A Prospective, Longitudinal Study of the Natural History of Niemann-Pick Disease Type B

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Outline

• Background on Niemann-Pick Disease Type B
• Design features of the Natural History Study
• Key baseline data from this study
• Selection of clinical endpoints for Phase 2 study
• Summary and Next Steps
Niemann-Pick B Disease Represents a Significant Unmet Medical Need

- Niemann-Pick B is a autosomal recessive lysosomal storage disorder that is chronically debilitating and, for some, life-threatening
- Premature death can occur due to cirrhosis, hemorrhage, respiratory failure, or coronary artery disease
- Age of presentation is variable (from infancy to adulthood) and symptoms are heterogeneous
- Current therapy is palliative
- Estimated incidence rate is 1:250,000, worldwide prevalence in developed countries is approximately 3,000 to 5,000 patients

A patient with Niemann-Pick B disease
Niemann-Pick Disease A and B are Caused by Acid Sphingomyelinase Deficiency (ASMD)

• ASMD causes the accumulation of sphingomyelin and cholesterol primarily in tissue macrophages
• Clinical spectrum believed related to ASM activity level
  - Acute neuronopathic (Type A, ~0-5% activity)
  - Chronic neuronopathic (Intermediate)
  - Non-neuronopathic (Type B, ~5-10% activity)
• Niemann-Pick B is highly variable in age at diagnosis, clinical features, and lifespan
• Some genotype/phenotype correlations
Niemann-Pick Type B and Gaucher Disease Type 1 Have Similar Clinical Presentations

- Hepatomegaly
- Splenomegaly
- Thrombocytopenia
- Bleeding/bruising
- Anemia
- Fatigue
- Growth retardation
- CNS and non-CNS forms
- GD>NP
  - Bone disease and pain
- NP>GD
  - Lung disease and cirrhosis

Niemann-Pick Disease Type B

Gaucher Disease Type 1
Genzyme is Developing Enzyme Replacement Therapy for Niemann-Pick B Disease

**Product Overview & Development Status**

- Recombinant human acid-sphingomyelinase (rhASM)
- An enzyme replacement therapy (ERT) that targets the underlying metabolic defect in acid-sphingomyelinase deficiency (ASMD, Niemann-Pick disease Types A & B)
- Phase 1 trial completed in 2009; Phase 2 trial preparations in progress
- 12-year observational, non-treatment study ongoing to help improve understanding of natural history

**Therapeutic Approach**

Target the underlying metabolic defect by replacing the missing enzyme

- **Sphingomyelin**
  - acid-sphingomyelinase
  - Phosphorylcholine
    - Ceramide
      - acid-ceramidase
      - Sphingosine

**Key Compounds**

- **Ceramide**
- **Sphingomyelin**
- **Phosphorylcholine**
- **Sphingosine**
We Are Conducting a Niemann-Pick B Natural History Study to Better Characterize the Disease

• A prospective, observational, natural history study
• 59 patients enrolled from 5 countries: US, Italy, France, Germany, and Brazil
• 3 study visits: baseline, 1-yr, and long-term follow-up (7-12 yrs)

The Study Timeline Spans 12 Years
Niemann-Pick B Natural History Study: Objectives

• Determine the prevalence and range of abnormalities in patients with NP-B

• Evaluate disease progression over time

• Improve the design of future clinical trials of rhASM for the treatment of Niemann-Pick B
  - Inclusion and exclusion criteria
  - Identify clinical endpoints
  - Identify biomarkers
Baseline & Pulmonary Findings from the Natural History Study Have Been Published

Baseline findings, McGovern et al., 2008

Pulmonary findings, Mendelson et al., 2006
Niemann-Pick B Natural History Study: Design

- Series of 2-3 day evaluations at each site
- 3 visits occurring at Baseline, Year 1, and Years 5-11
  - Demographics – incl. enzyme assay and genotype
  - Medical history – age at onset and diagnosis, medical problems, and treatment
  - Physical examination – incl. growth, ophthalmologic, and neurologic
  - Laboratory tests – chem, UA, hematol, lipids, biomarkers (chitotriosidase, SMN)
  - Evaluations – liver/spleen MRI, chest X-ray/HRCT, and echo/ECG
  - Functional status – 6MWT, cycle ergometry, pulmonary function tests
  - Quality of life – CHQ (pediatric) and SF-36 (adult)
  - Niemann-Pick HAQ – incl. validated fatigue, dyspnea, and pain questionnaires. Developed while study in progress and is being implemented at final visit
Niemann-Pick B Natural History Study: Design (cont’d)

• **Inclusion Criteria**
  - Informed consent from patient or legal guardian
  - ASM activity < 10% of normal
  - At least 2 disease-related symptoms
  - Age 6 yrs or older
  - Negative pregnancy test for women of childbearing age

• **Exclusion criteria**
  - Prior bone marrow transplant
  - Niemann-Pick A, C, D, or E
  - Other: complicating medical condition, received investigational drug within 30 days of enrollment, pregnant or lactating
Niemann-Pick B Natural History Study: Procedures and Minimization of Bias

- The Study was approved by the IRB, ethics committee, or human subjects committee at each site.
- Voluntary, written consent was obtained for each patient or guardian.
- All study procedures were conducted according to GCP.
- The data were managed and analyzed by an independent CRO.
- All clinically relevant information on NP-B patients was collected.
- Every effort was made to minimize the missing data.

• **Patients (N=59)**
  - Ages 7-65 yrs, median 17.6 yrs, 53% male, 92% Caucasian
    - R608del mutation accounted for 25% of disease alleles. Indicates milder manifestation of the disease

• **Presentation**
  - 78% splenomegaly, 73% hepatomegaly

• **Signs/Symptoms**
  - 49% bleeding, 42% pulmonary infections, 42% dypsnea, 39% joint/limb pain
  - Growth retardation, especially during puberty
  - Abnormal lipid profile (↑ cholesterol (91%), LDL (46%), TG (62%); low HDL (74%))
  - ↓ platelets (53%), hemoglobin (26%), white blood cells (21%)
  - ↑ ALT (51%), bilirubin (33%), chitotriosidase (95%)
### Natural History Study: Signs and Symptoms

#### TABLE 1: Presenting and Historical Signs and Symptoms

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At presentation</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>46 (78)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>43 (73)</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Excessive bleeding/bruising</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (8)</td>
</tr>
<tr>
<td>By history</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>25 (42)</td>
</tr>
<tr>
<td>Pulmonary Infections</td>
<td>25 (42)</td>
</tr>
<tr>
<td>Joint/limb pain</td>
<td>23 (39)</td>
</tr>
<tr>
<td>Bruising</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Headaches</td>
<td>14 (24)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Fractures</td>
<td>11 (19)</td>
</tr>
</tbody>
</table>

### Laboratory Studies

<table>
<thead>
<tr>
<th>Laboratory Study</th>
<th>$n$</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>% Abnormal</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/L</td>
<td>58</td>
<td>13.3 (1.5)</td>
<td>9.3–16.5</td>
<td>26</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>58</td>
<td>39.1 (4.5)</td>
<td>27.8–48.3</td>
<td>34</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>White blood cells, ×10⁹/L</td>
<td>58</td>
<td>6.4 (2.7 )</td>
<td>2.1–16.2</td>
<td>21</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>58</td>
<td>55 (11)</td>
<td>36–82</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Platelets, ×10⁹/L</td>
<td>58</td>
<td>158 (82)</td>
<td>59–459</td>
<td>53</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cholesterol/HDL ratio&lt;br&gt;</td>
<td>58</td>
<td>10.3 (5.6)</td>
<td>2.6–34.5</td>
<td>0</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>58</td>
<td>26 (10)</td>
<td>11–67</td>
<td>74</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol level</td>
<td>58</td>
<td>230 (72)</td>
<td>120–517</td>
<td>0</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>58</td>
<td>202 (99)</td>
<td>43–495</td>
<td>0</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>57</td>
<td>162 (56)</td>
<td>71–283</td>
<td>0</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>VLDL, mg/dL</td>
<td>34</td>
<td>38 (21)</td>
<td>4–99</td>
<td>15</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>58</td>
<td>69 (60)</td>
<td>9–250</td>
<td>0</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>AST, U/L</td>
<td>57</td>
<td>63 (50)</td>
<td>15–223</td>
<td>0</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>57</td>
<td>228 (166)</td>
<td>51–833</td>
<td>0</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>58</td>
<td>3.2 (7.3)</td>
<td>0.2–40.9</td>
<td>0</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Chitotriosidase, nmol/h per mL</td>
<td>56</td>
<td>549 (832)</td>
<td>20–5792</td>
<td>0</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Plasma sphingomyelin, nmol/mL</td>
<td>41</td>
<td>221 (33)</td>
<td>148–278</td>
<td>46</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood mononuclear cell sphingomyelin,&lt;br&gt;nmol/mg protein</td>
<td>41</td>
<td>77 (68)</td>
<td>15–322</td>
<td>22</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>IGF-1, ng/mL</td>
<td>52</td>
<td>198 (164)</td>
<td>2–742</td>
<td>35</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>IGF-1 BP, ng/mL</td>
<td>46</td>
<td>2100 (1820)</td>
<td>3–6801</td>
<td>9</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Thyrotropin, mIU/L</td>
<td>58</td>
<td>2.6 (1.3)</td>
<td>0.0–5.9</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; VLDL, very-low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, binding protein.

* A cholesterol/HD ratio of > 4.5 is considered abnormally high.
• Signs/Symptoms

- PFTs: ↓ % predicted DLco (73%), FVC (47%)
- Functional status: ↓ 6MWT <310 m (5%), % pred max workload (46%)
- Quality of Life:
  - Pediatric (CHQ-PF50): 4/10 subscales > 1 SD below general population norm
    - Physical functioning, mental health, general health perceptions, parental impact-emotional – indicates diminished QoL in these areas by parental reporting.
  - Adults (SF-36): 1/8 subscales > 1 SD below general population norm
    - General health subscale – indicates patients do not consider themselves to be as healthy, believe they get sick easier than others
### Cardiorespiratory Function Testing in NPD Type B

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>% Abnormal&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>% predicted FVC</td>
<td>55</td>
<td>82 (16)</td>
<td>48–118</td>
<td>47</td>
</tr>
<tr>
<td>% predicted FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>55</td>
<td>80 (18)</td>
<td>27–117</td>
<td>49</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC ratio</td>
<td>55</td>
<td>0.85 (0.12)</td>
<td>0.32–1.00</td>
<td>22</td>
</tr>
<tr>
<td>% predicted DL&lt;sub&gt;CO&lt;/sub&gt;</td>
<td>45</td>
<td>62 (25)</td>
<td>12–121</td>
<td>76</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>56</td>
<td>485 (96)</td>
<td>256–721</td>
<td>5</td>
</tr>
<tr>
<td>% predicted maximum workload</td>
<td>35</td>
<td>83 (26)</td>
<td>27–138</td>
<td>46</td>
</tr>
<tr>
<td>% predicted maximum O&lt;sub&gt;2&lt;/sub&gt; uptake</td>
<td>32</td>
<td>85 (25)</td>
<td>40–148</td>
<td>38</td>
</tr>
</tbody>
</table>

<sup>a</sup> Abnormal values were defined as follows: FVC, FEV<sub>1</sub>, DL<sub>CO</sub>, and maximum workload and O<sub>2</sub> uptake of <80% of the predicted normal values; FEV<sub>1</sub>/FVC ratio of <0.80; and 6MWT of <310 m. For the FEV<sub>1</sub>/FVC ratio, the lower limit of normal varies slightly according to patient demographics, and 0.80 represents an average value. For the 6MWT, 310 m is considered to be the lower limit of normal for adult women,<sup>30</sup> and it also approximates the 320-m minimum distance for normal community ambulation.
Ht and Wt below average. Delayed bone ages during adolescence are indicative of delayed puberty.
Spleen Volume Correlated with Several Aspects of Disease Severity

**Figure 2**
Correlations between normalized spleen volume and liver volume (A), triglyceride levels (B), HDL (C), height z-score (D), hemoglobin (E), white blood cell (WBC) count (F), platelets (G), and predicted PFC (H).
Correlation Between Normalized Spleen Volume and Liver Volume

Liver Volume (MN) vs. Spleen Volume (MN)

- Correlation coefficient: $r = 0.7603$
- Significance level: $P < 0.0001$
Correlation Between Normalized Spleen Volume and Triglycerides

Triglycerides vs. Spleen Volume (MN)

$r = 0.5453$

$P < 0.001$
Correlation Between Normalized Spleen Volume and HDL-Cholesterol

HDL - Cholesterol vs. Spleen Volume (MN)

\[ r = 0.6196 \]
\[ P = <0.001 \]
Correlation Between Normalized Spleen Volume and Height Z-Score

![Graph showing the correlation between Height Z-Score and Spleen Volume (MN). The correlation coefficient (r) is 0.5086, and the p-value (P) is 0.0001.]

- Height Z-Score vs. Spleen Volume (MN)
- \( r = 0.5086 \)
- \( P = 0.0001 \)
Correlation Between Normalized Spleen Volume and Hemoglobin

Hemoglobin vs. Spleen Volume (MN)

- Hemoglobin (G/DL)
- Spleen Volume (MN)

$r = .3297$
$p = .0194$
Correlation Between Normalized Spleen Volume and % Predicted FVC
Type B Niemann-Pick Natural History Study: Summary

• Study provided important new information about the spectrum of disease manifestations

• Diversity of the patient populations from various countries was identified (e.g., pulmonary involvement in Saudi Arabia patients whereas a high neurological prevalence in European patients)

• 6 patient deaths (10%) during follow-up, most in adolescence to mid-adulthood

• Degree of splenomegaly – one of the cardinal feature of the disease correlated with other signs of disease severity

• Chitotriosidase (Biomarker) may play a role in monitoring patient treatment responses
Type B Niemann-Pick Natural History Study: Next Steps

• Final study visit this year
• Prospective longitudinal follow-up for up to 11 years
• Analyze all the longitudinal data
• Initiate Phase 2 Study using Spleen Volume as the primary efficacy endpoint
  - Spleen volume is the most prevalent and abnormal feature
  - Changes will be useful for assessing dose-response relationship
  - Correlation with disease severity may predict clinical benefit
BACKUPS
ALT vs. Liver Volume (MN)

$r = .5966$

$P = < .001$
AST vs. Liver Volume (MN)

$r = .6440$

$P = < .001$
Liver Volume (MN) vs. Age

- Intact Spleen
- Total or Partial Splenectomy

$r = .2818$
$P = .0354$
Chest HRCT

Severe Interstitial Lung Disease

Normal
Chest HRCT Histograms

Normal

Severe Interstitial Lung Disease
Histological Hallmarks of Niemann-Pick A/B

Niemann-Pick Cell

Lysosomal Storage
Niemann-Pick A/B is a Sphingolipidosis

GM1
- GM1-Gangliosidosis
  - GM1-β-Galactosidase

GM2
- Tay-Sachs, Sandhoff AB variant
  - β-Hexosaminidase A, GM2 activator

GM3
- Sialidosis

Globoside
- Sandhoff
  - β-Hexosaminidase A, B

Globotriaosylceramide
- Fabry
  - α-Galactosidase A

Lactosylceramide
- GalCer-β-Galactosidase
  - GM1-β-Galactosidase

Glucosylceramide
- Gaucher
  - Glucocerebrosidase

Ceramide
- Farber
  - Acid Ceramidase

Sphingosine
- Niemann-Pick A/B (ASMD)
  - Acid Sphingomyelinase
  - Farber

Acid Sphingomyelinase
- Krabbe
  - Metachromatic Leukodystrophy

Galactosylceramide
- Fabry
  - α-Galactosidase A

Digalactosylceramide
- Arylsulfatase A

Sulfatide

Adapted from The Metabolic & Molecular Bases of Inherited Disease Fig. 134-1
Height Z-Score vs. Age

\[ r = 0.2102 \]
\[ P = 0.1101 \]
Weight Z-Score vs. Age

- $r = 0.3144$
- $P = 0.0153$

- Male
- Female
% Predicted DLco vs. Spleen Volume (MN)

$r = .3063$

$P = .0515$
Interstitial Lung Disease Score vs. Spleen Volume (MN)

$r = .3084$
$P = .0330$
Mean Six-Minute Walk Test Distance vs. Spleen Volume (MN)

$r = .2598$
$P = .0746$
% Predicted Maximum Oxygen Uptake vs. Spleen Volume (MN)

$r = .0100$
$P = .9496$
% Predicted Maximum Workload vs. Spleen Volume (MN)

$r = .1982$

$P = .2768$
Spleen Volume (MN) vs. Age

$r = .0331$

$P = .8202$
Niemann-Pick B Disease Represents a Significant Unmet Medical Need

Major Clinical Features

- Hepatosplenomegaly
  - Discomfort, pain, early satiety
  - Liver fibrosis, splenic rupture
- Thrombocytopenia – bruising, bleeding
- Delayed growth and puberty
- Interstitial lung disease
  - Dyspnea, exercise intolerance, infection
- Atherogenic lipid profile, CAD
  - High LDL, low HDL
- Low bone mineral density - fractures
- Low QoL – poor self-image, fatigue, pain, limitations in physical activities
- Death in childhood to adulthood

Causes of Death

- Cirrhosis
- Hemorrhage
- Respiratory failure
- Coronary artery disease
Niemann-Pick B Natural History Study: Background

• To define the range of abnormalities in Niemann-Pick B patients to assist in the design of future clinical trials of recombinant human acid sphingomyelinase (rhASM)

• Initiated in 2001 and will be completed in 2012

• Prospective, longitudinal study sponsored by Genzyme

• 59 patients at 5 sites in US, Brazil, France, Germany, and Italy
Niemann-Pick Natural History Study: Baseline Results

**Abstract**

**Objective**: The objective of this study was to characterize the clinical features of patients with Niemann-Pick disease type B and to identify efficacy end points for future clinical trials of enzyme replacement therapy.

**Methods**: Fifty-nine patients who had Niemann-Pick disease type B were at least 6 years of age, and manifested at least 2 disease symptoms participated in this multinational, cross-sectional survey study. Medical histories, physical examinations, assessments of cardiorespiratory function, clinical laboratory data, and liver and spleen volumes were radiographic evaluation of the lungs and bone age, and quality of life questionnaires were obtained during a 2- to 3-day period.

**Results**: Thirty-three percent of the patients were male, 92% were white, and the median age was 17.6 years. The R608X mutation was present in 21% of all disease alleles. Most patients initially presented with splenomegaly (78%) or hepatomegaly (73%). Frequent symptoms included bleeding (8%), pneumonia and infections (42%), and joint/limb pain (35%). Growth was markedly delayed during adolescence. Patients commonly had reduced levels of plasma lipoproteins, elevated levels of low-density lipoproteins, very-low-density lipoproteins, and serum cholesterol, and abnormal liver function test results. Nearly all patients had documented splenomegaly and hepatomegaly and interstitial lung disease. Patients commonly showed restrictive lung disease physiology with impaired pulmonary gas exchange and decreased maximal exercise tolerance. Quality of life was only mildly affected by standardized questionnaires. The study was completed with most aspects of disease, including hepatomegaly, growth, lipid profile, hematologic parameters, and pulmonary function.

**Conclusion**: This study characterizes the multisystem involvement and clinical variability of Niemann-Pick disease type B. Several efficacy end points were identified for future clinical treatment studies. Because of its correlation with disease severity, spleen volume may be a useful surrogate end point in treatment trials, whereas biomarkers such as chitotriosidase also may play a role in monitoring patient treatment responses.

A CID SPHINGOMYLINASE (ASM) deficiency (sphingomyelin phosphodiesterase 1, SCD8F; EC 3.1.4.10) is a rare autosomal recessive inborn error of metabolism that leads to the accumulation of sphingomyelin in cells and tissues causing the clinical disorder known as Niemann-Pick disease (NPD). ASM deficiency is rare, with an estimated prevalence of 1 in 100,000 live births.
Niemann-Pick Natural History Study: Baseline Results

  - Splenomegaly was the most common presenting feature (78%)
  - Spleen volume (mean 11.1 x normal) correlated with several aspects of disease severity, including hepatomegaly, triglycerides, HDL, LDL, cholesterol, height Z-score, hemoglobin, white blood cell count, and % predicted FVC
  - Spleen volume correlated with bleeding episodes, but not platelet count

  - All frequently abnormal, but no overall correlations between imaging and function
Niemann-Pick B Disease and rhASM
Data from the Natural History Study Supports Clinical Trial Design by...

- determining the range of values/performances of the planned tests in this patient population
- helping to define the most appropriate inclusion/exclusion criteria for clinical trials
- assisting in choosing the best clinical endpoints for determining efficacy in future clinical trials
- helping to characterize and understand the natural history of Niemann-Pick B disease