPT-D was  $\geq 20$  seconds and  $\leq 150$  seconds, the Investigating Physician had to determine whether improvement in functional aspect of gait or upper arm extremity were more clinically meaningful for the subject. In addition, when selecting the primary anchor test, the Investigating Physician could elicit from subjects and their family/caregivers which was their preferred or most relevant outcome for seeing improvement.

### 16.1.2. Other Efficacy Endpoints

The key secondary endpoints for the parent study of Trial IB1001-201 were as follows:

- The individual components of the primary endpoint (CI-CS from Visit 2 to Visit 4 and CI-CS from Visit 4 to Visit 6).
- Difference in the blinded rater's Clinical Impression of Severity values from baseline to end of treatment and from the end of treatment to the end of washout.
- Measurement of change in performance of the CI-CS score of either the 9HPT-D or the 8MWT reclassified to a 3-point scale.
- An evaluation of the CI-CS for the test (9HPT-D or 8MWT) that was not selected as the primary anchor test.

Secondary endpoints for the parent study of Trial IB1001-201 were as follows:

- Spinocerebellar ataxia functional index (SCAFI)
- SARA
- European Quality of Life, 5-Dimension, 5-Level for subjects aged  $\geq 18$ ; European Quality of Life, 5-Dimension, Youth for subjects aged 6 to 17 years (2 parts: the European Quality of Life visual analogue scale and the European Quality of Life descriptive system)
- Modified disability rating scale (mDRS)
- Clinical global impression scale of severity (CGI-S) by the treating physician; clinical global impression scale of severity by the caregiver; clinical global impression scale of severity by the subject
- Clinical Global Impression of Change by the treating physician; Clinical Global Impression of Change by the caregiver; Clinical Global Impression of Change by the subject

#### **SARA**

For the modified intent-to-treat population, the mean change in SARA total score during the treatment period (Visit 4 versus Visit 2) was -1.2 (SD: 2), indicating an improvement in SARA score with levacetylleucine. The mean change during the washout period (Visit 6 versus Visit 4) was 1.4 (SD: 2.6), indicating a deterioration in the subjects' condition at the end of the washout period.

## 16.2. Trial IB1001-301: Other Efficacy Endpoints

### **SCAFI**

The SCAFI is composed of a timed 8MWT to be carried out at maximum speed, the 9-Hole Peg Test (which evaluates both the dominant and non-dominant hand), and the performance auditory-perceptual assessment rate to evaluate speech performance. The 8MWT and 9-Hole Peg Test are measured in 0.1 second, and a lower time indicates a clinical improvement. The performance auditory-perceptual assessment test evaluates the severity of dysarthria, and higher score indicates a clinical improvement. After the assessment, raw scores were transformed into reciprocals and converted into subtest Z-scores. The final SCAFI was then generated as the arithmetic mean of all 3 Z-scores. Following the primary analysis method, the estimated treatment difference between levacetylleucine and placebo in SCAFI total score was 0.07 (95% confidence interval [CI]: 0.0, 0.15), indicating more improvement in the levacetylleucine treatment period.

### **mDRS**

The mDRS consists of 6 domains (ambulation, manipulation, seizures, language, swallowing, and ocular movements) and the scale ranges from 0 to 24, where 0 is the best neurological status and 24 is the worst. The mDRS composite score is calculated as the sum of the 6 components divided by 24, so is on a 0 to 1 scale.

In the intent-to-treat population, the mean baseline mDRS composite score was 0.44 (SD 1.7) in the levacetylleucine-placebo sequence and was 0.52 (SD 0.11) in the placebo-levacetylleucine sequence. The estimated treatment difference using the primary analysis method was -0.02 (95% CI: -0.04, -0.00), indicating improvement in mDRS composite score with levacetylleucine compared to placebo.

### **5DNPCCSS**

The 5-domain Niemann-Pick disease type C clinical severity scale sum score is defined as a composite score of 5 major domains (ambulation, speech, swallow, fine motor skills, and cognition) in Niemann-Pick disease type C clinical severity scale. Scoring of each domain ranges from 0 to 5. A lower score indicates a clinical improvement. See Section [16.3](#) for a scoring form. The estimated treatment difference based on the mixed model for repeated measures used in the primary analysis was -0.3 (95% CI: -0.74, 0.15) for the mean change from baseline in 5-domain Niemann-Pick disease type C clinical severity scale total score ([Table 86](#)).

**Table 86. Summary of 5DNPCSS by Treatment Sequence, Trial IB1001-301**

| <b>Parameter</b>                                                       | <b>Sequence 1<br/>N=30</b> | <b>Sequence 2<br/>N=30</b> |
|------------------------------------------------------------------------|----------------------------|----------------------------|
| Baseline (Visit 2)                                                     | N=30                       | N=30                       |
| Mean (SD)                                                              | 10.1 (4.78)                | 12.07 (4.53)               |
| Median (min, max)                                                      | 9 (3, 21)                  | 10.5 (6, 21)               |
| Change from baseline in Period 1 (Visit 4)                             | N=29                       | N=30                       |
| Mean (SD)                                                              | 0.17 (1.51)                | -0.13 (1.11)               |
| Median (min, max)                                                      | 0 (-3, 6)                  | 0 (-3, 3)                  |
| Change from baseline in Period 2 (Visit 6)                             | N=28                       | N=30                       |
| Mean (SD)                                                              | 0.54 (1.79)                | -0.63 (2.06)               |
| Median (min, max)                                                      | 0 (-2, 6)                  | -0.5 (-6, 6)               |
| Estimated mean change from baseline in 5DNPCSS Score (SE) <sup>1</sup> |                            |                            |
| Levacetylleucine                                                       |                            | -0.16 (0.21)               |
| Placebo                                                                |                            | 0.13 (0.22)                |
| Levacetylleucine–placebo (95% CI)                                      |                            | -0.30 (-0.74, 0.15)        |

Source: The statistical review team's analysis based on adnpccss.xpt located at

\\CDSESUB1\evsprod\NDA219132\0001\m5\datasets\lib1001-301\analysis\adam\datasets

Subjects in Sequence 1 received levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II. Subjects in Sequence 2 received placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II.

<sup>1</sup> MMRM adjusting for period, sequence, treatment, baseline value, and baseline-period interaction.

NPC-CSS was assessed at baseline (Visit 2), the end of Treatment Period I (Visit 4), and the end of Treatment Period II (Visit 6).

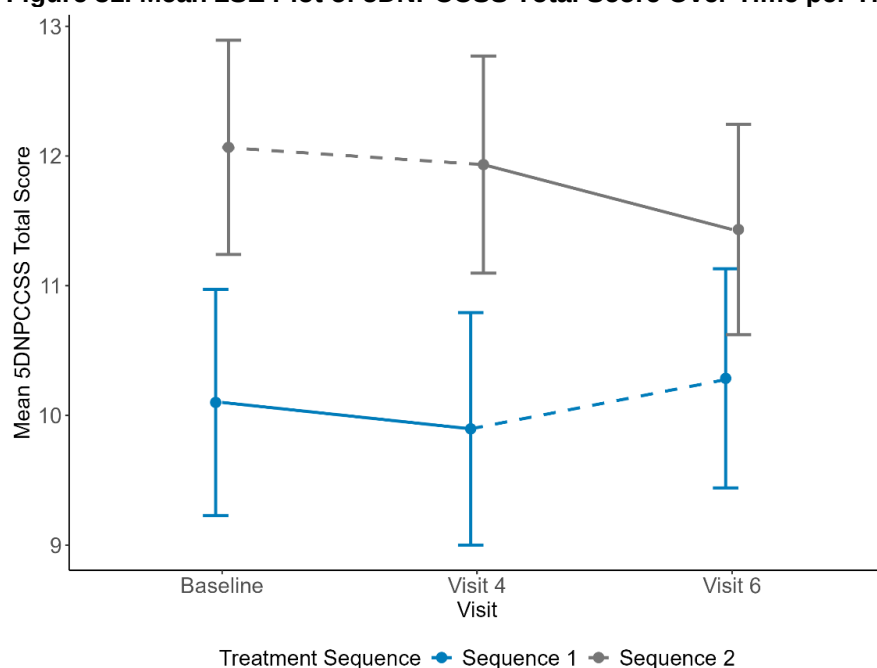
The 5-domain NPC-CSS (5DNPCSS) includes 5 major domains (ambulation, cognition, fine motor, speech, and swallowing). The score range is 0 to 25, where 0 is the best neurological status.

Last observation carried forward (LOCF) approach was not used for descriptive summaries and the MMRM.

Abbreviations: CI = confidence interval; 5DNPCSS = 5-domain Niemann-Pick disease type C clinical severity scale; max = maximum; min = minimum; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error

The estimated treatment difference using a two-sample t-test based on only Period I data was 0.34 (95% CI: -0.38, 1.06) favoring placebo. As shown in [Figure 31](#), subjects experienced more worsening when receiving placebo or improvement when receiving levacetylleucine during Treatment Period II compared to Treatment Period I, and thus an overall treatment effect using within-subject comparison favored levacetylleucine.

**Figure 31. Mean  $\pm$ SE Plot of 5DNPCSS Total Score Over Time per Treatment Sequence**



Source: The statistical review team's analysis based on adnpccss.xpt located at [\\CDSESUB1\evsprod\NDA219132\0001\m5\datasets\lib1001-301\analysis\adam\datasets](#). NPC-CSS was assessed at baseline (Visit 2), the end of Treatment Period I (Visit 4), and the end of Treatment Period II (Visit 6). The 5-domain NPC-CSS (5DNPCSS) includes 5 major domains (ambulation, cognition, fine motor, speech, and swallowing). The score range is 0 to 25, where 0 is the best neurological status. Subjects in Sequence 1 received levacetylleucine in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II. Subjects in Sequence 2 received placebo in Treatment Period I, followed by immediate crossover to levacetylleucine in Treatment Period II. The solid lines represent treatment period with levacetylleucine; the dashed lines represent treatment period with placebo. No last observation carried forward (LOCF) approach was used. Abbreviation: SE = standard error

[Table 87](#) shows the review team's analyses based on within-subject treatment differences in 58 subjects who completed both Visit 4 and Visit 6 assessments. Among the 58 completers, 22 (38%) subjects had a treatment difference favoring levacetylleucine, 11 (19%) subjects had a treatment difference favoring placebo, and 0 (43.1%) subjects had a treatment difference of zero score. The overall estimated treatment difference was -0.43 (95% CI: -0.86, -0.02) with a p-value of 0.08 based on a nonparametric sign test.

**Table 87. Results of Within-Subject Treatment Difference (Levacetylleucine – Placebo) in 5DNPCSS Total Score (58 Completers)**

| Treatment Difference                                                      | -6           | -4          | -3          | -2           | -1           | 0             | 1           | 2            | 3           |
|---------------------------------------------------------------------------|--------------|-------------|-------------|--------------|--------------|---------------|-------------|--------------|-------------|
| n (%)                                                                     | 1<br>(1.7%)  | 1<br>(1.7%) | 4<br>(6.9%) | 8<br>(13.8%) | 8<br>(13.8%) | 25<br>(43.1%) | 3<br>(5.2%) | 6<br>(10.3%) | 2<br>(3.4%) |
| Percent of subjects with a treatment difference favoring levacetylleucine | 38%          |             |             |              |              |               |             |              |             |
| 95% CI <sup>1</sup>                                                       | 0.26, 0.5    |             |             |              |              |               |             |              |             |
| Mean (SD)                                                                 | -0.43 (1.69) |             |             |              |              |               |             |              |             |
| 95% CI <sup>1</sup>                                                       | -0.86, -0.02 |             |             |              |              |               |             |              |             |

Source: The statistical review team's analysis based on adnpccss.xpt located at [\\CdseSub1\evsprod\NDA219132\0001\m5\datasets\lib1001-301\analysis\adam\datasets](#)

<sup>1</sup> Produced using a bootstrap method of sampling (10000 resampling datasets).

Abbreviations: CI = confidence interval; n = number of subjects with given characteristics; SD = standard deviation

### **Correlations Between SARA, mSARA, and fSARA Total Scores**

Both the functional scale for the assessment and rating of ataxia (fSARA) and the modified scale for the assessment and rating of ataxia (mSARA) are based on the modification to the original SARA. Using all available visits for 60 randomized subjects, the estimated Spearman's rank correlation coefficient (Spearman's  $\rho$ ) between SARA total score and fSARA total score was 0.94 (p-value <0.001). The estimated Spearman correlation between mSARA total score and fSARA total score was 0.89 (p-value <0.001). The estimated Spearman correlation between mSARA total score and SARA total score was 0.98 (p-value <0.001).

### **Correlations Between SARA, mDRS, and NPC-CSS in Ambulation and Speech Domains**

The ambulation and speech domains of mDRS and NPC-CSS are measured in a similar manner to the SARA. [Table 88](#) demonstrates that the three instruments are significantly correlated in total and domain-specific scores among 58 subjects who completed Visit 2, Visit 4, and Visit 6 assessments.

**Table 88. Estimated Spearman Correlations Between fSARA, mDRS, and NPC-CSS by Age Group**

| Domain Instruments | 4 to 9 Years Old<br>(N=7) | 10 Years and Older<br>(N=53) | Overall<br>(N=60) |
|--------------------|---------------------------|------------------------------|-------------------|
| Total              |                           |                              |                   |
| fSARA:mDRS         | 0.56**                    | 0.84***                      | 0.81**            |
| fSARA:5DNPPCCSS    | 0.60**                    | 0.74***                      | 0.72***           |
| mDRS:5DNPPCCSS     | 0.94***                   | 0.86***                      | 0.87***           |
| Gait               |                           |                              |                   |
| fSARA:mDRS         | 0.37                      | 0.80***                      | 0.77***           |
| fSARA: 5DNPPCCSS   | 0.41                      | 0.77***                      | 0.76***           |
| mDRS: 5DNPPCCSS    | 0.93***                   | 0.89***                      | 0.88***           |
| Speech             |                           |                              |                   |
| fSARA:mDRS         | 0.81***                   | 0.74***                      | 0.75***           |
| fSARA: 5DNPPCCSS   | 0.45*                     | 0.82***                      | 0.78***           |
| mDRS: 5DNPPCCSS    | 0.49*                     | 0.72***                      | 0.69***           |

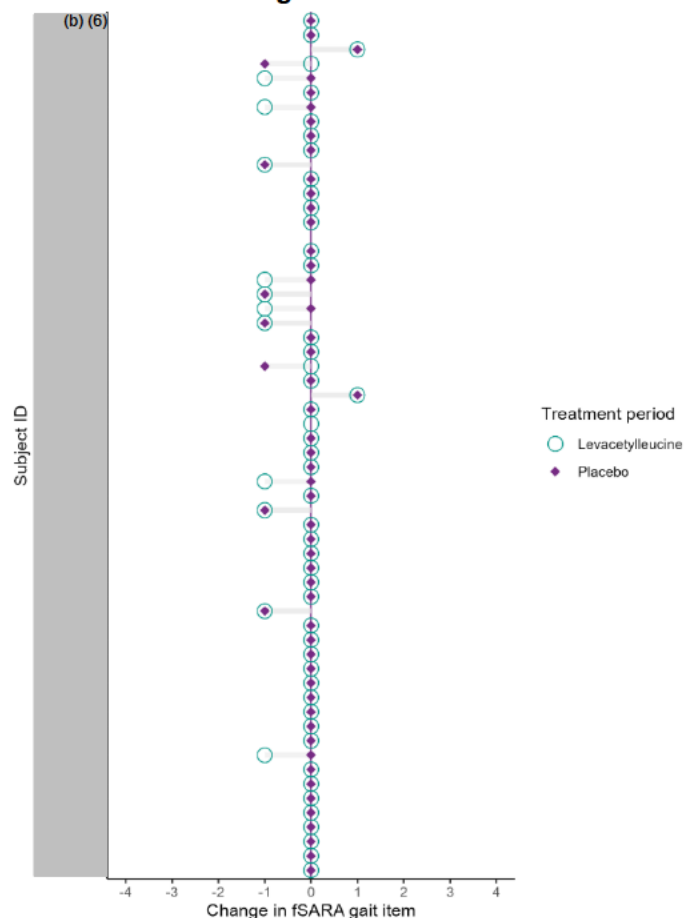
Source: The statistical review team's analysis based on admrs.xpt, adnpccss.xpt located at [\\Cdsub1\evsprod\NDA219132\0001\m5\datasets\lib1001-301\analysis\adam\datasets](#) and [adsara2.xpt](#) located at [\\Cdsub1\evsprod\NDA219132\0011\m5\datasets\lib1001-301\analysis\adam\datasets](#)  
No last observation carried forward (LOCF) approach was used. Scores of three instruments at Visit 2, Visit 4, and Visit 6 were used to estimate correlations based on Spearman's  $\rho$ .  
P-values are presented as \* if p-value <0.05, \*\* if p-value <0.01, \*\*\* if p-value <0.001.  
Abbreviations: 5DNPPCCSS = 5-domain Niemann-Pick disease type C clinical severity scale; fSARA = functional Scale for the Assessment and Rating of Ataxia; mDRS = modified disability rating scale; N = number of subjects in treatment sequence; NPC-CSS = NPC type C clinical severity scale

Using the same visualization as [Figure 8](#), [Figure 32](#) to [Figure 35](#) display the dumbbell plots of change from Baseline to end of the treatment period (i.e., Visit 4 or Visit 6) in the four domains of fSARA.

Specifically, as shown in [Figure 32](#), for gait, most subjects (74.1%), regardless of period, experienced no change over the course of treatment. Approximately 10.3% of subjects experienced clinically meaningful improvement (i.e., at least 1-point improvement) while receiving levacetylleucine but did not experience a clinically meaningful improvement in gait while in the placebo period; 3.5% of subjects had a clinically meaningful improvement in the gait domain while in the placebo period but did not while in the levacetylleucine period; 77.6% of subjects did not have a clinically meaningful improvement in gait while in the

levacetylleucine period or in the placebo period; 8.6% of subjects had a clinically meaningful improvement in gait while receiving levacetylleucine and while receiving placebo.

**Figure 32. Dumbbell Plot of Change From Baseline to End of Treatment (i.e., Visit 4 or Visit 6) in the Gait Domain Using fSARA**



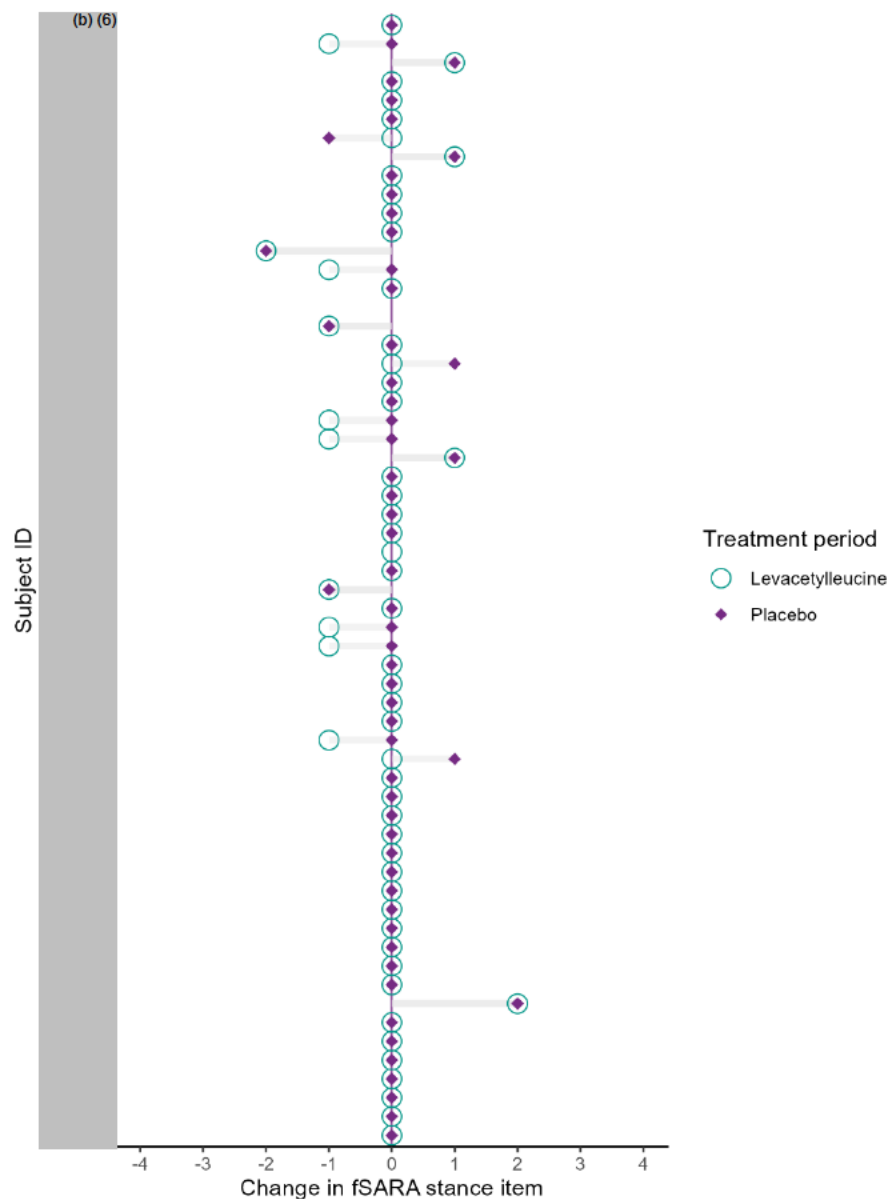
Source: Reviewer's Figure using adsara2.xpt

Abbreviation: fSARA = functional Scale for the Assessment and Rating of Ataxia

For the stance domain, 12.1% of the subjects had clinically meaningful improvement while receiving levacetylleucine but did not have a clinically meaningful improvement while in the placebo period; 1.7% of subjects improved at least 1-point while in the placebo period but did not in the levacetylleucine period; 81.0% of subjects did not have at least 1-point improvement

while in the levacetylleucine period or in the placebo period; 5.2% of subjects had clinically meaningful improvement while receiving levacetylleucine and while receiving placebo.

**Figure 33. Dumbbell Plot of Change From Baseline to End of Treatment (i.e., Visit 4 or Visit 6) in the Stance Domain Using fSARA**



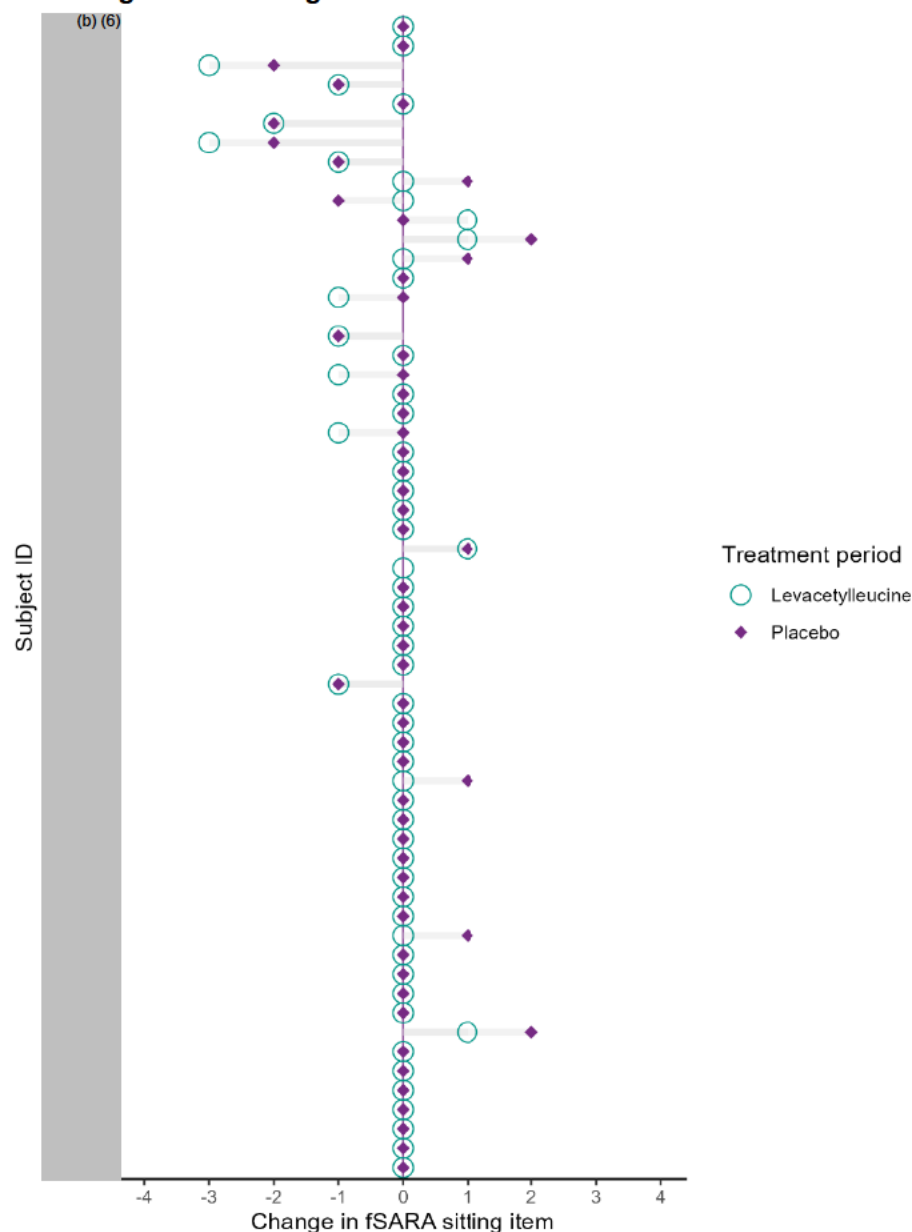
Source: Reviewer's Figure using adsara2.xpt

Abbreviation: fSARA = functional scale for the Assessment and Rating of Ataxia

For the sitting domain, 5.2% of the subjects had clinically meaningful improvement while receiving levacetylleucine but did not have at least 1-point improvement while in the placebo period; 1.7% of subjects improved at least 1-point while on placebo but did not in the levacetylleucine period; 81.0% of subjects did not have at least 1-point improvement while in the

levacetylleucine period or in the placebo period; 12.1% of subjects had clinically meaningful improvement while receiving levacetylleucine and while receiving placebo.

**Figure 34. Dumbbell Plot of Change From Baseline to End of Treatment (i.e., Visit 4 or Visit 6) in the Sitting Domain Using fSARA**



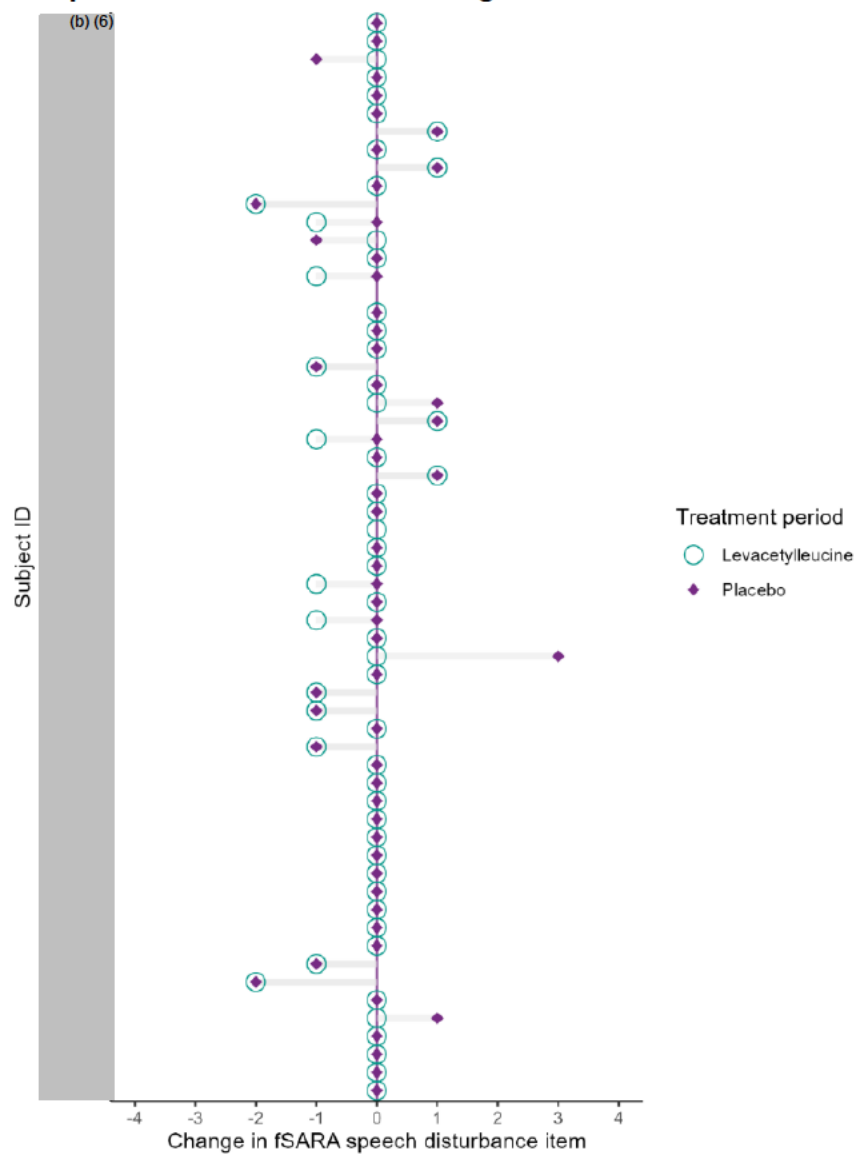
Source: Reviewer's Figure using adsara2.xpt

Abbreviation: fSARA = functional Scale for the Assessment and Rating of Ataxia

For the speech disturbance domain, 8.6% of the subjects had clinically meaningful improvement while receiving levacetylleucine but did not have at least 1-point improvement while in the placebo period; 3.5% of subjects improved at least 1-point while in the placebo period but did not in the levacetylleucine period; 75.9% of subjects did not have at least 1-point improvement

while in the levacetylleucine period or placebo period; 12.0% of subjects had clinically meaningful improvement while receiving levacetylleucine and while receiving placebo.

**Figure 35. Dumbbell Plot of Change From Baseline to End of Treatment (i.e., Visit 4 or Visit 6) in the Speech Disturbance Domain Using fSARA**

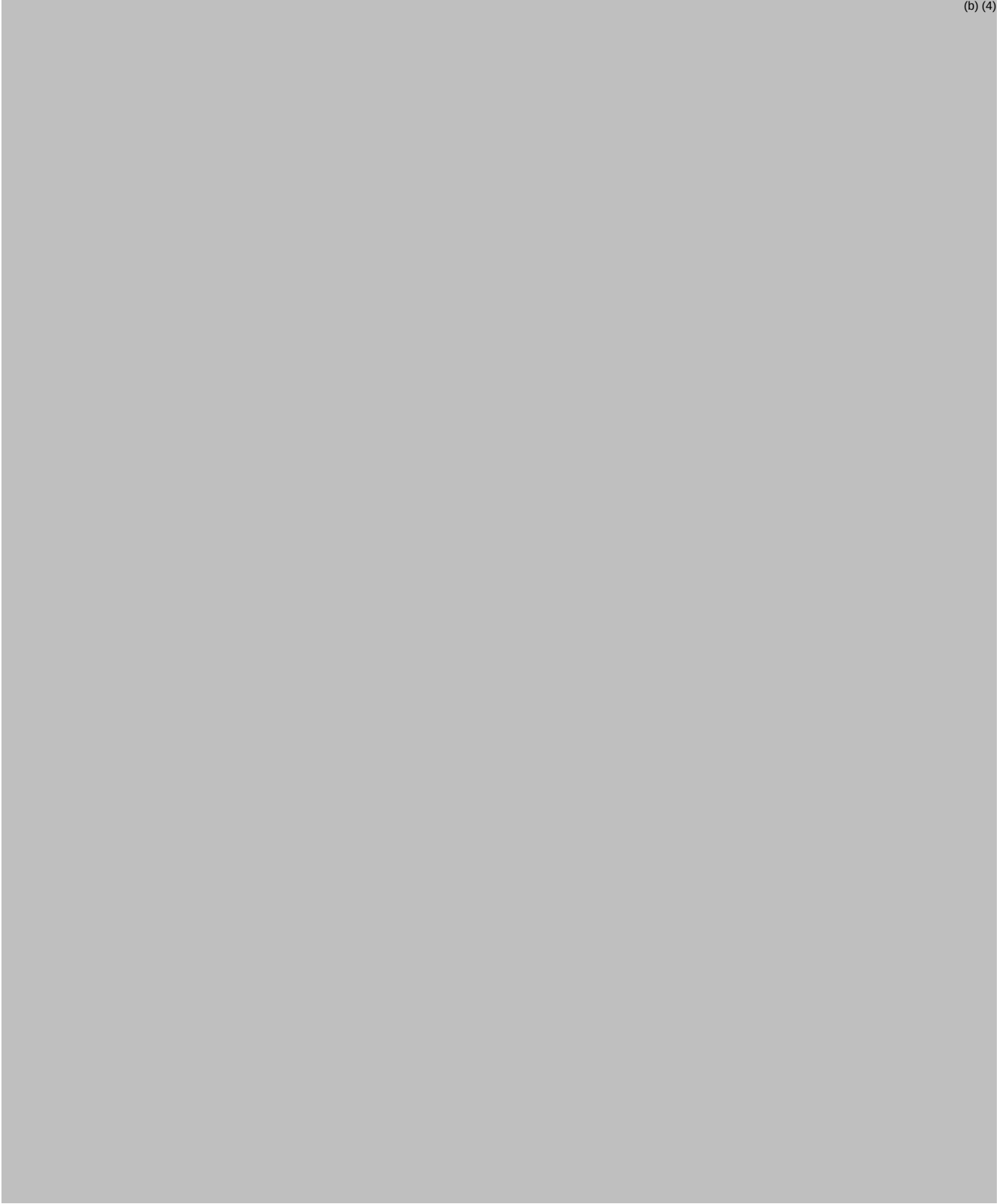


Source: Reviewer's Figure using adsara2.xpt

Abbreviation: fSARA = functional Scale for the Assessment and Rating of Ataxia

### 16.3. Copy of the Scale for Assessment and Rating of Ataxia

(b) (4)



## 17. Clinical Safety

Not applicable. The safety analysis was conducted on individual studies rather than pooled studies.

## 18. Clinical Virology

Not applicable.

## 19. Clinical Microbiology

Not applicable.

## 20. Mechanism of Action / Drug Resistance

Not applicable.

## 21. Other Drug Development Considerations

Not applicable.

## 22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Trial IB1001-301 was an adequate and well-controlled trial and Trial IB1001-201 provided data that served as CE. Three clinical investigators, Drs. Gascon-Bayarri, Bremova-Ertl, and Martakis, were inspected in this NDA. During the clinical investigator inspections, source records documenting the following were reviewed and verified against the Applicant's data line listings:

- For Protocol IB1001-201: for all 10 participants enrolled by Dr. Gascon-Bayarri, the treating physician's CI-CS scores for the 9HPT-D or 8MWT and the central blinded rater's CI-CS scores for 9HPT-D or 8MWT (i.e., primary efficacy endpoint).
- For Protocol IB1001-301: for all 12 randomized participants at Dr. Bremova-Ertl's site and for all 9 randomized participants at Dr. Martakis' site, the mean change of mSARA (i.e., primary efficacy endpoint) and the original SARA (i.e., key secondary efficacy endpoint).

No discrepancies were noted. However, a data reliability concern was noted in the Visit 6 mSARA and SARA assessment for Subject (b) (6) (enrolled in Protocol IB1001-301 by Dr. Bremova-Ertl). The investigator noted in this subject that the mSARA/SARA was performed

remotely over videoconference using “WhatsApp” for Visit 6. In addition, the investigator performed the assessment on (b) (6) (Visit 6) but did not document the assessment and scores until (b) (6). The investigator also made multiple changes to the individual assessment domains on (b) (6) (see Clinical Inspection Summary for details).

A sensitivity analysis is recommended regarding the Visit 6 assessment for the mSARA, and SARA data generated from Subject (b) (6). Notwithstanding the above concern with how the data were documented for Subject (b) (6) in Protocol IB1001-301, the trials appear to have been conducted adequately. The study data, including the primary and key secondary efficacy endpoint data for the two trials (i.e., Protocols IB1001-201 and IB1001-301), generated by these three sites appear acceptable in support of the respective indication.

The review team concluded that inspection of these three clinical investigators was sufficient to assess the data quality and integrity. The Office of Scientific Investigations concluded that, other than the issues described above, the clinical data collected at the three sites appeared reliable. No significant trial conduct issues or regulatory violations were identified at any of the three sites.

See the Clinical Inspection Summary dated July 24, 2024 for additional details.

## 23. Labeling: Key Changes

This prescribing information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant’s draft PI (Table 89). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

**Table 89. Key Labeling Changes and Considerations**

| Full PI Sections <sup>1</sup> | Rationale for Major Changes to Finalized PI <sup>2</sup> Compared to Applicant’s Draft PI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BOXED WARNING                 | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 1 INDICATIONS AND USAGE       | <ul style="list-style-type: none"><li>Revised population of patients for indication (b) (4) to ≥15 kg as available data support use in patients at least 15 kg.</li><li>Added ‘neurological manifestations’ since efficacy was demonstrated on these NPC symptoms (see Section 6.3).</li></ul>                                                                                                                                                                                                                                                                             |
| 2 DOSAGE AND ADMINISTRATION   | <p><b>2.1 Important Recommendation Prior to AQNEURSA Treatment Initiation</b></p> <ul style="list-style-type: none"><li>Added statement to verify female of reproductive potential is not pregnant prior to initiating treatment due to embryofetal toxicity risk seen with this drug.</li></ul> <p><b>2.2 Recommended Dosage</b></p> <ul style="list-style-type: none"><li>Revised recommended dosage (b) (4) to actual body weight.</li><li>Included instructions on how and when to administer AQNEURSA relative to the ingestion of food or food substances.</li></ul> |

| Full PI Sections <sup>1</sup> | Rationale for Major Changes to Finalized PI <sup>2</sup> Compared to Applicant's Draft PI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                               | <ul style="list-style-type: none"> <li>• Determined population PK is not adequate to assess food effect. Included information pertaining to food in Section 14 and modified cross-reference (b) (4) to Section 14.</li> <li>• Clarified that for a 2-gram dose, 2 AQNEURSA packets should be used since there are 1.7 grams of drug product powder in each packet.</li> <li>• Moved reconstitution instructions to subsection 2.3.</li> <li>• Removed (b) (4) and used only body weight tiers in Table 1 (b) (4)</li> <li>• Removed proposed (b) (4)</li> <li>• For Table 1, included a footnote on the strength per packet (1 gram of API (levacetylleucine) to reduce redundancy within the table and deleted (b) (4) and used "gram" (b) (4) for consistency with strength statement on carton and container.</li> </ul> <p><b>2.3 Preparation and Administration Instructions</b></p> <ul style="list-style-type: none"> <li>• Revised subsection considering multiple packets and dosage form reclassification.</li> <li>• Changed (b) (4) to "packet" and (b) (4) to "suspension."</li> <li>• Agreed with 40 mL measurement as amount of liquid to be measured to mix drug product since the distribution plan for AQNEURSA involves a single specialty pharmacy and an appropriate measuring cup will be provided to patients.</li> </ul> |
| 4 CONTRAINDICATIONS           | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 5 WARNINGS AND PRECAUTIONS    | <p><b>5.1 Embryo-Fetal Toxicity</b></p> <ul style="list-style-type: none"> <li>• Created subsection 5.1 due to risk of potential embryo-fetal toxicity observed in dose-range finding nonclinical studies.</li> <li>• Included pregnancy testing and contraception for females of reproductive potential along with language for the HCP to consider the benefits/risks of continuation vs. discontinuation of treatment during pregnancy. Pregnancy testing and contraceptive use for a certain duration is recommended. The applicability of this warning may be revisited when safety risks to females of reproductive potential and the fetus are determined.</li> <li>• Included duration of 7 days for contraception based on short half-life of the product which has concerns for EF toxicity. Refer to Guidance for Industry: <i>Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations</i> (May 2019).</li> </ul> <p>(b) (4)</p>                                                                                                                                                                                                                                                                                                                                                                         |

| Full PI Sections <sup>1</sup>                                                                                                                                               | Rationale for Major Changes to Finalized PI <sup>2</sup> Compared to Applicant's Draft PI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6 ADVERSE REACTIONS                                                                                                                                                         | <ul style="list-style-type: none"> <li>Added a description of the overall clinical trial database from which the adverse reaction data were drawn to include duration of exposure to AQNEURSA (mean SD and range) with a cross-reference to Section 14 for full details.</li> <li>Revised Table 2 to include adverse reactions during Treatment Period 1 occurring in 2 or more patients.</li> <li>(b) (4) only adverse reactions causally related to the drug were included. (b) (4)</li> </ul> <p>(b) (4)</p> <ul style="list-style-type: none"> <li>Included laboratory finding of thrombocytopenia even though thrombocytopenia may be due to underlying disease and/or miglustat use because there were more subjects with thrombocytopenia on AQNEURSA than placebo during the trial.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 7 DRUG INTERACTIONS                                                                                                                                                         | <ul style="list-style-type: none"> <li>Added subsection 7.2 to include the effect of AQNEURSA on other drugs.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment) | <p><b>8.1 Pregnancy</b></p> <ul style="list-style-type: none"> <li>Revised Applicant-proposed language to align with Pregnancy and Lactation Labeling Rule.</li> <li>Added embryofetal risk under <u>Risk Summary</u> based on animal reproduction studies in pregnant rats and rabbits.</li> <li>Added header for <u>Animal Data</u> and included information on skeletal malformations seen from dose-range finding rat and rabbit embryo-fetal development studies.</li> </ul> <p><b>8.2 Lactation</b></p> <ul style="list-style-type: none"> <li>Revised Applicant proposed language to align with Pregnancy and Lactation Labeling Rule.</li> </ul> <p><b>8.3 Females and Males of Reproductive Potential</b></p> <ul style="list-style-type: none"> <li>Added header for <u>Pregnancy Testing</u> and included information that for females of reproductive potential, verification that patient is not pregnant should occur.</li> <li>Added header for <u>Contraception</u> and included information that females of reproductive potential should use effective contraception during treatment with AQNEURSA and for 7 days after the last dose if DRUG is discontinued.</li> </ul> <p><b>8.4 Pediatric Use</b></p> <ul style="list-style-type: none"> <li>Revised Applicant proposed language to align with the Guidance for Industry: <i>Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling</i> (<a href="#">March 2019</a>).</li> </ul> <p><b>8.5 Geriatric Use</b></p> <ul style="list-style-type: none"> <li>Revised Applicant proposed language to align with the Draft Guidance for Industry: <i>Geriatric Information in Human Prescription Drug and Biological Product Labeling</i> (<a href="#">September 2020</a>).</li> </ul> |

| Full PI Sections <sup>1</sup> | Rationale for Major Changes to Finalized PI <sup>2</sup> Compared to Applicant's Draft PI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9 DRUG ABUSE AND DEPENDENCE   | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 10 OVERDOSAGE                 | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 12 CLINICAL PHARMACOLOGY      | <p><b>12.1 Mechanism of Action</b></p> <ul style="list-style-type: none"> <li>Revised subsection to include that mechanism of action of levacetylleucine in treatment of NPC is unknown as data does not support stating otherwise.</li> </ul> <p><b>12.2 Pharmacodynamics</b></p> <ul style="list-style-type: none"> <li>Revised subsection per 21 CFR 201.57(c)(13)(i)(B) which required that 'Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known.' If the information is unknown, then this subsection must contain a statement about the lack of information.</li> </ul> <p><b>12.3 Pharmacokinetics</b></p> <ul style="list-style-type: none"> <li>Added SD value, median, max and min.</li> <li>Removed (b) (4)</li> <li>Included total body clearance under <u>Elimination</u> heading.</li> <li>Added subheading <u>Metabolism</u>. (b) (4)</li> <li>Included statement under heading of <u>Specific Populations</u> that the effect of renal impairment, hepatic impairment, or pregnancy on levacetylleucine pharmacokinetics is unknown.</li> <li>Added subheading for <i>Body Weight</i> to describe the body effect.</li> <li>Included specific CYP enzymes under the subheading <i>In Vitro Studies</i>.</li> <li>Removed (b) (4)</li> </ul> |
| 13 NONCLINICAL TOXICOLOGY     | <ul style="list-style-type: none"> <li>Clarified that animal studies to evaluate the carcinogenic potential of levacetylleucine have not been conducted.</li> <li>Added a statement that levacetylleucine was not mutagenic or clastogenic in a battery of in vitro and in vivo assays (see Section <a href="#">5.1</a> and <a href="#">13</a>).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| Full PI Sections <sup>1</sup>                                                                               | Rationale for Major Changes to Finalized PI <sup>2</sup> Compared to Applicant's Draft PI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 14 CLINICAL STUDIES                                                                                         | <ul style="list-style-type: none"> <li>• Included NCT numbers.</li> <li>• Included number enrolled, who completed the study, and who discontinued from the study.</li> <li>• Included baseline demographics including age distribution, biological sex, racial groups, and ethnic groups.</li> <li>• Included baseline disease characteristics for NPC to help interpret and apply the study results.</li> <li>• Removed (b) (4)</li> <li>• (b) (4)</li> <li>revised the description of the original SARA and fSARA to further clarify the differences between these 2 scales.</li> <li>• Labeled the domains of the SARA comprising gait, stance, sitting, and speech. Rescored SARA so that all domains are equally represented in the total score and where a 1-point change can be clearly interpreted.</li> <li>• Revised Table 4 to show efficacy results based on recommended fSARA and information provided by treatment sequence.</li> <li>• Described the mean change from baseline per period within each treatment sequence in the text together with mean fSARA score <math>\pm</math>SE by time and sequence plot.</li> <li>• Used the mean <math>\pm</math>SE plots of the fSARA in Figure 1.</li> <li>• Removed (b) (4)</li> </ul> |
| 17 PATIENT COUNSELING INFORMATION                                                                           | <ul style="list-style-type: none"> <li>• Revised for consistency with the revisions to the full prescribing information while focusing on major risks of the drug (e.g., W&amp;P) and when appropriate, how the patient may mitigate or manage these risks.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) | <p><b>3 Dosage Forms and Strengths</b></p> <ul style="list-style-type: none"> <li>• Changed (b) (4) to packet.</li> </ul> <p><b>11 Description</b></p> <ul style="list-style-type: none"> <li>• Included statement on the solubility of the drug substance.</li> </ul> <p><b>16 How Supplied/Storage and Handling</b></p> <ul style="list-style-type: none"> <li>• Included the nonproprietary name.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

<sup>1</sup> Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

<sup>2</sup> For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Abbreviations: API = active pharmaceutical ingredient; AUC = area under the concentration-time curve; BID = twice daily; CGI-I = clinical global impression scale of improvement;  $C_{max}$  = maximum plasma concentration; COVID-19 = coronavirus disease of 2019; CYP = cytochrome P450; fSARA = functional Scale for the Assessment and Rating of Ataxia; HCP = healthcare provider; mDRS = modified disability rating scale; SARA = Scale for the Assessment and Rating of Ataxia; NPC = Niemann-Pick disease type C; PI = Prescribing Information; PK = pharmacokinetics; QD = once a day; SD = standard deviation; SE = standard error; TID = three times daily

## 23.1. Approved Labeling Types

Upon approval of this application the following labeling documents will be FDA-approved:

- PI
- Instructions For Use

## 24. Postmarketing Requirements and Commitments

### **Nonclinical**

#### **PMR #1**

Daily oral gavage embryofetal development toxicity and TK study with levacetylleucine in rodent.

Final Study Report: 12/2024

#### **PMR #2**

Daily oral gavage EFD toxicity and TK study with levacetylleucine in non-rodent.

Final Study Report: 12/2024

#### **PMR #3**

Daily oral gavage juvenile toxicity and TK study with levacetylleucine in rodent.

Study Complete: 09/2024

Final Study Report: 05/2025

#### **PMR #4**

Daily oral gavage fertility and early embryonic development toxicity study with levacetylleucine in rodent.

Final Study Report: 12/2024

#### **PMR #5**

Daily oral gavage pre- and postnatal development toxicity study with levacetylleucine in rodent.

Final Study Report: 01/2025

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**PMR #6**

26-week carcinogenicity study with levacetylleucine in rasH2 mice (with TK evaluations, if not supported by data in DRF)

1. Special protocol assessment for 26-week rasH2 mouse carcinogenicity study
  - a. 4-week daily oral gavage toxicity and TK dose-range finding study with IB1001 in the wild-type rasH2 mice.
  - b. Final protocol for 26-week rasH2 mouse carcinogenicity

Study Completion: 09/2025

Final Report Submission: 06/2026

**PMR #7**

2-year carcinogenicity study with levacetylleucine in rats (with toxicokinetics if not supported by data in DRF study)

1. Special protocol assessment for 2-year rat carcinogenicity study
2. Final protocol for 2-year rat carcinogenicity study
3. Alternatively, a weight-of-evidence risk assessment of carcinogenicity as outlined in the International Council for Harmonisation S1B(R1) guideline to support.
  - a. A 2-year rat study is unnecessary based on a presumed absence of human carcinogenic risk and
  - b. A 2-year rat study is unnecessary based on a presumption of likely human carcinogenic risk.

Draft Protocol Submission: 03/ 2026

Final Protocol Submission: 06/2026

Study Completion: 12/2028

Final Report Submission: 12/2029

**Clinical Pharmacology**

**PMR #8**

A drug-drug interaction study to evaluate the effect of levacetylleucine on a probe substrate of P-gp to thoroughly assess its inhibitory potential and ensure patient safety.

Draft Protocol Submission: 03/2025

Final Protocol Submission: 09/2025

Study Completion: 09/2026

Final Report Submission: 09/2027

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### Postmarketing Commitment #9

A dedicated food effect study to evaluate food-drug interactions and its potential impact on PK of levacetylleucine.

Draft Protocol Submission: 12/2024

Final Protocol Submission: 03/2025

Study Completion: 09/2025

Final Report Submission: 03/2026

## 25. Financial Disclosure

**Table 90. Covered Clinical Studies: Trial IB1001-301, Trial IB1001-201**

|                                                                                                                                                                                                                        |                                         |                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                         | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant)        |
| Total number of investigators identified: Trial IB1001-301: 51, Trial IB1001-201: 29                                                                                                                                   |                                         |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): None                                                                                                             |                                         |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None                                                                                                                        |                                         |                                                                  |
| 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)): N/A |                                         |                                                                  |
| Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A                                                                                         |                                         |                                                                  |
| Significant payments of other sorts: N/A                                                                                                                                                                               |                                         |                                                                  |
| Proprietary interest in the product tested held by investigator: N/A                                                                                                                                                   |                                         |                                                                  |
| Significant equity interest held by investigator: N/A                                                                                                                                                                  |                                         |                                                                  |
| Sponsor of covered study: N/A                                                                                                                                                                                          |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements: N/A                                                                                                                        | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided: N/A                                                                                                                                           | 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): 0                                                                                                                                  |                                         |                                                                  |
| Is an attachment provided with the reason: N/A                                                                                                                                                                         | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request explanation from Applicant) |

## 26. References

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## Guidances

Draft Guidance for Industry: *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making* (April 2023), <https://www.fda.gov/media/166830/download>.

Draft Guidance for Industry: *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019), <https://www.fda.gov/media/133660/download>.

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Guidance for Industry: *Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice* (March 2019), <https://www.fda.gov/media/84949/download>.

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### **Other**

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## 27. Review Team

**Table 91. Reviewers of Integrated Assessment**

| <b>Role</b>                                                       | <b>Names</b>                                                                                                                                             |
|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Regulatory Project Manager                                        | Jenny Doan, MSN, BSN                                                                                                                                     |
| Chief Program Management Staff (CPMS)                             | Michael White, PhD                                                                                                                                       |
| OND Nonclinical Reviewer                                          | Saryu Goel, DVM, MVSc, MS, PhD, DABT, Senior Pharmacologist                                                                                              |
| Nonclinical Team Leader                                           | Shawna Weis, PhD, Lead Pharmacologist (Acting)                                                                                                           |
| Office of Clinical Pharmacology (OCP) Reviewers                   | Nayeem Hossain, PhD, Clinical Pharmacology Reviewer<br>Jihye Ahn, PharmD, Pharmacometrics Reviewer                                                       |
| OCP Team Leaders                                                  | Ruojing Li, PhD, Lead Pharmacokineticist<br>Jiang Liu, PhD, Associate Direct for Division of Pharmacometrics                                             |
| OPQ Application Team Leader                                       | Hamid Shafiei, PhD                                                                                                                                       |
| Clinical Reviewer                                                 | Maura Ruzhnikov, MD, FACMG                                                                                                                               |
| Clinical Team Leader                                              | Jacqueline Karp, MD                                                                                                                                      |
| Biometrics Reviewer                                               | Jung Won, PhD                                                                                                                                            |
| Biometrics Team Leader                                            | Yan Wang, PhD                                                                                                                                            |
| Biometrics Reviewer/Patient-Focused Statistical Scientists (PFSS) | Weimeng Wang, PhD                                                                                                                                        |
| Biometrics Team Leader/PFSS                                       | Monica Morell, PhD, Secondary Reviewer<br>Weiya Zhang, PhD, Supervisory Mathematical Statistician<br>Lili Garrard, PhD, Master Mathematical Statistician |
| Cross-Disciplinary Team Leader                                    | Jacqueline Karp, MD                                                                                                                                      |
| Division of Clinical Outcome Assessment (DCOA) Reviewer           | Dilorom Sass, PhD<br>Naomi Knoble, PhD, Associate Director                                                                                               |
| Labeling                                                          | Mona Patel, PharmD, RAC Associate Director Labeling                                                                                                      |
| Division Director (DCOA)                                          | David Reasner, PhD, Director                                                                                                                             |
| Division Director (pharm/tox)                                     | Kimberly Hatfield, PhD                                                                                                                                   |
| Deputy Division Director (OCP)                                    | Robert Schuck, PhD                                                                                                                                       |
| Division Director (Office of Biostatistics)                       | Nie Lie, PhD, Supervisory Mathematical Statistician                                                                                                      |
| Division Director (clinical)                                      | Catherine Pilgrim-Grayson, MD, MPH                                                                                                                       |
| Office Director                                                   | Janet Maynard, MD, MHS                                                                                                                                   |

Abbreviations: CPMS = chief program management staff; DCOA = Division of Clinical Outcome Assessment; OCP = Office of Clinical Pharmacology; OPQ = Office of Pharmaceutical Quality; PFSS = Patient-Focused Statistical Scientists

**Table 92. Additional Reviewers of Application**

| <b>Office or Discipline</b>                                              | <b>Names</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Biomedical Informatics                                                   | Linda Jeng, MD, MHS, Associate Director for Biomedical Informatics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Division of Neurology 1                                                  | Peggy Lazerow, MD, Clinical Reviewer<br>Emily Freilich, MD, Clinical Team Leader                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Division of Pediatrics and Maternal Health                               | Kristie Baisden, DO, Maternal Health Reviewer<br>Tamara Johnson, MD, MS, Maternal Health Team Leader<br>Ethan Hausman, MD, Pediatrics Reviewer<br>Shetarra Walker, MD, Pediatrics Team Leader<br>Meshaun Payne, PharmD, Regulatory Project Manager<br>Rosemary Addy, CPMS                                                                                                                                                                                                                                                                                        |
| Division of Rare Diseases and Medical Genetics                           | Yuliya Yasinskaya, MD, Deputy Director<br>Cheronda Cherry-France, RN, MHA, BSN, Safety<br>Regulatory Project Manager                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| New Drug Transition Team/IAMA Support                                    | Shuang (Sarah) Zhou, PhD, Clinical Data Scientist (CDS)<br>DeAngelo McKinley, PhD, CDS Team Leader<br>Jesse Taylor, Medical Editor-Writer<br>Irum Syed, PhD, Medical Editor-Writer<br>Priyanka Joseph, Medical Editor-Writer<br>Katharine Bradley, Medical Editor-Writer                                                                                                                                                                                                                                                                                         |
| Office of Medical Policy Initiatives/Division of Medical Policy Programs | Helen Young, PharmD, Regulatory Reviewer, Patient Labeling<br>Barbara Fuller, PharmD, Team Leader, Patient Labeling                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Office of Pharmaceutical Quality                                         | Hamid Shafiei, PhD, Application Team Leader<br>Teshara Bouie, PharmD, Regulatory Business Project Manager<br>Sam Bain, PhD, ONDP Drug Substance (DS) Assessor<br>Larry Perez, ONDP DS Team Leader<br>Donna Christner, PhD, ONDP, Branch Chief<br>Caroline Strasinger, PhD, ONDP, Drug Product (DP) Assessor<br>Lloyd Alfonso, PhD, Primary Reviewer, Process and Facility, OPMA<br>Prabhu Vaikunth, PhD, Team Leader, Process and Facility, OPMA                                                                                                                 |
| Office of Prescription Drug Promotion                                    | Carrie Newcomer, PharmD, MBA, Regulatory Reviewer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Office of Scientific Investigations                                      | Cheryl Grandinetti, MD, Clinical Reviewer<br>Phillip Kronstein, MD, Clinical Team Leader                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Office of Surveillance & Epidemiology                                    | Sally Peprah, PhD, Safety Evaluator, DEPI<br>Benjamin Booth, PhD, Team Leader, DEPI<br>Sali Mahmoud, PharmD, BCPS, Safety Evaluator, DMEPA<br>Tingting Gao, PharmD, Team Leader, DMEPA<br>Mohamed Mohamoud, PharmD, Safety Evaluator, DPV<br>Ivone Kim, MD, Clinical Reviewer, DPV<br>Carmen Cheng, MD, Team Leader, DPV<br>Theresa Ng, PharmD, Safety Evaluator, DRM<br>Yasmeen Abou-Sayed, PharmD, Team Leader, DRM<br>Baoguang Wang, PharmD, Clinical Data Science Analyst<br>Su-Lin Sun, RPh, PharmD, GWCPM, SRPM<br>Aleksander Winiarski, PharmD, RPh, CPMS |

Abbreviations: DEPI = Division of Epidemiology; DMEPA = Division of Medication Error Prevention and Analysis; IAMA = Integrated Assessment of Marketing Applications; ONDP = Office of New Drug Products; OPMA = Office of Pharmaceutical Manufacturing Assessment; OPQ = Office of Pharmaceutical Quality; DPV = Division of Pharmacovigilance; DRM = Division of Risk Management

## 27.1. Reviewer Signatures

**Table 27-93 Signatures of Reviewers**

| Discipline and Role                                                                                                                              | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Biostatistics<br>Discipline<br><br>Secondary Reviewer                                                                                            | Monica Morell<br><br>OB<br><br>DBIII                | Sections: 6.3.1.3,<br>16.3              | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Monica Morell</b> <b>Digitally signed by Monica Morell</b><br><br><b>Date: 9/24/2024 1:21 PM EDT</b><br><b>GUID: 2024924172156</b> |                                                     |                                         |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                                                                                              | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| CMC (OPQ/ONDP)<br>Discipline<br><br>Secondary Reviewer                                                                                           | Hamid Shafiei<br><br>OPQAI<br>DPQAVII               | Sections: 9                             | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Hamid Shafiei</b> <b>Digitally signed by Hamid Shafiei</b><br><br><b>Date: 9/24/2024 1:22 PM EDT</b><br><b>GUID: 2024924172217</b> |                                                     |                                         |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                                                                                             | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                           | Comments on<br>Recommendation to<br>Signatory |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| CMC (OPQ/ONDP)<br>Discipline<br>Primary Reviewer                                                                                                | Hamid Shafiei<br>OPQAII<br>DPQAVII                  | Sections: 9                             | Based on my<br>assessment of the<br>application:<br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Hamid Shafiei</b><br><b>Digitally signed by Hamid Shafiei</b><br><b>Date: 9/24/2024 1:22 PM EDT</b><br><b>GUID: 2024924172251</b> |                                                     |                                         |                                                                                                                                                                                                                                          |                                               |

| Discipline and Role                                                                                                                       | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                           | Comments on<br>Recommendation to<br>Signatory |
|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Associate Director<br>for Labeling<br>Discipline<br>Primary Reviewer                                                                      | Mona Patel<br>ORDPURM<br>DRDMG                      | Sections: 23                            | Based on my<br>assessment of the<br>application:<br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Mona Patel</b><br><b>Digitally signed by Mona Patel</b><br><b>Date: 9/24/2024 1:23 PM EDT</b><br><b>GUID: 2024924172313</b> |                                                     |                                         |                                                                                                                                                                                                                                          |                                               |

| Discipline and Role                                                          | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                                                    | Recommendation<br>to Signatory                                                                                                                                                                                                           | Comments on<br>Recommendation to<br>Signatory |
|------------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical Outcomes<br>Assessment<br>Reviewer Discipline<br>Secondary Reviewer | Naomi Knoble<br>ODES<br>DCOA                        | Sections: 3.1.1 Key<br>efficacy review<br>issues; 4 Patient<br>experience data, 16<br>Efficacy - create sub-<br>header sections for<br>COA | Based on my<br>assessment of the<br>application:<br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Naomi Knoble</b>                                               |                                                     | <b>Digitally signed by Naomi Knoble</b><br><br><b>Date: 9/24/2024 1:23 PM EDT</b><br><b>GUID: 2024924172344</b>                            |                                                                                                                                                                                                                                          |                                               |

| Discipline and Role                                          | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                       | Recommendation<br>to Signatory                                                                                                                                                                                                           | Comments on<br>Recommendation to<br>Signatory |
|--------------------------------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical<br>Pharmacology<br>Discipline<br>Secondary Reviewer | Ruojing Li<br>OCP<br>DTPM                           | Sections: 5.2, 6.1,<br>6.3, 7.7, 8.1, 8.2, 14,<br>24                                                          | Based on my<br>assessment of the<br>application:<br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Ruojing Li</b>                                 |                                                     | <b>Digitally signed by Ruojing Li</b><br><br><b>Date: 9/24/2024 1:23 PM EDT</b><br><b>GUID: 2024924172354</b> |                                                                                                                                                                                                                                          |                                               |

| Discipline and Role                                                                                                                            | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Biostatistics<br>Discipline<br><br>Primary Reviewer                                                                                            | Weimeng<br>Wang<br><br>OB<br><br>DBIII              | Sections: 6.3.1.3,<br>16.3              | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Weimeng Wang</b> <b>Digitally signed by Weimeng Wang</b><br><br><b>Date: 9/24/2024 1:24 PM EDT</b><br><b>GUID: 2024924172410</b> |                                                     |                                         |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                                                                                                                      | Reviewer Name,<br>Office/Center,<br>and<br>Division          | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Associate Director<br>for Labeling<br>Discipline<br><br>Tertiary Reviewer                                                                                                | Catherine<br>Pilgrim-<br>Grayson<br><br>ORDPURM<br><br>DRDMG | Sections: 23                            | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Catherine Pilgrim-Grayson</b> <b>Digitally signed by Catherine Pilgrim-Grayson</b><br><br><b>Date: 9/24/2024 1:24 PM EDT</b><br><b>GUID: 2024924172458</b> |                                                              |                                         |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                                                                                              | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Regulatory Project<br>Manager Discipline<br>Secondary Reviewer                                                                                   | Michael White<br>ORO<br>DRORDPURM                   | Sections: 27, 24, 12                    | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Michael White</b> <b>Digitally signed by Michael White</b><br><br><b>Date: 9/24/2024 1:25 PM EDT</b><br><b>GUID: 2024924172526</b> |                                                     |                                         |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                                                                                      | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical<br>Pharmacology<br>Reviewer Discipline<br>Primary Reviewer                                                                      | Jihye Ahn<br>OCP<br>DPM                             | Sections: 5.2, 6.1,<br>6.3, 7.7, 8.1, 8.2,<br>14.5, 24 | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Jihye Ahn</b> <b>Digitally signed by Jihye Ahn</b><br><br><b>Date: 9/24/2024 1:26 PM EDT</b><br><b>GUID: 2024924172642</b> |                                                     |                                                        |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                                                                                                                              | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Regulatory Project<br>Manager Discipline<br>Primary Reviewer                                                                                                                     | Michael White<br>ORO<br>DRORDPURM                   | Sections: 27, 24, 12                    | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Michael White</b> Digitally signed by Michael White<br>Signed on behalf of Signed on behalf of CAPT Jenny Do<br>Date: 9/24/2024 1:28 PM EDT<br>GUID: 2024924172835 |                                                     |                                         |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                                                                         | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical Discipline<br>Secondary Reviewer                                                                                   | Jacqueline<br>Karp<br>ORDPURM<br>DRDMG              | Sections: All                           | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Jacqueline Karp</b> Digitally signed by Jacqueline Karp<br>Date: 9/24/2024 1:30 PM EDT<br>GUID: 2024924173040 |                                                     |                                         |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                    | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                            | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Associate Director<br>for Labeling<br>Discipline<br>Secondary Reviewer | Jacqueline<br>Karp<br><br>ORDPURM<br><br>DRDMG      | Sections: 23                                                                                                       | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Jacqueline Karp</b>                                      |                                                     | <b>Digitally signed by Jacqueline Karp</b><br><br><b>Date: 9/24/2024 1:31 PM EDT</b><br><b>GUID: 2024924173128</b> |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                         | Reviewer Name,<br>Office/Center,<br>and<br>Division          | Sections Authored<br>in Full or in Part                                                                                      | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|---------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical Discipline<br>Tertiary Reviewer    | Catherine<br>Pilgrim-<br>Grayson<br><br>ORDPURM<br><br>DRDMG | Sections: all                                                                                                                | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Catherine Pilgrim-Grayson</b> |                                                              | <b>Digitally signed by Catherine Pilgrim-Grayson</b><br><br><b>Date: 9/24/2024 1:36 PM EDT</b><br><b>GUID: 2024924173623</b> |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                        | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                                                    | Recommendation<br>to Signatory                                                                                                                                                                                                           | Comments on<br>Recommendation to<br>Signatory |
|----------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical Outcomes<br>Assessment<br>Reviewer Discipline<br>Primary Reviewer | Dilorom Sass<br>ODES<br>DCOA                        | Sections: 3.1.1 Key<br>efficacy review<br>issues; 4 Patient<br>experience data, 16<br>Efficacy - create sub-<br>header sections for<br>COA | Based on my<br>assessment of the<br>application:<br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Dilorom Sass</b>                                             |                                                     | <b>Digitally signed by Dilorom Sass</b><br><br><b>Date: 9/24/2024 1:42 PM EDT</b><br><b>GUID: 2024924174236</b>                            |                                                                                                                                                                                                                                          |                                               |

| Discipline and Role                                        | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                              | Recommendation<br>to Signatory                                                                                                                                                                                                           | Comments on<br>Recommendation to<br>Signatory |
|------------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical<br>Pharmacology<br>Discipline<br>Primary Reviewer | Md Nayeem<br>Hossain<br>OCP<br>DTPM                 | Sections: 5.2, 6.1,<br>6.3, 7.7, 8.1, 8.2, 14,<br>24                                                                 | Based on my<br>assessment of the<br>application:<br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Md Nayeem Hossain</b>                        |                                                     | <b>Digitally signed by Md Nayeem Hossain</b><br><br><b>Date: 9/24/2024 1:53 PM EDT</b><br><b>GUID: 2024924175343</b> |                                                                                                                                                                                                                                          |                                               |

| Discipline and Role                                                | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                          | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|--------------------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical<br>Pharmacology<br>Reviewer Discipline<br>Deputy Director | Robert Schuck<br>OCP<br>DTPM                        | Sections: 5.2, 6.1,<br>6.3, 7.7, 8.1, 8.2,<br>14.5, 24                                                           | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Robert Schuck</b>                                    |                                                     | <b>Digitally signed by Robert Schuck</b><br><br><b>Date: 9/24/2024 1:54 PM EDT</b><br><b>GUID: 2024924175448</b> |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                         | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                        | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|-------------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Pharm-tox/Non-<br>clinical Discipline<br>Secondary Reviewer | Shawna Weis<br>ORDPURM<br>DPTRDPURM                 | Sections: 5, 7, 8, 13,<br>23, 1-3, 6                                                                           | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Shawna Weis</b>                               |                                                     | <b>Digitally signed by Shawna Weis</b><br><br><b>Date: 9/24/2024 1:55 PM EDT</b><br><b>GUID: 2024924175518</b> |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                           | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                          | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|---------------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical<br>Pharmacology<br>Discipline<br><br>Deputy Director | Robert Schuck<br><br>OCP<br><br>DTPM                | Sections: 5.2, 6.1,<br>6.3, 7.7, 8.1, 8.2, 14,<br>24                                                             | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Robert Schuck</b>                               |                                                     | <b>Digitally signed by Robert Schuck</b><br><br><b>Date: 9/24/2024 1:55 PM EDT</b><br><b>GUID: 2024924175536</b> |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                            | Reviewer Name,<br>Office/Center,<br>and<br>Division  | Sections Authored<br>in Full or in Part                                                                              | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|----------------------------------------------------------------|------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Pharm-tox/Non-<br>clinical Discipline<br><br>Tertiary Reviewer | Kimberly<br>Hatfield<br><br>ORDPURM<br><br>DPTRDPURM | Sections: 5, 7, 8, 13,<br>23, 1-3, 6                                                                                 | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Kimberly Hatfield</b>                            |                                                      | <b>Digitally signed by Kimberly Hatfield</b><br><br><b>Date: 9/24/2024 1:58 PM EDT</b><br><b>GUID: 2024924175845</b> |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                 | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                          | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|-----------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Biostatistics<br>Discipline<br><br>Primary Reviewer | Jung Yeon Won<br><br>OB<br><br>DBIV                 | Sections: 6.2, 6.3.1.3,<br>16.3                                                                                  | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Jung Yeon Won</b>                     |                                                     | <b>Digitally signed by Jung Yeon Won</b><br><br><b>Date: 9/24/2024 1:59 PM EDT</b><br><b>GUID: 2024924175953</b> |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                              | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                     | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Pharmacometrics<br>Reviewer Discipline<br><br>Associate Director | Jiang Liu<br><br>OCP<br><br>DPM                     | Sections: 5.2, 6.1,<br>6.3, 7.7, 8.1, 8.2,<br>14.5, 24                                                      | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Jiang Liu</b>                                      |                                                     | <b>Digitally signed by Jiang Liu</b><br><br><b>Date: 9/24/2024 2:01 PM EDT</b><br><b>GUID: 202492418146</b> |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                                                                                     | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical<br>Pharmacology<br>Reviewer Discipline<br>Associate Director                                                                   | Jiang Liu<br>OCP<br>DPM                             | Sections: 5.2, 6.1,<br>6.3, 7.7, 8.1, 8.2,<br>14.5, 24 | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Jiang Liu</b> <b>Digitally signed by Jiang Liu</b><br><br><b>Date: 9/24/2024 2:03 PM EDT</b><br><b>GUID: 202492418315</b> |                                                     |                                                        |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                                                                                             | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part                                                                                                    | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical Outcomes<br>Assessment<br>Reviewer Discipline<br>Associate Director                                                                    | David Reasner<br>ODES<br>DCOA                       | Sections: 3.1.1 Key<br>efficacy review<br>issues; 4 Patient<br>experience data, 16<br>Efficacy - create sub-<br>header sections for<br>COA | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: David Reasner</b> <b>Digitally signed by David Reasner</b><br><br><b>Date: 9/24/2024 2:08 PM EDT</b><br><b>GUID: 202492418835</b> |                                                     |                                                                                                                                            |                                                                                                                                                                                                                                                      |                                               |

| Discipline and Role                                                                                                                                                           | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                   | Comments on<br>Recommendation to<br>Signatory |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Pharm-tox/Non-clinical Discipline<br>Primary Reviewer                                                                                                                         | Shawna Weis<br>ORDPURM<br>DPTRDPURM                 | Sections: 5, 7, 8, 13,<br>23, 1-3, 6    | Based on my assessment of the application:<br><br><input checked="" type="checkbox"/> No deficiencies preclude approval.<br><input type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Shawna Weis</b><br>Digitally signed by Shawna Weis<br>Sign on behalf of Signing as proxy for Dr. Saryu Goel<br>Date: 9/24/2024 2:09 PM EDT<br>GUID: 20249241894 |                                                     |                                         |                                                                                                                                                                                                                                  |                                               |

| Discipline and Role                                                                                                                                                                                        | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                   | Comments on<br>Recommendation to<br>Signatory |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Clinical Discipline<br>Primary Reviewer                                                                                                                                                                    | Catherine Pilgrim-Grayson<br>ORDPURM<br>DRDMG       | Sections: All                           | Based on my assessment of the application:<br><br><input checked="" type="checkbox"/> No deficiencies preclude approval.<br><input type="checkbox"/> Deficiencies preclude approval.<br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Catherine Pilgrim-Grayson</b><br>Digitally signed by Catherine Pilgrim-Grayson<br>Sign on behalf of signing as proxy for Maura Ruzhnik<br>Date: 9/24/2024 2:18 PM EDT<br>GUID: 2024924181812 |                                                     |                                         |                                                                                                                                                                                                                                  |                                               |

NDA 219132  
Aqneursa (levacetylleucine)

| Discipline and Role                                                                                                                                 | Reviewer Name,<br>Office/Center,<br>and<br>Division | Sections Authored<br>in Full or in Part | Recommendation<br>to Signatory                                                                                                                                                                                                                       | Comments on<br>Recommendation to<br>Signatory |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Biostatistics<br>Discipline<br>Secondary Reviewer                                                                                                   | Yan Wang<br>OB<br>DBIV                              | Sections: 6.2, 6.3.1.3,<br>and 16.2     | Based on my<br>assessment of the<br>application:<br><br><input checked="" type="checkbox"/> No deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Deficiencies<br>preclude approval.<br><br><input type="checkbox"/> Not applicable. |                                               |
| <b>Signature: Yan Wang</b> <div> <b>Digitally signed by Yan Wang</b><br/> <b>Date: 9/24/2024 2:19 PM EDT</b><br/> <b>GUID: 2024924181923</b> </div> |                                                     |                                         |                                                                                                                                                                                                                                                      |                                               |

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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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JACQUELINE E KARP  
09/24/2024 01:32:13 PM

CATHERINE A PILGRIM-GRAYSON  
09/24/2024 02:28:41 PM

JANET W MAYNARD  
09/24/2024 02:42:36 PM