Miglustat Therapy for Niemann-Pick Type C Disease

Isaac Kobrin, MD
Chief Medical Officer
Actelion Pharmaceuticals Ltd
Advisors

- Marc C. Patterson, MD
  - Division of Child and Adolescent Neurology Mayo Clinic, Rochester, MN

- Frits Wijburg, MD
  - Academic Medical Center, Amsterdam, The Netherlands

- Elizabeth Jacklin, RGN
  - Royal Manchester Children's Hospital, UK
    Niemann-Pick Disease Group
## Actelion Representatives

<table>
<thead>
<tr>
<th>Department</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical Development</td>
<td>Ulrich Mentzel, PhD</td>
</tr>
<tr>
<td>Preclinical Pharmacology</td>
<td>Olivier Morand, PhD</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Jasper Dingemanse, PhD</td>
</tr>
<tr>
<td>Clinical</td>
<td>Ruben Giorgino, MD Per Nilsson, MD</td>
</tr>
<tr>
<td>Biometry</td>
<td>Maurizio Rainisio, PhD</td>
</tr>
<tr>
<td>Drug Regulatory Affairs</td>
<td>Frances Duffy-Warren, PhD</td>
</tr>
<tr>
<td></td>
<td>Samar Kelly, PhD</td>
</tr>
</tbody>
</table>
Agenda

- Overview
- NP-C disease and the rationale for miglustat treatment
- Clinical pharmacology, efficacy and safety
- Benefit – Risk assessment
- Clinical perspective
NP-C Disease Overview

- NP-C is an extremely rare ("ultra-orphan") genetic disease
  - About 500 known cases worldwide; approximately 200 in the US
- NP-C is dominated by progressive nervous system involvement leading to premature death
- There is no approved therapy in the US
Miglustat Development Overview

- Miglustat is the first potentially disease-modifying agent studied in NP-C disease
- Large proportion of known NP-C patients participated in the miglustat development program
- Spontaneous improvement of neurological disease is not observed in long term follow up
  - Creates a basis for documenting efficacy outside conventional methodology of RCTs
- Totality of data indicates that miglustat stabilizes the progression of neurological disease in NP-C
- Safety of miglustat is well characterized and manageable
Miglustat (Zavesca®)

- 2003: approved in US for type 1 Gaucher disease (GD-1) in patients for whom enzyme replacement therapy is not a therapeutic option
  - Also approved in EU and 10 other countries
- 2009: approved in the EU for progressive neurological manifestations in adult and pediatric NP-C patients
  - Also approved in Brazil, South Korea, Russia (and Australia)
Niemann-Pick Type C Disease and the Rationale for Miglustat Treatment

Marc C. Patterson, MD
Professor of Neurology, Pediatrics and Medical Genetics
Chair, Division of Child and Adolescent Neurology
Mayo Clinic, Rochester, MN
Niemann-Pick Type C Disease

Extremely rare pan-ethnic inherited lysosomal storage disorder (LSD)

Autosomal recessive inheritance
- 90–95% of cases due to mutations in NPC1 gene
- 4% due to mutations in NPC2 gene

NPC1 and NPC2 have roles in intracellular lipid trafficking
- Abnormal intracellular lipid accumulation of mainly unesterified cholesterol and glycosphingolipids (GSL)
- Imbalance between normal production (Golgi) and defective trafficking / degradation (late endosomes, lysosomes)
Niemann-Pick Type C Disease

Calculated birth incidence: approximately 1:150,000
- Approximately 500 known NP-C patients worldwide
  - ~200 NP-C patients in the US

Wide heterogeneity of clinical picture
- Delayed diagnosis
- CNS manifestations
- Visceral manifestations (e.g., liver, spleen, lungs)
## Age at Onset and Disease Manifestation

<table>
<thead>
<tr>
<th>Age at Onset</th>
<th>Systemic manifestations</th>
<th>Hypotonia and developmental delay</th>
<th>VSGP, cerebellar and brain stem signs</th>
<th>VSGP, cerebellar, cortical and brain stem signs</th>
<th>Cortical signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo to</td>
<td>Hypotonia</td>
<td>VSGP, cerebellar and brain stem</td>
<td>VSGP, cerebellar, cortical and brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 yrs</td>
<td></td>
<td>signs</td>
<td>stem signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 to &lt; 6 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-15 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NP-C Disease: Neuropathological Changes

Meganeurites

Balloon cells

New ectopic dendrites
Brain MRI in NP-C Disease

Normal

NP-C Disease
Diagnosis of NP-C Filipin Staining

Normal fibroblasts  NP-C fibroblasts
Age at Diagnosis and at Death

N=82
Mean (SD): 10.4 (9.3) years
Median: 6.9 years

N=50
Mean (SD): 16.2 (11.1) years
Median: 12.5 years

Mail survey conducted among NP-C patients’ families and caregivers. Data from 87 questionnaires available.

Neurological Manifestations of NP-C Disease Do Not Improve Spontaneously

Natural History Data from Survey II (n=57)
Composite Neurological Disability Score in Patients with ≤ 2.5 Years of Follow-Up
Composite Neurological Disability Score in Patients with 2.5 - 4 Years of Follow-Up
Composite Neurological Disability Score in Patients with 4 - 6 Years of Follow-Up
Composite Neurological Disability Score in Patients with 6 - 8 Years of Follow-Up
Composite Neurological Disability Score in Patients with >8 Years of Follow-Up
Goal of Therapy in NP-C Disease

- Neurological function is proportional to the sum pool of CNS neurons retaining functional capacity.
- This pool forms the primary therapeutic target in NP-C disease.
- Slowing or stabilization of neurological disease progression is likely the best attainable goal for long-term therapy.
GSL Metabolism in NP-C

- **GM1** → **Ceramide**
- **GM2** → **Ceramide**
- **GM3** → **Ceramide**

Sugar moieties

- Synthesis (Golgi/ER)
- Degradation (lysosome)

NP-C

- Lactosylceramide
- Glucosylceramide
- Glucosylceramide synthase

Ceramide
GSL Metabolism in NP-C

GM1
Ceramide

GM2
Ceramide

GM3
Ceramide

NP-C

Synthesis (Golgi/ER)

Degradation (lysosome)

Sugar moieties

Ceramide

Lactosylceramide

Glucosylceramide

Glucosylceramide synthase

Miglustat
Miglustat in the NPC\textsuperscript{NIH} Mouse Model

untreated and miglustat treatment comparison for various age groups and tissues.

- 11-week and 5-day-old
- 9-week and 5-day-old

Cerebral Cortex and Cerebellum images showing untreated and miglustat treatment.

Average lifespan (days) comparison:

- Untreated: 67
- Miglustat: 89

+25% increase in lifespan with miglustat treatment.

Conclusions

- NP-C is a predictably and invariably progressive neurodegenerative disease
- Therapeutic goal is to slow down or stabilize disease progression by salvaging dysfunctional or normal neurons
- Based on mode of action and preclinical observations, miglustat could slow disease progression in NP-C patients
Clinical Program

Isaac Kobrin, MD
Clinical Pharmacology
Miglustat Pharmacokinetic (PK) Characteristics (Current USPI)

- Rapid absorption
- No clinically relevant food effect
- Low inter-subject variability
- Elimination half-life: 6 - 7 hours
- Dose proportional
- Independent of treatment duration
- Independent of age, gender, body weight or disease
Metabolism and Excretion (Current USPI)

- Eliminated unchanged mainly by the kidneys
- Exposure not affected by liver impairment
- Low potential for drug-drug interactions
  - No inhibition of cytochrome P450 isoenzymes
  - Not metabolized by cytochrome P450 isoenzymes
Miglustat New PK Data

40 patients; 18 patients < 12 years

- NP-C (n = 10)
  - 4 patients < 12 years

- GD-3 (n = 13)
  - 6 patients < 12 years

- Adult $G_{M2}$ gangliosidosis (n = 6)

- Pediatric and Adolescent $G_{M2}$ gangliosidosis (n = 11)$^1$
  - 8 patients < 12 years

Miglustat Exposure Across Indications

Horizontal bars represent the geometric means

GD-1: 100 mg t.i.d.
NLSD: 200 mg t.i.d.
< 12 y adjusted to BSA
Miglustat Exposure Across Age Groups

- **Adjustment by BSA**
  - ≥ 12 years (200 mg t.i.d.)
  - < 12 years (200 mg t.i.d.)

**Horizontal bars represent the geometric means**

**AUC** $\text{0-8 h (ng.h/mL)}$

- ≥ 18 years (100 mg t.i.d.)
- ≥ 12 years (200 mg t.i.d.)
- < 12 years (200 mg t.i.d.)

3029.01
Miglustat Dose Rationale in NP-C Patients

- Inhibition of systemic glucosylceramide synthase is the goal of treatment in GD-1
- Effective dosing regimen in GD–1 is 100 mg t.i.d.
- Inhibition of CNS glucosylceramide synthase is the goal of treatment in NP-C disease
- CSF concentration of miglustat is approximately 40% of plasma levels (200 mg t.i.d.)
  - Evaluated in 8 patients (4 pts < 12 years)
- Regimen of 200 mg t.i.d. is required to achieve effective concentration in CNS
  - Adjusted to BSA in patients < 12 years of age
Clinical Program
Efficacy Evaluation
To evaluate the effects of miglustat on clinically relevant neurological manifestations in adult / adolescent and pediatric NP-C patients

- Reduction in the rate of neurological progression or disease stabilization are considered appropriate treatment goals
Development Considerations

- Randomized controlled trials are a recognized method for assessing efficacy in diseases whose clinical course in individual patients is unpredictable.
- Cohort studies can provide essential data for assessing efficacy in diseases whose clinical course in individual patients is highly predictable.  
  - Have formed the basis of regulatory approval of some drugs for rare disorders.
Randomized Controlled Trials in NP-C Disease

- Challenging because rarity of disease makes patient recruitment difficult
- Clinical or surrogate endpoints have not been established
- Availability of miglustat for GD-1 led to off-label use in a large proportion of NP-C patients
- Required sample size based on traditional clinical outcome measures is likely to exceed the total number of available patients
Cohort Studies in NP-C Disease

- Natural history is characterized by inexorable progression of neurological disease over time.
- Off-label utilization in NP-C patients created a miglustat-treated cohort representing a large proportion of patients with the disease.
- Cohort studies were feasible because most patients with NP-C disease are seen in a few specialized centers and undergo standardized assessments.
Development of Miglustat in NP-C Disease

- Retrospective cohort studies
  - Survey II (Natural History)
  - Survey I
- Prospective randomized trial
  - OGT 918-007 (Study 007)
Cohort Studies

- **Survey II**: retrospective study of the natural history of neurological disease progression
  - 57 patients
- **Survey I**: retrospective study of neurological disease progression prior to and during treatment with miglustat
  - 66 patients not enrolled in clinical trials
- Neurologic disease progression assessed by NP-C disability scale based on rating of:
  - Swallowing, ambulation, manipulation (dysmetria / dystonia) and language abilities
Cohort Studies
Organization and Data Collection

Survey II (Natural History)

- 7 sites from 6 countries identified by the coordinating PI
- Data collected for each NP-C patient at multiple time points (at least 3) during the natural course of the disease

Survey I (prior to and during miglustat)

- 25 sites from 12 countries identified by the coordinating PI
- Data collected for each NP-C patient treated with commercially available miglustat
  - At diagnosis, treatment start and last visit during miglustat treatment
### Cohort Studies

#### Demographics

<table>
<thead>
<tr>
<th></th>
<th>Survey II N=57</th>
<th>Survey I N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M:F (%)</strong></td>
<td>44:56</td>
<td>47:53</td>
</tr>
<tr>
<td><strong>Age at diagnosis (yrs)</strong></td>
<td>10.7 ± 9.6</td>
<td>9.7 ± 7.6</td>
</tr>
<tr>
<td><strong>Age groups (&lt;12, ≥ 12) (%)</strong></td>
<td>61, 39</td>
<td>67, 33</td>
</tr>
<tr>
<td><strong>Time between diagnosis and treatment (yrs)</strong></td>
<td>-</td>
<td>3.1 ± 3.4</td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td>-</td>
<td>1.5 ± 1.1</td>
</tr>
<tr>
<td><strong>Time from diagnosis to last visit (yrs)</strong></td>
<td>5.5 ± 4.8</td>
<td>4.6 ± 3.5</td>
</tr>
<tr>
<td><strong>Mean dose (mg) (min., max.)</strong></td>
<td>-</td>
<td>361 (18, 600)</td>
</tr>
</tbody>
</table>

Numbers are % or mean ± SD
## NP-C Functional Disability Scale

### Original Iturriaga Score

<table>
<thead>
<tr>
<th>Swallowing</th>
<th>Score</th>
<th>Manipulation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>Occasional dysphagia</td>
<td>2</td>
<td>Slight dysmetria/dystonia</td>
<td>2</td>
</tr>
<tr>
<td>Daily dysphagia</td>
<td>3</td>
<td>Mild dysmetria/dystonia</td>
<td>3</td>
</tr>
<tr>
<td>NG tube or gastric button feeding</td>
<td>4</td>
<td>Severe dysmetria/dystonia</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ambulation</th>
<th>Score</th>
<th>Language</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>Autonomous ataxic gait</td>
<td>2</td>
<td>Mild dysarthria</td>
<td>2</td>
</tr>
<tr>
<td>Outdoor-assisted ambulation</td>
<td>3</td>
<td>Severe dysarthria</td>
<td>3</td>
</tr>
<tr>
<td>Indoor-assisted ambulation</td>
<td>4</td>
<td>Non-verbal communication</td>
<td>4</td>
</tr>
<tr>
<td>Wheelchair bound</td>
<td>5</td>
<td>Absence of communication</td>
<td>5</td>
</tr>
</tbody>
</table>

Iturriaga et al. J Neurol Sci. 2006; 249:1-6
<table>
<thead>
<tr>
<th>Swallowing</th>
<th>Score</th>
<th>Manipulation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Occasional dysphagia</td>
<td>.33</td>
<td>Slight dysmetria/dystonia</td>
<td>.33</td>
</tr>
<tr>
<td>Daily dysphagia</td>
<td>.67</td>
<td>Mild dysmetria/dystonia</td>
<td>.67</td>
</tr>
<tr>
<td>NG tube or gastric button feeding</td>
<td>1</td>
<td>Severe dysmetria/dystonia</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ambulation</th>
<th>Score</th>
<th>Language</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Autonomous ataxic gait</td>
<td>.25</td>
<td>Mild dysarthria</td>
<td>.25</td>
</tr>
<tr>
<td>Outdoor-assisted ambulation</td>
<td>.50</td>
<td>Severe dysarthria</td>
<td>.50</td>
</tr>
<tr>
<td>Indoor-assisted ambulation</td>
<td>.75</td>
<td>Non-verbal communication</td>
<td>.75</td>
</tr>
<tr>
<td>Wheelchair bound</td>
<td>1</td>
<td>Absence of communication</td>
<td>1</td>
</tr>
</tbody>
</table>
## Cohort Studies
### NP-C Characteristics at Diagnosis

<table>
<thead>
<tr>
<th>Variable / Domain</th>
<th>Survey II N=57</th>
<th>Survey I N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swallowing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td>n=56</td>
<td>n=62</td>
</tr>
<tr>
<td></td>
<td>11 (20%)</td>
<td>20 (32%)</td>
</tr>
<tr>
<td>Ambulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td>n=57</td>
<td>n=64</td>
</tr>
<tr>
<td></td>
<td>35 (61%)</td>
<td>42 (66%)</td>
</tr>
<tr>
<td>Manipulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td>n=57</td>
<td>n=64</td>
</tr>
<tr>
<td></td>
<td>29 (51%)</td>
<td>40 (62%)</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td>n=57</td>
<td>n=64</td>
</tr>
<tr>
<td></td>
<td>24 (42%)</td>
<td>40 (62%)</td>
</tr>
</tbody>
</table>
Statistical Analysis
Cohort Studies

Survey II
- Annualized progression rate in each domain and composite score
  - Between diagnosis and last visit
  - Across multiple time points

Survey I
- Similar to Survey II
  - Between diagnosis and treatment start
  - Between treatment start and last visit on treatment
Composite Disability Score During Natural History (Survey II, n=57)
Survey II (Natural History): Annualized Progression Rate Across Neurological Domains

- Swallowing (N=57)
- Ambulation (N=57)
- Manipulation (N=57)
- Language (N=57)
- Composite Score (N=57)

Annualized score changes (mean and 95% CI)
Survey I: Annualized Progression Across Neurological Domains

Swallowing (N=61)

Ambulation (N=63)

Manipulation (N=62)

Language (N=61)

Composite Score (N=63)

Annualized score changes (mean and 95% CI)
Survey I: Annualized Progression Across Neurological Domains

- **Swallowing (N=61)**
- **Ambulation (N=63)**
- **Manipulation (N=62)**
- **Language (N=61)**
- **Composite Score (N=63)**

Annualized score changes (mean and 95% CI)

- Before Treatment
- During Treatment
Survey I (Treatment Effect): Annualized Progression Across Neurological Domains

Swallowing (N=61)

Ambulation (N=63)

Manipulation (N=62)

Language (N=61)

Composite Score (N=63)

Treatment Effect (mean and 95% CI)

-0.40  -0.20  0.00  0.20  0.40
Composite Score Pre- and During Treatment with Miglustat in Survey I

Individual Annualized Progression Rate (N=63)

Pre-miglustat
- Unchanged (n=19)
- Progressing (n=44)

On-miglustat
- Slower Progression (n=37)
- Progression Unchanged (n=11)
- Faster Progression (n=15)
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys

![Graph showing the clinical course before and during Miglustat in 19 patients.](image-url)
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys

![Graph showing the clinical course before and during Miglustat treatment. The x-axis represents years from diagnosis and years from miglustat start, while the y-axis represents the composite score.]
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys

- Years from Diagnosis
- Composite Score
- From miglustat start

3915.01
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys

![Graph showing clinical course before and during Miglustat in 19 patients.](image)
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys
Survey I: Annualized Progression in Patients with Progressive Neurological Disease

- Swallowing (N=42)
- Ambulation (N=45)
- Manipulation (N=44)
- Language (N=45)
- Composite Score (N=45)

Annualized score changes (mean and 95% CI)

Before Treatment
Survey I: Annualized Progression in Patients with Progressive Neurological Disease

Survey I: Annualized Progression in Patients with Progressive Neurological Disease

Swallowing (N=42)

Ambulation (N=45)

Manipulation (N=44)

Language (N=45)

Composite Score (N=45)

Before Treatment

During Treatment

Annualized score changes (mean and 95% CI)
Survey I (Treatment Effect): Annualized Progression in Patients with Progressive Neurological Disease

- Swallowing (N=42)
- Ambulation (N=45)
- Manipulation (N=44)
- Language (N=45)
- Composite Score (N=45)

Treatment Effect (mean and 95% CI)
Survey I: Patients with Progressive Neurologic Disease – Composite Score

All patients
N = 45

Age at diagnosis

< 6 years
N = 13

6-11 years
N = 16

≥ 12 years
N = 16

Annualized composite score changes (mean and 95% CI)

Before Treatment

N = 45

< 6 years
N = 13

6-11 years
N = 16

≥ 12 years
N = 16

3932.01

Annualized composite score changes (mean and 95% CI)
Survey I: Patients with Progressive Neurologic Disease – Composite Score

All patients
N = 45

Age at diagnosis
< 6 years
N = 13

6-11 years
N = 16

≥ 12 years
N = 16

Annualized composite score changes (mean and 95% CI)

Before Treatment
During Treatment

3933.01
Survey I (Treatment Effect): Patients with Progressive Neurologic Disease – Composite Score

All patients
N = 45

Age at diagnosis
< 6 years
N = 13

6-11 years
N = 16

≥ 12 years
N = 16

Treatment Effect (mean and 95% CI)

3934.01
Summary of Cohort Studies

- The cohort studies demonstrate the relentless progression of neurological disease in untreated patients.

- Treatment with miglustat was characterized by slowing down or stabilization of neurologic disease progression over clinically meaningful durations of follow-up.

- Effect was most pronounced in patients with progressive neurologic disease in the pre-treatment phase.
Randomized Controlled Trials in NP-C Disease

- Recruitment difficult in such rare disease
- No established endpoints
- Unrealistic sample size requirement
- Miglustat already available on the market
Development of Miglustat in NP-C Disease

- Retrospective cohort studies
  - Survey II (Natural History)
  - Survey I
- Prospective randomized trial
  - OGT 918-007 (Study 007)
Main Study (Adults / Adolescents)

Patient Disposition

N = 29

Miglustat
n = 17

Randomized
Completed
12 months

Miglustat
n = 8

Completed
24 months

No treatment
n = 9

Completed extension beyond 24 months

Miglustat
n = 20

Randomized

1 w/d

Miglustat
n = 17

Completed
24 months

n = 15

3 w/d

Miglustat
n = 14

2 w/d

n = 20

3037.01
Pediatric Sub-study
Patient Disposition

Miglustat
n = 12

Entered

2 w/d

Completed
12 months

n = 10

Completed
24 months

n = 10

Completed
extension beyond
24 months

n = 10
Study 007
Baseline NP-C Manifestations

<table>
<thead>
<tr>
<th>NP-C disease manifestations (%)</th>
<th>Adult/Adolescent</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Treatment (n = 9)</td>
<td>Miglustat (n = 20)</td>
</tr>
<tr>
<td>At least 1</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Vertical gaze palsy</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td>Ataxia</td>
<td>56</td>
<td>100</td>
</tr>
<tr>
<td>Impaired cognition</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>44</td>
<td>90</td>
</tr>
<tr>
<td>Dystonia</td>
<td>44</td>
<td>70</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>Pyramidal tract dysf.</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>56</td>
<td>35</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>44</td>
<td>30</td>
</tr>
</tbody>
</table>
Choice of Horizontal SEM-$\alpha$
Primary Endpoint

- Quantitative measure expected to be evaluable in a small study
- Horizontal saccadic eye movements (HSEM) are affected later than Vertical SEM
- HSEM-$\alpha$ reflects SEM velocity for large saccades
  - Expressed as ms/deg
  - Decrease in $\alpha =$ improvement of SEM
- Assessed by blinded central assessor
Limitations of HSEM-α Endpoint

- HSEM-α is not a validated surrogate for clinical manifestations in NP-C
  - Not used in clinical practice
- HSEM-α not previously used as a primary endpoint in a clinical study
- HSEM-α assessments carried out using two different methods
  - One method was associated with higher degree of scatter, causing uncertainty in the evaluation
# HSEM-α Over 12 Months
## Adult / Adolescent Patients

<table>
<thead>
<tr>
<th></th>
<th>No Treatment</th>
<th>Miglustat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td><strong>Baseline (mean ± SD)</strong></td>
<td>2.48 ± 1.43</td>
<td>3.02 ± 2.17</td>
</tr>
<tr>
<td><strong>Main analysis (baseline values, age)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ from baseline (mean)</td>
<td>-0.05</td>
<td>-0.37</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-0.61, 0.51)</td>
<td>(-0.75, -0.01)</td>
</tr>
<tr>
<td>Treatment effect (mean, 95% CI)</td>
<td>-0.33 (-1.00, 0.35)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P-value = 0.327</td>
<td></td>
</tr>
<tr>
<td><strong>Supplemental analysis (baseline values, center)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ from baseline (mean)</td>
<td>0.06</td>
<td>-0.46</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-0.44, 0.55)</td>
<td>(-0.80, -0.13)</td>
</tr>
<tr>
<td>Treatment effect (mean, 95% CI)</td>
<td>-0.52 (-1.12, 0.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nominal P-value = 0.091</td>
<td></td>
</tr>
</tbody>
</table>

All means are adjusted, except baseline
## Key Efficacy Variables
### Study 007 and Cohort Studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study 007</th>
<th>Cohort Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horizontal saccadic eye movement α</td>
<td>√ (primary EP)</td>
<td></td>
</tr>
<tr>
<td>Swallowing</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Ambulation</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Manipulation (dysmetria / dystonia)</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Language function</td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>
Swallowing Assessment Study 007

Four substances
- 5 mL water
- 1 teaspoon puree
- 1 teaspoon soft lumps
- One-third cookie

Investigator evaluation of patient’s ease of swallowing of each substance
- Easy swallowing
- Mild, moderate or severe problems
- Could not swallow the substance at all

Deterioration defined as worsening of swallowing of at least 1 food substance
## Hauser Standard Ambulation Index (SAI)

Mobility assessed by time and degree of assistance required to walk 25 feet

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic; fully active.</td>
</tr>
<tr>
<td>1</td>
<td>Walks normally but reports fatigue which interferes with athletic or other demanding activities.</td>
</tr>
<tr>
<td>2</td>
<td>Abnormal gait or episodic imbalance; gait disorder is noticeable to family and friends. Able to walk 25 feet in 10 seconds or less.</td>
</tr>
<tr>
<td>3</td>
<td>Walks independently; able to walk 25 feet in 20 seconds or less.</td>
</tr>
<tr>
<td>4</td>
<td>Requires unilateral support to walk; uses support more than 80% of the time. Walks 25 feet in 20 seconds or less.</td>
</tr>
<tr>
<td>5</td>
<td>Requires bilateral support and walks 25 feet in greater than 20 seconds.</td>
</tr>
<tr>
<td>6</td>
<td>Requires bilateral support and walks 25 feet in greater than 20 seconds. May use wheelchair on occasion.</td>
</tr>
<tr>
<td>7</td>
<td>Walking limited to several steps with bilateral support; unable to walk 25 feet. May use wheelchair for most activities.</td>
</tr>
<tr>
<td>8</td>
<td>Restricted to wheelchair; able to transfer independently.</td>
</tr>
<tr>
<td>9</td>
<td>Restricted to wheelchair; unable to transfer independently.</td>
</tr>
</tbody>
</table>
# Cognitive Function – MMSE

<table>
<thead>
<tr>
<th>Item</th>
<th>Max. score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date orientation</td>
<td>5</td>
</tr>
<tr>
<td>Place orientation</td>
<td>5</td>
</tr>
<tr>
<td>Register 3 objects</td>
<td>3</td>
</tr>
<tr>
<td>Serial sevens</td>
<td>5</td>
</tr>
<tr>
<td>Recall 3 objects</td>
<td>3</td>
</tr>
<tr>
<td>Naming</td>
<td>2</td>
</tr>
<tr>
<td>Repeating a phrase</td>
<td>1</td>
</tr>
<tr>
<td>Verbal commands</td>
<td>3</td>
</tr>
<tr>
<td>Written commands</td>
<td>1</td>
</tr>
<tr>
<td>Writing</td>
<td>1</td>
</tr>
<tr>
<td>Drawing</td>
<td>1</td>
</tr>
</tbody>
</table>

Max. score = 30

Score ≤ 24 indicates cognitive disorders
Treatment Effect Across Variables
Study 007 – Initial 12 Months

HSEM-α
(Mean, 95% CI)
(n_c = 8, n_m = 18)

Swallowing Deterioration
(Relative Risk, 95% CI)
(n_c = 8, n_m = 20)

Ambulation
(Mean, 95% CI)
(n_c = 9, n_m = 20)

MMSE
(Mean, 95% CI)
(n_c = 9, n_m = 19)
Survey I (Treatment Effect): Annualized Progression in Patients with Progressive Neurologic Disease

Swallowing (N=42)
Ambulation (N=45)
Manipulation (N=44)
Language (N=45)
Composite Score (N=45)

Treatment Effect (mean and 95% CI)
## Pediatric Sub-Study
### Change from Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>At Month 12</th>
<th>At Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 10</td>
<td>n = 9</td>
</tr>
<tr>
<td>HSEM-α mean change (95% CI)</td>
<td>-0.47 (-0.75, -0.18)</td>
<td>-0.08 (-1.02, 0.87)</td>
</tr>
<tr>
<td>Swallowing Deterioration % patients (95% CI)</td>
<td>n = 11</td>
<td>n = 10</td>
</tr>
<tr>
<td></td>
<td>27 (6, 61)</td>
<td>10 (2, 41)</td>
</tr>
<tr>
<td>Ambulation mean change (95% CI)</td>
<td>n = 11</td>
<td>n = 10</td>
</tr>
<tr>
<td></td>
<td>0.4 (-0.1, 0.8)</td>
<td>0.6 (-0.4, 1.6)</td>
</tr>
</tbody>
</table>
Survey I: Patients with Progressive Neurological Disease – Composite Score

All patients
N = 45

Age at diagnosis

< 6 years
N = 13

6-11 years
N = 16

≥ 12 years
N = 16

Annualized composite score changes (mean and 95% CI)

3941.01
Survey I: Patients with Progressive Neurological Disease – Composite Score

All patients
N = 45

Age at diagnosis

< 6 years
N = 13

6-11 years
N = 16

≥ 12 years
N = 16

Annualized composite score changes (mean and 95% CI)
Composite Score Pre- and During Treatment with Miglustat in Survey I – Pediatric Patients

Individual Annualized Progression Rate (N=29)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Estimate at 1 year</th>
<th>Miglustat start</th>
<th>Estimate at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-miglustat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unchanged (n=2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressing (n=27)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| On-miglustat |
| Slow Progress (n=23) |
| Progress Unchanged (n=1) |
| Faster Progress (n=5) |
Efficacy Conclusions

Treatment with miglustat in NP-C patients is associated with stabilization of clinically important neurologic manifestations

- Swallowing
- Ambulation
- Manipulation (dysmetria / dystonia)
- Cognition
- Language
- Composite disability score

Treatment effect of miglustat is more pronounced in NP-C patients with progressive neurologic disease and is independent of age at diagnosis in these patients
Clinical Program

Safety and Tolerability
Miglustat
Safety Database in LSD

LSD Clinical Studies
(n = 206)

GD-1 studies
100 mg t.i.d.
(n = 90)

918-001
(n = 28)

918-003
(n = 18)

918-004
(n = 34)

918-005
(n = 10)

NLSD studies
200 mg t.i.d.
(n = 100)

NP-C
918-007
(n = 40)

GD-3
918-006
(n = 30)

GM2
918-009
(n = 30)

HIV Positive
NS8-93-06-004
NS8-94-06-009
500-1000 mg t.i.d.
(n = 111)

Fabry
918-002
100 mg o.d. – b.i.d.
(n = 16)
## Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=206)</th>
<th>NP-C (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (% M:F)</strong></td>
<td>53:47</td>
<td>48:52</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>33 ± 17</td>
<td>20 ± 11</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>62 ± 21</td>
<td>59 ± 27</td>
</tr>
<tr>
<td><strong>Race (% W:B:O)</strong></td>
<td>84:4:9</td>
<td>78:5:15</td>
</tr>
<tr>
<td><strong>US : Non-US (%)</strong></td>
<td>41:59</td>
<td>55:45</td>
</tr>
</tbody>
</table>

Percent or mean ± SD
Exposure to Miglustat

Overall (N = 206)

- 6 months: 183 (88.8%)
- 12 months: 157 (76.2%)
- 18 months: 128 (62.1%)
- 24 months: 98 (47.6%)
- 3 years: 52 (25.2%)

Mean: 2.2 ± 1.5 years

NP-C (N = 40)

- 6 months: 35 (87.5%)
- 12 months: 31 (77.5%)
- 18 months: 28 (70.0%)
- 24 months: 26 (65.0%)
- 3 years: 15 (37.5%)

Mean: 2.6 ± 1.6 years
## Patient Demographics By Age Group

<table>
<thead>
<tr>
<th></th>
<th>Adults (N=161)</th>
<th>Adolescents (N=16)</th>
<th>Pediatrics (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (% M:F)</strong></td>
<td>56:44</td>
<td>50:50</td>
<td>38:62</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>39 ± 13</td>
<td>14 ± 2</td>
<td>7 ± 2</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>69 ± 16</td>
<td>53 ± 18</td>
<td>26 ± 8</td>
</tr>
</tbody>
</table>

Numbers are % or mean ± SD
## Patient Disposition by Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Adults (N=161) n (%)</th>
<th>Adolescents (N=16) n (%)</th>
<th>Pediatrics (N=29) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP-C</td>
<td>21 (13.0)</td>
<td>7 (43.8)</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>GD-1</td>
<td>90 (55.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GD-3</td>
<td>4 (2.5)</td>
<td>9 (56.3)</td>
<td>17 (58.6)</td>
</tr>
<tr>
<td>G_{M2}</td>
<td>30 (18.6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fabry</td>
<td>16 (9.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Exposure (years)</td>
<td>2.1 ± 1.5</td>
<td>2.3 ± 1.5</td>
<td>2.4 ± 1.1</td>
</tr>
</tbody>
</table>
## Frequent AEs
### Overall and by Indication

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall (N=206) %</th>
<th>NP-C (N=40) %</th>
<th>NLSD (N=100) %</th>
<th>GD-1 (N=90) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>85</td>
<td>83</td>
<td>77</td>
<td>91</td>
</tr>
<tr>
<td>Weight Decrease</td>
<td>63</td>
<td>60</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>Tremor</td>
<td>46</td>
<td>58</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>Flatulence</td>
<td>44</td>
<td>55</td>
<td>34</td>
<td>53</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>43</td>
<td>35</td>
<td>40</td>
<td>51</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>45</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Headache</td>
<td>29</td>
<td>43</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>27</td>
<td>40</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>35</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>25</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Fall</td>
<td>20</td>
<td>25</td>
<td>37</td>
<td>6</td>
</tr>
</tbody>
</table>

AEs ≥ 20% in miglustat overall population
### Frequent AEs in NLSD Studies (Initial 12 months)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Miglustat (N = 72) %</th>
<th>No Treatment (N = 29) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>82</td>
<td>31</td>
</tr>
<tr>
<td>Weight Decrease</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>Tremor</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Flatulence</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Cough</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>14</td>
<td>3</td>
</tr>
</tbody>
</table>
## Frequent AEs
### NP-C Patients (Initial 12 months)

<table>
<thead>
<tr>
<th>AEs</th>
<th>Miglustat (N = 20)</th>
<th>No Treatment (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>85%</td>
<td>44%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>70%</td>
<td>0%</td>
</tr>
<tr>
<td>Weight Decrease</td>
<td>65%</td>
<td>0%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td>Headache</td>
<td>45%</td>
<td>33%</td>
</tr>
<tr>
<td>Tremor</td>
<td>45%</td>
<td>22%</td>
</tr>
<tr>
<td>Nausea</td>
<td>35%</td>
<td>11%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35%</td>
<td>11%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Gait Spastic</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>Appetite Decrease</td>
<td>25%</td>
<td>0%</td>
</tr>
</tbody>
</table>
### Frequent AEs Overall and by Age Group

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall (N=206)</th>
<th>Adults (N=161)</th>
<th>Adolescents (N=16)</th>
<th>Pediatrics (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>85</td>
<td>88</td>
<td>81</td>
<td>66</td>
</tr>
<tr>
<td>Weight Decrease</td>
<td>63</td>
<td>71</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>Tremor</td>
<td>46</td>
<td>46</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>Flatulence</td>
<td>44</td>
<td>50</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>43</td>
<td>43</td>
<td>63</td>
<td>35</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>32</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Headache</td>
<td>29</td>
<td>26</td>
<td>56</td>
<td>31</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>21</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>22</td>
<td>38</td>
<td>7</td>
</tr>
<tr>
<td>Cough</td>
<td>19</td>
<td>13</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>16</td>
<td>17</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15</td>
<td>11</td>
<td>25</td>
<td>28</td>
</tr>
</tbody>
</table>

Based on the frequent AEs observed during the first 12 months in NLSD patients.
# Dosing Regimen and AEs
## First 6 Months of Treatment

<table>
<thead>
<tr>
<th></th>
<th>GD-1 N=18 50mg t.i.d. %</th>
<th>GD-1 N=72 100mg t.i.d. %</th>
<th>NLSD N=100 200mg t.i.d. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>94</td>
<td>88</td>
<td>76</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>67</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>Flatulence</td>
<td>50</td>
<td>49</td>
<td>32</td>
</tr>
<tr>
<td>Tremor</td>
<td>44</td>
<td>25</td>
<td>41</td>
</tr>
<tr>
<td>Headache</td>
<td>44</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>28</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>15</td>
<td>19</td>
</tr>
</tbody>
</table>
### Frequent AEs
(1000 mg t.i.d. for 12 - 24 Weeks)
**HIV-Positive Patients**

<table>
<thead>
<tr>
<th></th>
<th>Miglustat (N = 87) %</th>
<th>Placebo (N = 74) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>89</td>
<td>34</td>
</tr>
<tr>
<td>Flatulence</td>
<td>59</td>
<td>22</td>
</tr>
<tr>
<td>Nausea</td>
<td>46</td>
<td>28</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45</td>
<td>28</td>
</tr>
<tr>
<td>Headache</td>
<td>44</td>
<td>30</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>31</td>
<td>20</td>
</tr>
</tbody>
</table>

*AEs incidence with miglustat > 5% difference from Placebo*
Deaths Among NP-C Patients

- 22 year old female
  - Died of respiratory distress
  - 2 weeks after stopping treatment due to disease progression
  - Treatment duration 13 months

- 20 year old male
  - Died of traffic accident
  - 6 months after stopping treatment at his own request
  - Treatment duration > 3 years

- 11 year old female
  - Died of pneumonia
  - 8 months after stopping treatment because of painful defecation / Crohn’s disease
  - Treatment duration 4 years
Serious AEs

41 of 206 (19.9%) patients experienced an SAE
- Viral infection in 3 patients (1.5%)
- Other SAEs were reported in 1-2 patients each

11 of 40 (27.5%) NP-C patients experienced an SAE
- Viral infection in 2 patients (5%)

Initial 12-month period in NLSD studies
- 8 of 72 (11.1%) of miglustat patients and 4 of 29 (13.8 %) of No-Treatment patients had at least 1 SAE
AEs Leading to Discontinuation (D/C)

37 of 206 (18.0%) patients experienced an AE leading to D/C
- Diarrhea (8 patients – 3.9%)
- Tremor (5 patients – 2.4%)
- Flatulence and weight loss (4 patients each – 1.9%)

9 of 40 (22.5%) NP-C patients
- Depression (2 patients – 5%)

Initial 12-month period in NLSD studies
- 6 of 72 (8.3%) patients D/C miglustat treatment
- Depression and weight loss (2 patients each – 2.8%)
Other Safety Observations

Laboratory tests
- Small reduction in platelets during the first year of treatment
- No clinically relevant changes in any other laboratory tests

Vital signs
- No evidence for any effect on heart rate or blood pressure

ECGs
- No clinically relevant changes in ECG variables
AEs of Interest

GI disorders
- Diarrhea, flatulence, nausea, vomiting and abdominal pain

Nervous system disorders
- Tremor, headache and paresthesia

Other AEs
- Weight loss

Laboratory abnormalities
- Decreased platelets
Gastrointestinal AEs

Diarrhea, flatulence, nausea, vomiting and abdominal pain
- Most AEs mild or moderate, not dose related
- Inhibition of intestinal sucrase and isomaltase
- 4 (1.9%) patients experienced GI SAEs
  - Diarrhea / Crohn’s disease and vomiting / viral infection (NP-C)
  - Constipation 2 patients (GD-3)
- 8 (3.9%) patients D/C due to diarrhea
  - 1 NP-C patient
- Manageable in clinical practice, decrease over time, most patients tolerate long term treatment, reversible upon D/C
Neurological AEs

- Tremor, headache and paresthesia
  - Most AEs were mild to moderate
  - No cases reported as SAEs
  - Relatedness difficult to assess in patients with neurological disease
- New-onset tremor led to D/C of 5 pts (2.4%), none in NP-C
- Paresthesia led to D/C in 2 GD-1 patients
- 3 NP-C patients (7.5%) D/C due to neurological AEs
- Most patients tolerate long-term treatment
- Reversible upon D/C
Weight Loss

The second most frequently reported AE
- 129 (63%) patients of the overall population
- Mild or moderate in 95% of the cases
- Observed mainly during the first year of treatment
- No SAE
- Led to D/C in 4 cases (< 2%)
  - No D/C among children
  - No D/C in NP-C patients
Weight and Height Changes
Pediatric NLSD Patients

Initial 12 Months

Weight

Height

Data displayed as mean and 95% CI
Weight and Height Changes
Adolescent NLSD Patients

Initial 12 Months

Weight

Height

Data displayed as mean and 95% CI

Miglustat (N = 12) No treatment (N = 4)

Weight (kg)

Height (cm)

Baseline
Month 12/LV
Baseline
Month 12/LV

53.6 51.4 59.1 58.7

152 156 163 165

3122.01
Platelet Count in NP-C

- No progressive reduction over time
- 6 patients with platelet count $< 100 \times 10^9$/L
- No patient with platelet count $< 50 \times 10^9$/L
- No D/C due to thrombocytopenia and no bleeding episodes
- Reduced platelet count is known to be associated with NP-C (residual splenomegaly)
- Platelet monitoring recommended
Safety Conclusions

- Safety profile of miglustat in neuronopathic LSD (including NP-C) is comparable with GD-1
- AE profile of miglustat treatment is well characterized and consistent across doses, diseases and age groups
- With the proposed recommendations for monitoring (platelets and growth) the USPI provides adequate information to physicians and patients
Benefit – Risk Assessment
Benefit – Risk Background

- NP-C disease is a very rare, genetic disorder dominated by central nervous system involvement.
- NP-C neurologic disease is progressively disabling and leads to early death.
- There is no approved therapy for NP-C disease in the US.
- Availability of treatment that can stabilize or reduce the rate of neurologic deterioration would represent an important advancement in the clinical management of NP-C disease.
Benefits of Miglustat Treatment

Treatment with miglustat in patients suffering from NP-C disease is associated with stabilization of clinically important neurologic manifestations

- Swallowing
- Ambulation
- Manipulation (dysmetria / dystonia)
- Cognition
- Language
- Composite disability score
Risks of Miglustat Treatment

- GI intolerance
  - Diarrhea, flatulence, abdominal pain, nausea and vomiting
- Nervous system side effects
  - Tremor, headache and paresthesia
- Weight loss
- Growth in children
- Platelet reduction
NP-C Disease Registry

Ongoing registry collecting prospective data in NP-C patients (treated or not treated with miglustat)

- Natural history of the disease
- Treatment outcomes / effectiveness
  - NP-C disability scale
- Monitoring of safety
  - Gastrointestinal, neurological and other AEs
  - Platelet counts
  - Growth in children
Benefit – Risk Conclusions

- Treatment with miglustat has clinically meaningful benefits that outweigh its well characterized and manageable risks
- Miglustat addresses an unmet medical need in the treatment of patients with progressive neurologic manifestations of NP-C disease
Miglustat is indicated for the treatment of progressive neurological manifestations in adult and pediatric patients with Niemann-Pick type C disease
Clinical Perspective

Marc C. Patterson, MD
Professor of Neurology, Pediatrics and Medical Genetics
Chair, Division of Child and Adolescent Neurology
Mayo Clinic, Rochester, MN
Clinical Experience Before Miglustat Availability

N=78

[unpublished data of the CETNP]
Case History 1 – Early Development and Presentation

- Normal gestation, delivery and infancy
- Speech therapy (articulation) for one year pre-kindergarten
- 3 years – impaired attention, impulsivity, impaired language
  - composite score 0.15
- 6 years – absence seizures
- 7 years – complex partial seizures
- 10 years – increasing hypersomnolence, dysarthria, dysphagia, dystonia, vertical gaze palsy, intractable seizures
- 10 years, 7 months
  - composite score 0.28
Case History 1 – Current (13 years old)

- **Cerebellum**
  - severely ataxic, walking only with assistance
  - severe dysarthria, drooling, coughing
  - gastrostomy tube feeding

- **Brainstem**
  - sleep inversion, cataplexy
  - complete VSGP, early HSGP

- **Basal ganglia**
  - dystonia

- **Cortex**
  - pseudobulbar affect, depression
  - uncontrolled seizures
  - school failure

- **No organomegaly, systemic findings**
  - composite score – 0.73
Case History 2

- Normal gestation, delivery and infancy
- 3.5 years – splenomegaly
- 5 years – NP-C diagnosed
- 9 years – early VSGP
  - Composite score 0
- 19.25 years – mild ataxia, dystonia, dysarthria
  - Composite score 0.21
  - Miglustat introduced
- 24.75 years – last follow-up
  - Ataxia, dystonia, dysarthria stable
  - Composite score 0.21
Conclusions

- Relentlessly progressive, lethal neurologic disease
- Until miglustat, no disease-modifying therapy available
- Treatment with miglustat in NP-C patients is associated with stabilization of neurologic disease
Miglustat Therapy for Niemann-Pick Type C Disease

Actelion Pharmaceuticals Ltd
### Physician’s assessment of the change in patient’s general health since treatment start - Survey I

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much better</td>
<td>6</td>
<td>10.0</td>
</tr>
<tr>
<td>Somewhat better</td>
<td>16</td>
<td>26.7</td>
</tr>
<tr>
<td>About the same</td>
<td>24</td>
<td>40.0</td>
</tr>
<tr>
<td>Somewhat worse</td>
<td>12</td>
<td>20.0</td>
</tr>
<tr>
<td>Much worse</td>
<td>2</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Missing value N=6
Physician’s assessment of patient’s benefit
Survey I

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Good</td>
<td>22</td>
<td>37.9</td>
</tr>
<tr>
<td>Fair</td>
<td>19</td>
<td>32.8</td>
</tr>
<tr>
<td>Poor</td>
<td>10</td>
<td>17.2</td>
</tr>
<tr>
<td>None</td>
<td>5</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Missing value N=8
# Withdrawals up to Month 24 in Study 007 Adult/Adolescent Patient

<table>
<thead>
<tr>
<th>Study phase/treatment</th>
<th>Patient No</th>
<th>Reason for withdrawal</th>
<th>Time in study / time on miglustat (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>12-month comparative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miglustat</td>
<td>007-102</td>
<td>NP-C disease progression</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>007-103</td>
<td>NP-C disease progression</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>007-109</td>
<td>Diarrhea, Crohn’s disease</td>
<td>6.6</td>
</tr>
<tr>
<td>No-Treatment</td>
<td>007-213</td>
<td>Family request (return to alternative therapy)</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>12-month extended therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continued miglustat</td>
<td>007-104</td>
<td>Axonal neuropathy</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>007-212</td>
<td>Patient request (travel difficulties)</td>
<td>23.5</td>
</tr>
<tr>
<td>No-Treatment switched to</td>
<td>007-101</td>
<td>Hemorrhagic diarrhea</td>
<td>22.1 / 10.6</td>
</tr>
<tr>
<td>miglustat after Month 12</td>
<td>007-108</td>
<td>Patient request (based on impression of risk and GI adverse events [abdominal pain,</td>
<td>13.5 / 1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diarrhea, flatulence])</td>
<td></td>
</tr>
<tr>
<td></td>
<td>007-113</td>
<td>Patient request (concern about side effects [adverse events]; abdominal pain, diarrhea,</td>
<td>16.4 / 4.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nausea, flatulence and aggravated tremor)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>007-208</td>
<td>Worsening of Tremor</td>
<td>20.3 / 8.7</td>
</tr>
</tbody>
</table>
### Withdrawals beyond Month 24 in Study 007 Adult/Adolescent Patient

<table>
<thead>
<tr>
<th>Study phase/treatment</th>
<th>Patient No</th>
<th>Reason for withdrawal</th>
<th>Time in study / time on miglustat (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continued extension therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miglustat</td>
<td>007-210</td>
<td>Non-compliance (refusal to take drug)</td>
<td>30.7 / 18.7</td>
</tr>
<tr>
<td></td>
<td>007-105</td>
<td>Lost to follow up</td>
<td>59.2 / 47.5</td>
</tr>
<tr>
<td></td>
<td>007-112</td>
<td>Patient request</td>
<td>38.7 / 27.0</td>
</tr>
<tr>
<td>No-Treatment switched to miglustat after Month 12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### HSEM-α by Center

#### 12 Months Adult/Adolescent Patients

<table>
<thead>
<tr>
<th>Center</th>
<th>No Treatment</th>
<th>Miglustat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Center 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>BL (mean ± SD)</td>
<td>1.77 ± 1.16</td>
<td>2.94 ± 2.09</td>
</tr>
<tr>
<td>Δ from BL (mean) (95% CI)</td>
<td>-0.12 (-0.36, 0.12)</td>
<td>-0.76 (-1.47, -0.05)</td>
</tr>
<tr>
<td><strong>Center 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>BL (mean ± SD)</td>
<td>3.68 ± 1.01</td>
<td>3.07 ± 2.31</td>
</tr>
<tr>
<td>Δ from BL (mean) (95% CI)</td>
<td>+0.49 (-1.19, 1.98)</td>
<td>-0.22 (-0.76, 0.32)</td>
</tr>
</tbody>
</table>
## Responder Analysis

<table>
<thead>
<tr>
<th></th>
<th>Swallowing</th>
<th>Ambulation</th>
<th>Cognitive function</th>
<th>Overall disease stability†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults/ Adolescents with available data*</td>
<td>19</td>
<td>19</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Improved / stable, n (%)</td>
<td>15 (79)</td>
<td>17 (90)</td>
<td>14 (78)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>Children with available data*</td>
<td>9</td>
<td>10</td>
<td>–</td>
<td>10</td>
</tr>
<tr>
<td>Improved / stable, n (%)</td>
<td>9 (100)</td>
<td>8 (80)</td>
<td>–</td>
<td>8 (80)</td>
</tr>
</tbody>
</table>

† Patients were classified as having stable disease if there was no deterioration in swallowing, ambulation (SAI) and cognitive function (MMSE; in adolescents and adults only)
### SF-36® Over 12 Months
**Adult / Adolescent Patients**

<table>
<thead>
<tr>
<th></th>
<th>No Treatment</th>
<th></th>
<th>Miglustat</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Baseline value (Mean ± SD)</td>
<td>Mean change from baseline (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>8</td>
<td>81.3 ± 24.6</td>
<td>2.5 (-11.4, 16.4)</td>
<td>17</td>
</tr>
<tr>
<td>Role-physical</td>
<td>8</td>
<td>87.5 ± 26.7</td>
<td>-12.5 (-37.0, 12.0)</td>
<td>17</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>8</td>
<td>90.0 ± 17.0</td>
<td>-6.6 (-21.8, 8.6)</td>
<td>17</td>
</tr>
<tr>
<td>General health</td>
<td>7</td>
<td>71.7 ± 19.5</td>
<td>-2.6 (-13.8, 8.6)</td>
<td>17</td>
</tr>
<tr>
<td>Vitality</td>
<td>8</td>
<td>62.5 ± 16.5</td>
<td>-1.5 (-11.6, 8.6)</td>
<td>17</td>
</tr>
<tr>
<td>Social functioning</td>
<td>8</td>
<td>89.1 ± 14.1</td>
<td>-6.3 (-22.4, 9.8)</td>
<td>17</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>8</td>
<td>75.0 ± 38.8</td>
<td>20.8 (-6.6, 48.2)</td>
<td>17</td>
</tr>
<tr>
<td>Mental health</td>
<td>8</td>
<td>80.5 ± 12.6</td>
<td>-3.0 (-13.5, 7.5)</td>
<td>17</td>
</tr>
<tr>
<td>Physical component</td>
<td>7</td>
<td>51.2 ± 6.5</td>
<td>-3.6 (-8.3, 1.1)</td>
<td>17</td>
</tr>
<tr>
<td>Mental component</td>
<td>7</td>
<td>49.9 ± 7.2</td>
<td>2.5 (-3.9, 8.9)</td>
<td>17</td>
</tr>
</tbody>
</table>

SD = standard deviation
Normalization in Lysosomal Volume with Miglustat Treatment

Evaluated in B-lymphocytes of an NP-C patient

Days of treatment with miglustat

% fluorescence relative to control

0 50 100 150 200 250

0 100 200 300 400 500 600 700

Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Diagnosis | Estimate at 1 year | Miglustat start | Estimate at 1 year

Pre-miglustat
- Unchanged
- Progressing

On-miglustat
- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Composite Score

Pre-miglustat

- Unchanged
- Progressing

On-miglustat

- Slower Progression
- Progression Unchanged
- Faster Progression

Diagnosis

Estimate at 1 year

Miglustat start

Estimate at 1 year
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Pre-miglustat
- Unchanged
- Progressing

On-miglustat
- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Pre-miglustat
- Unchanged
- Progressing

On-miglustat
- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Pre-miglustat
- Unchanged
- Progressing

On-miglustat
- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Pre-miglustat

- Changed
- Progressing

On-miglustat

- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Pre-miglustat
- Unchanged
- Progressing

On-miglustat
- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Pre-miglustat
- Unchanged
- Progressing

On-miglustat
- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

- Pre-miglustat
  - Unchanged
  - Progressing

- On-miglustat
  - Slower Progression
  - Progression Unchanged
  - Faster Progression

Diagnosis
Estimate at 1 year
Miglustat start
Estimate at 1 year
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Pre-miglustat
- Unchanged
- Progressing

On-miglustat
- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

- **Pre-miglustat**
  - Yellow: Unchanged
  - Red: Progressing

- **On-miglustat**
  - Green: Slower Progression
  - Yellow: Progression Unchanged
  - Red: Faster Progression

Diagnosis

Estimate at 1 year

Miglustat start

Estimate at 1 year
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

- Diagnosis
- Estimate at 1 year
- Miglustat start
- Estimate at 1 year

Pre-miglustat
- Unchanged
- Progressing

On-miglustat
- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Pre-miglustat
- Unchanged
- Progressing

On-miglustat
- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

- Pre-miglustat
  - Unchanged
  - Progressing

- On-miglustat
  - Slower Progression
  - Progression Unchanged
  - Faster Progression
Composite Score Pre- and During Treatment with Miglustat in Survey I

Individual Annualized Progression Rate

- **Pre-miglustat**
  - Yellow: Unchanged
  - Red: Progressing

- **On-miglustat**
  - Green: Slower Progression
  - Yellow: Progression Unchanged
  - Red: Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

![Graph showing progression rates before and during miglustat treatment.](chart)

- **Pre-miglustat**
  - Unchanged
  - Progressing

- **On-miglustat**
  - Slower Progression
  - Progression Unchanged
  - Faster Progression
Composite Score Pre- and During Treatment with Miglustat in Survey I

Individual Annualized Progression Rate

- **Pre-miglustat**
  - Unchanged
  - Progressing

- **On-miglustat**
  - Slower Progression
  - Progression Unchanged
  - Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Diagnosis

Estimate at 1 year

Miglustat start

Estimate at 1 year

Composite Score

Pre-miglustat

On-miglustat

Unchanged

Progressing

Slower Progression

Progression Unchanged

Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

Pre-miglustat

On-miglustat

Estimate at 1 year

Estimate at 1 year

Diagnosis

Miglustat start

- Unchanged
- Progressing

- Slower Progression
- Progression Unchanged
- Faster Progression
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate (N=19)

- Diagnosis
- Estimate at 1 year
- Miglustat start
- Estimate at 1 year

Pre-miglustat:
- Unchanged (n=2)
- Progressing (n=17)

On-miglustat:
- Slower Progression (n=14)
- Progression Unchanged (n=2)
- Faster Progression (n=3)