Restabilization of chronic inflammatory demyelinating polyneuropathy patients with IVIG: restabilization phase of the PATH study
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

- Symmetric (motor and sensory) proximal and distal neuropathy
- Follows a monophasic, progressive or relapsing course
- Developing over 2 months or more\(^1,2\)

1.6–8.9 cases per 100,000 adults
- Can occur in children and adults at any age, with a peak prevalence in adults aged 50 to 60\(^1\)

First-line treatments include\(^5\)
- IVIG (intravenous immunoglobulin)
- Corticosteroids
- Plasma exchange

CIDP: chronic inflammatory demyelinating polyneuropathy; IVIG: intravenous immunoglobulin

PATH Study: Restabilization Phase
PATH Study Design

A randomized, multicenter, double-blind, placebo-controlled, parallel-group, phase III study

Inclusion criteria
- Definite or probable CIDP according to the EFNS/PNS criteria 2010
- An IVIG treatment during the last 8 weeks prior to enrollment
- Age ≥18 years

CIDP: chronic inflammatory demyelinating polyneuropathy; EFNS: European Federation of Neurological Societies; IVIG: intravenous immunoglobulin; SCIG: subcutaneous immunoglobulin; PNS: Peripheral Nerve Society

PATH IVIG Restabilization Phase\textsuperscript{1,2}

Pre-randomization phase

<table>
<thead>
<tr>
<th>Loading dose</th>
<th>Maintenance dose (Weeks 4, 7, 10 and 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g/kg bw over 2 to 5 consecutive days (maximum 1 g/kg bw on a single day)</td>
<td>1 g/kg bw every 3 weeks over 1 or 2 consecutive days (3 or 4 doses as required)</td>
</tr>
</tbody>
</table>

Those achieving CIDP stability\* continued to SC randomized period

Those not achieving CIDP stability\* discontinued

\*CIDP stability:
- Recovery of CIDP status to at least the status at screening
- No clinically meaningful difference in CIDP status at the last 2 consecutive visits

bw: body weight; CIDP: chronic inflammatory demyelinating polyneuropathy; SC: subcutaneous

PATH Restabilization Phase Objectives

Primary Objective
• To investigate the efficacy of IVIG for restabilization of patients with CIDP

Secondary Objective
• To investigate the safety of IVIG for restabilization of patients with CIDP

Exploratory Objective
• To investigate serum IgG levels within the IVIG restabilization period

CIDP: chronic inflammatory demyelinating polyneuropathy; IgG: immunoglobulin G; IVIG: intravenous immunoglobulin
*All Data on file references will be updated upon publication of the PATH manuscript
1. CSL Behring Data on file.
Secondary Endpoint Efficacy Assessments¹

- **Adjusted INCAT Score**: 10-point score assessing functionality of legs and arms. Arm disability: 0 “no upper limb problems” to 5 ‘inability to use either arm for any purposeful movement”. Leg disability: 0 “walking not affected” to 5 ‘restricted to wheelchair, unable to stand and walk a few steps with help”.

- **MRC Sum Score**: Sum of 8 muscle group scores. Grades muscle movement from 0 ‘no visible contraction’ to 5 ‘normal’.

- **Mean Grip Strength**: Grip strength measured by Martin Vigorimeter.

- **R-ODS Centile Score**: 24-item questionnaire capturing activity and social participation.

**Improvement**: ≥1 point decrease in adjusted INCAT score*, ≥3 point increase in MRC sum score, ≥8 kPa increase in mean grip strength, or ≥4 point increase in R-ODS centile score.

*Adjusted INCAT score: changes in upper limb function from 0 to 1 or 1 to 0 were not recorded as deterioration or improvement.

INCAT: Inflammatory Neuropathy Cause and Treatment; MRC: Medical Research Council; R-ODS: Rasch-built Overall Disability Scale.

CIDP: chronic inflammatory demyelinating polyneuropathy; IVIG: intravenous immunoglobulin

1. Mielke O et al. Poster and abstract presented at Annual Meeting of the Peripheral Nerve Society (PNS); July 8-12, 2017; Sitges, Spain.
# Patient Demographics: IVIG Restabilization Period

<table>
<thead>
<tr>
<th></th>
<th>Overall N=207</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>56.5 (12.8)</td>
</tr>
<tr>
<td><strong>Sex, N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male / Female</td>
<td>131 (63.3) / 76 (36.7)</td>
</tr>
<tr>
<td><strong>Race, N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>186 (89.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>17 (8.2)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td><strong>Weight (at screening), kg</strong></td>
<td>82.2 (18.3)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>27.3 (5.0)</td>
</tr>
<tr>
<td><strong>Time since initial CIDP diagnosis, years</strong></td>
<td>4.66 (5.2)</td>
</tr>
<tr>
<td><strong>EFNS/PNS CIDP diagnostic criteria, N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>185 (89.4)</td>
</tr>
<tr>
<td>Probable</td>
<td>22 (10.6)</td>
</tr>
<tr>
<td><strong>Screening INCAT total score</strong></td>
<td>2.7 (1.67)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation) unless otherwise stated.
Efficacy: IVIG Restabilization Period

- 91% of patients with improvement in ≥1 outcome measure\(^1\)
- 83% of patients achieved CIDP stability\(^1\)
- 73% of patients achieved CIDP improvement by adjusted INCAT score\(^1\)
  - 21% of patients improved beyond their CIDP status at study entry\(^2\)

<table>
<thead>
<tr>
<th>Number of events (improvements), N (%)</th>
<th>Adjusted INCAT Score*</th>
<th>R-ODS Centile Score</th>
<th>Mean Grip Strength, Dominant Hand</th>
<th>MRC Sum Score</th>
<th>First Improvement in Any Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall N=207</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>151 (72.9)</td>
<td>84 (40.6)</td>
<td>123 (59.4)</td>
<td>117 (56.5)</td>
<td>188 (90.8)</td>
<td></td>
</tr>
<tr>
<td>Time to first improvement, days</td>
<td>Median</td>
<td>26.0</td>
<td>71.0</td>
<td>65.0</td>
<td>23.0</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>24.0–41.0</td>
<td>66.0–86.0</td>
<td>64.0–66.0</td>
<td>22.0–23.0</td>
</tr>
</tbody>
</table>

*Adjusted INCAT score: changes in upper limb function from 0 to 1 or 1 to 0 were not recorded as deterioration or improvement

CIDP: chronic inflammatory demyelinating polyneuropathy; INCAT: Inflammatory Neuropathy Cause and Treatment; IVIG: intravenous immunoglobulin; MRC: Medical Research Council; R-ODS: Rasch-built Overall Disability Scale

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2. CSL Behring Data on file.
Percentage of Responders in IVIG Restabilization Period

*Responders = improvement in terms of ≥ 1 point in adjusted INCAT score
Changes in upper limb function from 1 to 0 were not recorded as improvement. Mean baseline adjusted INCAT score: 2.7
INCAT: Inflammatory Neuropathy Cause and Treatment; IVIG: intravenous immunoglobulin

1. CSL Behring Data on file.
PATH Study: Restabilization with IVIG

INCAT: Inflammatory Neuropathy Cause and Treatment; MRC: Medical Research Council; IVIG: intravenous immunoglobulin; R-ODS: Rasch-built Overall Disability Scale

1. Mielke O et al. Poster and abstract presented at Annual Meeting of the Peripheral Nerve Society (PNS); July 8-12, 2017; Sitges, Spain.
PATH Study: IVIG Efficacy Overview

- 91% of patients improved in ≥1 predefined outcome measure\(^1\)
- 21% of patients improved CIDP status beyond that at study entry\(^2\)
- CIDP status improved rapidly after treatment with IVIG\(^1\)
  - Median 23 days to improvement in ≥1 outcome measure
- 83% of patients achieved CIDP stability with IVIG\(^1\)
- All efficacy outcome measures showed clinically relevant improvements during the Restabilization Period\(^1\)
  - 1.2 points in INCAT score
  - 5.7 points in R-ODS
  - 12.15 kPa in mean grip strength (dominant hand)
  - 3.6 points in MRC sum score

CIDP: chronic inflammatory demyelinating polyneuropathy; INCAT: Inflammatory Neuropathy Cause and Treatment; IVIG: intravenous immunoglobulin; MRC: Medical Research Council; R-ODS: Rasch-built Overall Disability Score

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2. CSL Behring Data on file.
### PATH Study: Adverse Events in IVIG Restabilization Period\(^1,\!^2\)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Patients, N (%)</th>
<th>Number of AEs</th>
<th>Rate per Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL</td>
<td>100 (48.3)</td>
<td>284</td>
<td>0.175</td>
</tr>
<tr>
<td>Headache</td>
<td>34 (16.4)</td>
<td>53</td>
<td>0.033</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12 (5.8)</td>
<td>12</td>
<td>0.007</td>
</tr>
</tbody>
</table>

AEs reported in ≥5% of subjects are listed

- 57 (27.5%) patients experienced an AE considered related to IVIG
- 11 (5.3%) patients experienced a serious AE\(^1\)
- 4 (1.9%) patients withdrew as a result of an AE\(^1\)

AE: adverse event; IVIG: intravenous immunoglobulin

1. CSL Behring Data on file.
2. Mielke O et al. Poster and abstract presented at Annual Meeting of the Peripheral Nerve Society (PNS); July 8-12, 2017; Sitges, Spain.
**PATH Study: IVIG Safety Overview**

- Mean (range) duration of exposure: 65.9 (2–100) days
- Mean (range) number of infusions: 7.8 (2–13)
- 100 (48.3%) patients experienced an AE, 27.5% experienced an AE considered related to IVIG
  - The majority were mild or moderate
- 11 (5.3%) patients experienced a serious AE
  - 7 serious AEs were considered related to IVIG: hypersensitivity; pulmonary embolism; increased blood pressure; exacerbation of CIDP; respiratory failure; rash; migraine
  - All serious AEs resolved without sequelae
- 4 patients withdrew as a result of an AE
- Hemolysis was seen in 3.4% of patients, most did not present with clinical symptoms and no subjects required clinical intervention (no serious AEs)

AE: adverse event; CIDP: chronic inflammatory demyelinating polyneuropathy; IVIG: intravenous immunoglobulin

1. CSL Behring Data on file.
2. Mielke O et al. Poster and abstract presented at Annual Meeting of the Peripheral Nerve Society (PNS); July 8-12, 2017; Sitges, Spain.
• Following the IVIG loading dose, the mean increase in serum IgG levels was 19.3 g/L

• At Week 4, before the first maintenance dose, IgG levels had decreased to a level above that at the Reference Visit

IgG: immunoglobulin G; IVIG: intravenous immunoglobulin

1. CSL Behring Data on file.
PATH Study: IVIG Conclusions

IVIG reduces disability in patients with CIDP by improving neuromuscular disability after previous clinical deterioration.

IVIG demonstrated clinically relevant improvements in a variety of clinical outcome measures: a rapid response to therapy, CIDP stability, and improvement even beyond the CIDP status at study entry.

IVIG was well tolerated when administered as loading and maintenance intravenous infusions.

CIDP: chronic inflammatory demyelinating polyneuropathy; IVIG: intravenous immunoglobulin