The “GRIPPER” study: Quantifying IVIG Treatment-Related Fluctuations in CIDP Using Daily Grip Strength Measurements
Treatment of inflammatory neuropathy with IVIG

- IVIG therapy is FDA-approved for CIDP\(^1\)

**ICE study\(^2\)**

- Loading dose: 2 g/kg bw
- Maintenance: 1 g/kg bw every 3 weeks
- 54% of participants in the IVIG group improved vs 21% in the placebo group through week 24 (statistically significant)


\(^1\) IVIG products approved for CIDP are Gammunex-C, Gammaked, and Privigen


Utilization of IVIG in clinical practice

- Based on the ICE study,¹ a loading dose of 2 g/kg bw with 1 g/kg bw every 3 weeks for maintenance (or equivalent) is recommended

- EFNS/PNS guidelines² suggest “individualization of therapy;” however, the best strategy to reach this goal is unknown

- In clinical practice, IVIG infusion intervals as short as 7–14 days may be needed for some patients, while in others the dose requirement is much less

- One major obstacle to IVIG optimization is how best to manage and measure IVIG wear-off

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EFNS: European Federation of Neurological Societies, IVIG: intravenous immunoglobulin, PNS: Peripheral Nerve Society

Wear-off: Cyclic or periodic occurrence of clinical deterioration at an interval following an IVIG infusion.

IVIG: intravenous immunoglobulin

Grip strength is a sensitive tool for assessing clinically relevant changes in patients with CIDP.

The Jamar Dynamometer is a reliable measure of global neurologic status in CIDP, not limited to upper limb or exclusively motor function.

Grip strength is not a time-consuming procedure.

Grip strength is easy to perform, immediately available results, and can be conducted by patients at home as in the Gripper study.

CIDP: chronic inflammatory demyelinating polyneuropathy

Primary objective:
• Determine the frequency and extent of wear-off and other treatment-related fluctuations to IVIG in patients with CIDP by collecting daily grip strength and less frequent measures of disability

Hypothesis:
• CIDP patients on IVIG therapy will have statistically and clinically significant variation in strength and disability between peak and trough IgG cycles, resulting in treatment-related fluctuations with increased disability towards the end of the dosing interval

Clinical application:
By better understanding wear-off, we expect that these results will directly impact CIDP treatment by facilitating development of evidence-based treatment optimization strategies

CIDP: chronic inflammatory demyelinating polyneuropathy, IgG, immunoglobulin G, IVIG: intravenous immunoglobulin
Data on the GRIPPER study presented by Dr J Allen as a poster at the peripheral nerve society (PNS) 2016 and American Academy of Neurology (AAN) 2017. NCT02414490
GRIPPER: Study methods

- **Design**: Prospective observational multicenter study
- **Target enrollment**: 25 subjects
- **Duration**: Subjects followed for 6 months
- **Outcomes**:
  - **Daily**: Grip strength by Jamar Dynamometer (primary outcome)
  - **Weekly**:
    - Inflammatory Rasch-built overall disability scale (I-RODS)
    - Inflammatory neuropathy cause and treatment (INCAT) disability score
    - Fatigue severity score (FSS)
    - Visual analog pain scale (VAS)
    - Timed up and go (TUG) test
  - **Periodically**: HRQoL short form physical component summary (SF-36)
  - IgG levels drawn immediately before IVIG (trough), 5 minutes after IVIG (peak) and 2 weeks after IVIG (mid cycle)

HRQoL: health-related quality of life, IVIG: intravenous immunoglobulin
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### Key inclusion criteria
- Definite or probable CIDP according to EFNS/PNS criteria (2010)
- Diagnosis confirmed by expert panel (2 of 3 must agree)
- Treated with IVIG with dosing frequency between 20 and 42 days
- CDAS classification of stable active disease or improvement at time of screening
- Eligible for infusion services by BriovaRx

### Key exclusion criteria
- Any polyneuropathy of another cause, including MMN
- CDAS classification of cure, remission, or unstable active disease
- Receiving pulse dose corticosteroids or SCIG during study participation (daily corticosteroids are allowed if the dose is equal to or < than prednisone 20 mg daily and no anticipated dose changes during the study)
**Industry partners:**
The study is funded by CSL Behring and is performed in collaboration with BriovaRx specialty pharmacy. Tim Walton (BriovaRx) serves as the study manager.

**Expert panel:**
Ken Gorson, Richard Lewis, John Kissel

**Investigator sites:**
University of Minnesota (Jeffrey Allen)
Kansas University (Mamatha Pasnoor and Mazen Dimachkie)
Columbia (Thomas Brannagan)
Neurology at Johns Creek (Albert Cook)
Northwestern University (Senda Ajroud-Driss)

**Statistician:**
John Ney

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**GRIpper: Study methods**

1. **Patient meeting criteria enrolled by study site**
   - Diagnosis not confirmed (agreement by 2 of 3)

2. **De-identified patient data reviewed by expert panel**
   - Subject withdrawn from study
   - Diagnostic confirmation by panel (agreement by 2 of 3)

3. **Data collection begins**
   - Daily: Jamar grip strength measurements
     - Collected at home by patient
   - Weekly: R-ODS ONLS FSS VAS TUG
     - Collected by trained nurse
   - Baseline, mid-study final: HRQoL SF-36 physical component
     - Collected by trained nurse
   - Pre-IVIG, immediate post IVIG, 2 weeks post IVIG: IgG level biomarker storage
     - Collected by trained nurse

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Results: Enrollment

- First subject enrolled: June 2015
- Last subject enrolled: April 2018

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Results: Analysis plan

- The following analyses will be performed:
  - The extent of fluctuations in grip strength
  - Other assessments within IVIG treatment cycles
  - The proportion of subjects who experience any given degree of fluctuation

- Descriptive statistics will be used to compare all of the measurements within each treatment cycle and the degree of difference between maximum and minimum

- The proportion of subjects with any given degree of fluctuation and the proportion of cycles in which any given fluctuation occurs will be described

- As of July 2018 a final formal statistical analysis is not complete
Results: Representative case 1

Grip strength

Disability

IgG levels

Subject specific infusion cycles

IgG: immunoglobulin G, MFSS: modified fatigue severity scale, ONLS: overall neuropathy limitations score, RODS: Rasch-built overall disability scale, TUG: timed up and go score, VAS: visual analog scale
Results: Representative case 2

IgG levels
Subject specific infusion cycles

Immunoglobulins

Grip strength

Disability

IgG: immunoglobulin G, MFSS: modified fatigue severity scale, ONLS: overall neuropathy limitations score, RODS: Rasch-built overall disability scale, TUG: timed up and go score, VAS: visual analog scale.
GRIPPER: Future timeline

- Last subject enrolled: April 2018
- Last subject study completion: December 2018
- Data analysis completed: Early 2019
- First publication: Mid 2019

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GRIPPER: Lessons learned thus far

• Frequent measurement of grip strength by patients at home is feasible and practical

• Representative data highlight the ability of frequent grip strength collection to capture IVIG wear-off

• Preliminary observations suggest that intra-cycle grip strength fluctuations may predict relapse with dose reduction, even if clinical examination and patient-reported symptoms do not fluctuate (case 1)
GRIPPER: Lessons learned thus far

- We expect that completed results analysis will help facilitate the development of CIDP treatment strategies by:
  - Optimizing doses to individual patients by minimizing wear-off
  - Identifying patients who are likely to fail taper if wear-off is present
  - Identifying which patients should be tapered if wear-off is absent
  - Identifying relapse in the early stages

- The data may help to:
  - Guide future studies that explore different IVIG doses and utilize serum IgG levels to guide treatment optimization
  - Assess the long-term outcomes of short-term, cycle-to-cycle fluctuations

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