20% Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomized, double-blind, placebo-controlled, phase 3 trial
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\(^3,4\)
- Can occur in children and adults at any age, with a peak prevalence in adults aged 50 to 60\(^1\)

First-line treatments include\(^5\)
- Intravenous immunoglobulins (IVIG)
- Corticosteroids
- Plasma exchange

CIDP: chronic inflammatory demyelinating polyneuropathy; IVIG: intravenous immunoglobulin

First large-scale, randomized, placebo-controlled, phase 3 clinical trial investigating SCIG for the treatment of CIDP, and the largest CIDP study to date

Rationale

- IVIG products have become an established treatment for CIDP
- As compared to hospital-based IVIG, subcutaneous immunoglobulin (SCIG) offers self-administration at a time and place that suits patients resulting in increased autonomy, increased QoL, a lower rate of systemic reactions, potential cost savings, and more stable IgG levels which are associated with a reduction in wear-off effects
- Small studies previously indicated potential benefits of SCIG for CIDP
- Before PATH, no large-scale randomized clinical trials had unequivocally demonstrated the efficacy and safety of SCIG in CIDP

CIDP: chronic inflammatory demyelinating polyneuropathy; IgG: immunoglobulin G; IVIG: intravenous immunoglobulin; QoL: quality of life; SCIG: subcutaneous immunoglobulin
**PATH Study Objective:** To determine the efficacy and safety of SCIG using 2 different doses of 20% SCIG 0.2 g/kg bw weekly and 0.4 g/kg bw weekly, in the maintenance treatment of CIDP in comparison with placebo.

### Primary Endpoint

The percentage of patients with a CIDP relapse (based on adjusted INCAT) or who were withdrawn for any other reason during 24 weeks of SCIG treatment.

### Secondary Endpoints

- **Time to CIDP relapse or withdrawal for any other reason (primary endpoint) in the SCIG treatment period**

- **Differences between groups of the median changes from baseline to completion visits in:**
  - INCAT score
  - R-ODS
  - Mean grip strength (measured using a Martin Vigorimeter)
  - MRC sum score

- **Safety**

- **Exploratory endpoints include serum IgG levels and QoL assessments**

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bw: body weight; CIDP: chronic inflammatory demyelinating polyneuropathy; IgG: immunoglobulin G; INCAT: Inflammatory Neuropathy Cause and Treatment; IVIG: intravenous immunoglobulin; MRC: Medical Research Council; QoL: quality of life; R-ODS: Rasch-built Overall Disability Scale; SCIG: subcutaneous immunoglobulin

Efficacy Assessments

Primary Efficacy Endpoint

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”

Secondary Efficacy Endpoints

MRC 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 Score
- 24-item questionnaire capturing activity and social participation

Improvement = 1 point in adjusted INCAT score*, 3 points in the MRC sum score, 8 kPa in mean grip strength, or 4 points 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

A randomized, multicenter, double-blind, placebo-controlled, parallel-group phase 3 study of subcutaneous immunoglobulin following re-stabilization on intravenous immunoglobulin following treatment.

**Screening**
- N=276

**IVIG dependency**
- N=245
  - No deterioration after 12 weeks
    - STOP
    - 4-12 weeks

**IVIG re-stabilization**
- N=207
  - Not re-stabilized after 12 weeks
    - STOP
    - 10-13 weeks

**Pre-randomization Phase**

**Post-randomization Phase**
- Placebo
- SCIG 0.2 g/kg bw weekly
- SCIG 0.4 g/kg bw weekly
  - N=172
  - CIDP relapse within 24 weeks
  - STOP

**Historical Notes**

bw: body weight; CIDP: chronic inflammatory demyelinating polyneuropathy; IVIG: intravenous immunoglobulin; SCIG: subcutaneous immunoglobulin
PATH: Study Design & Patient Disposition

276 screened
- 31 (11%) screen failures

245 entered IVIG dependency test period
- 28 (11%) were not IVIG dependent
- 10 (4%) withdrew for other reasons

207 entered IVIG re-stabilization period
- 22 (11%) no re-stabilization in 13 weeks
- 14 (7%) withdrew for other reasons

172 randomized

Placebo (N=57)

SCIG 0.2 g/kg bw weekly (N=57)

SCIG 0.4 g/kg bw weekly (N=58)

Screening ≤ 2 weeks

Ig dependency up to 12 weeks

Re-stabilization 10-13 weeks

SC treatment 25 weeks

bw: body weight; Ig: immunoglobulin; IVIG: intravenous immunoglobulin; SC: subcutaneous

1. van Schaik IN et al. Poster and abstract presented at Annual Meeting of the American Academy of Neurology (AAN); April 22-28, 2017; Boston, MA.
### PATH: Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=57)</th>
<th>SCIG 0.2 g/kg bw weekly (N=57)</th>
<th>SCIG 0.4 g/kg bw weekly (N=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>57.6</td>
<td>58.9</td>
<td>55.2</td>
</tr>
<tr>
<td>Min, Max</td>
<td>28.6, 77.0</td>
<td>25.8, 77.6</td>
<td>24.7, 82.7</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>85.8</td>
<td>83.3</td>
<td>79.4</td>
</tr>
<tr>
<td>Min, Max</td>
<td>41.7, 130.2</td>
<td>55.0, 125.0</td>
<td>42.0, 133.0</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (64.9)</td>
<td>42 (73.7)</td>
<td>31 (53.4)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (35.1)</td>
<td>15 (26.3)</td>
<td>27 (46.6)</td>
</tr>
<tr>
<td><strong>Time since initial diagnosis, (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.7</td>
<td>2.8</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>Previous IVIG treatments prior to enrollment, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>6 (10.5)</td>
<td>5 (8.8)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>≥4</td>
<td>51 (89.5)</td>
<td>52 (91.2)</td>
<td>54 (93.1)</td>
</tr>
</tbody>
</table>

bw: body weight; IVIG: intravenous immunoglobulin; SCIG: subcutaneous immunoglobulin

Efficacy
PATH Randomization Results: CIDP Relapse Or Withdrawal (Primary Endpoint)¹

- When assessing CIDP relapse only, relapse rates were 56% for placebo, 33% for SCIG 0.2 g/kg bw weekly, and 19% for SCIG 0.4 g/kg bw weekly

bw: body weight; CIDP: chronic inflammatory demyelinating polyneuropathy; SCIG: subcutaneous immunoglobulin

PATH: Primary Endpoint Analysis

- **Placebo**: 37% No relapse, 56% Relapse, 7% Withdrawal
- **SCIG 0.2 g/kg bw weekly**: 61% No relapse, 33% Relapse, 5% Withdrawal
- **SCIG 0.4 g/kg bw weekly**: 67% No relapse, 19% Relapse, 14% Withdrawal

bw: body weight; SCIG: subcutaneous immunoglobulin

PATH Secondary Endpoints: Time To CIDP Relapse (Kaplan-Meier)

bw: body weight; CIDP: chronic inflammatory demyelinating polyneuropathy; SCIG: subcutaneous immunoglobulin

### PATH Secondary Endpoints: Changes From Baseline In Efficacy Outcomes

Baseline scores were the last scores before randomization. All tests were one-sided p values. Statistical significance was defined at a p value of <0.025 (explorative). For INCAT, an increase in score is a deterioration; for R-ODS, grip strength, and MRC, a decrease in score (negative number) is a deterioration.

*Changes were statistically significant vs placebo. No significant differences were observed between the two dose groups

†kPa dominant hand

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SCIG 0.2 g/kg bw weekly</th>
<th>p vs Placebo</th>
<th>SCIG 0.4 g/kg bw weekly</th>
<th>p vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INCAT total score</strong></td>
<td>1.0</td>
<td>0.0*</td>
<td>0.005</td>
<td>0.0*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>R-ODS score</strong></td>
<td>−3.0</td>
<td>−2.0</td>
<td>0.030</td>
<td>0.0*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Grip strength (kPa)</strong></td>
<td>−6.6</td>
<td>−0.6*</td>
<td>0.004</td>
<td>−2.7*</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>MRC sum score</strong></td>
<td>−2.0</td>
<td>0.0*</td>
<td>0.003</td>
<td>0.0*</td>
<td>0.002</td>
</tr>
</tbody>
</table>

bw: body weight; INCAT: Inflammatory Neuropathy Cause and Treatment; I-RODS: Inflammatory Rasch-built Overall Disability Scale; MRC: Medical Research Council; SCIG: subcutaneous immunoglobulin

Safety
### PATH: Safety – General

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=57), n (%)</th>
<th>SCIG 0.2 g/kg bw weekly (N=57), n (%)</th>
<th>SCIG 0.4 g/kg bw weekly (N=58), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any subjects with AEs</td>
<td>21 (36.8)</td>
<td>33 (57.9)</td>
<td>30 (51.7)</td>
</tr>
<tr>
<td>AE severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>18 (31.6)</td>
<td>31 (54.4)</td>
<td>25 (43.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (19.3)</td>
<td>13 (22.8)</td>
<td>9 (15.5)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (1.8)</td>
<td>4 (7.0)</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>Any serious AEs with SCIG</td>
<td>1 (1.8)</td>
<td>3 (5.3)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Local reactions</td>
<td>4 (7.0)</td>
<td>11 (19.3)</td>
<td>17 (29.3)</td>
</tr>
</tbody>
</table>

AE: adverse event; bw: body weight; SCIG: subcutaneous immunoglobulin

1. van Schaik IN et al. Poster and abstract presented at Annual Meeting of the American Academy of Neurology (AAN); April 22-28, 2017; Boston, MA.
Local reactions decreased over time
Most local reactions were mild

AE: adverse event; bw: body weight; SCIG: subcutaneous immunoglobulin

1. van Schaik IN et al. Poster and abstract presented at Annual Meeting of the American Academy of Neurology (AAN); April 22-28, 2017; Boston, MA.
Exploratory Endpoints
Compared with the baseline measurement, serum IgG levels increased in the high-dose group, remained stable in the low-dose group, and decreased in the placebo group.
• Most patients found SCIG easy to use

*Last post-dose observation

1. van Schaik IN et al. Poster and abstract presented at Annual Meeting of the American Academy of Neurology (AAN); April 22–28, 2017; Boston, MA.
**Primary Endpoint**

- A statistically significant lower percentage of subjects treated with SCIG had CIDP relapse and/or were withdrawn for other reasons (0.2 g/kg bw weekly: 39%, p=0.007; 0.4 g/kg bw weekly: 33%, p<0.001) compared with placebo (63%)

**Secondary Endpoints**

- Median INCAT, grip strength, and MRC scores remained stable in both SCIG groups and deteriorated in the placebo group
- R-ODS was maintained for the SCIG 0.4 g/kg bw weekly group and deteriorated in the SCIG 0.2 g/kg bw weekly and placebo groups
- Adverse event rate was similar in both SCIG groups (57.9% of 0.2 g/kg bw weekly; 51.7% of 0.4 g/kg bw weekly)

**Exploratory Endpoints**

- 88% of patients found SCIG somewhat or extremely easy to use
- Serum IgG levels increased in the SCIG 0.4 g/kg bw weekly group (+4.1 g/L change), remained stable in the 0.2 g/kg bw group weekly (−0.9 g/L change), and decreased in the placebo group (−4.8 g/L change)