PolyNeuro exchange

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)

bw: bodyweight, CIDP: chronic inflammatory demyelinating polyneuropathy, FDA: US Food and Drug Administration, IVIG: intravenous immunoglobulin.
IVIG products approved for CIDP are Gammunex-C, Gammaked, and Privigen)

1. FDA Immune Globulin Intravenous Indications. Available at: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/ LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm. Accessed Mar 2016.
2. Hughes RAC *et al.* Lancet Neurol. 2008;7(2):136–144.

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 guidelines[2] 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

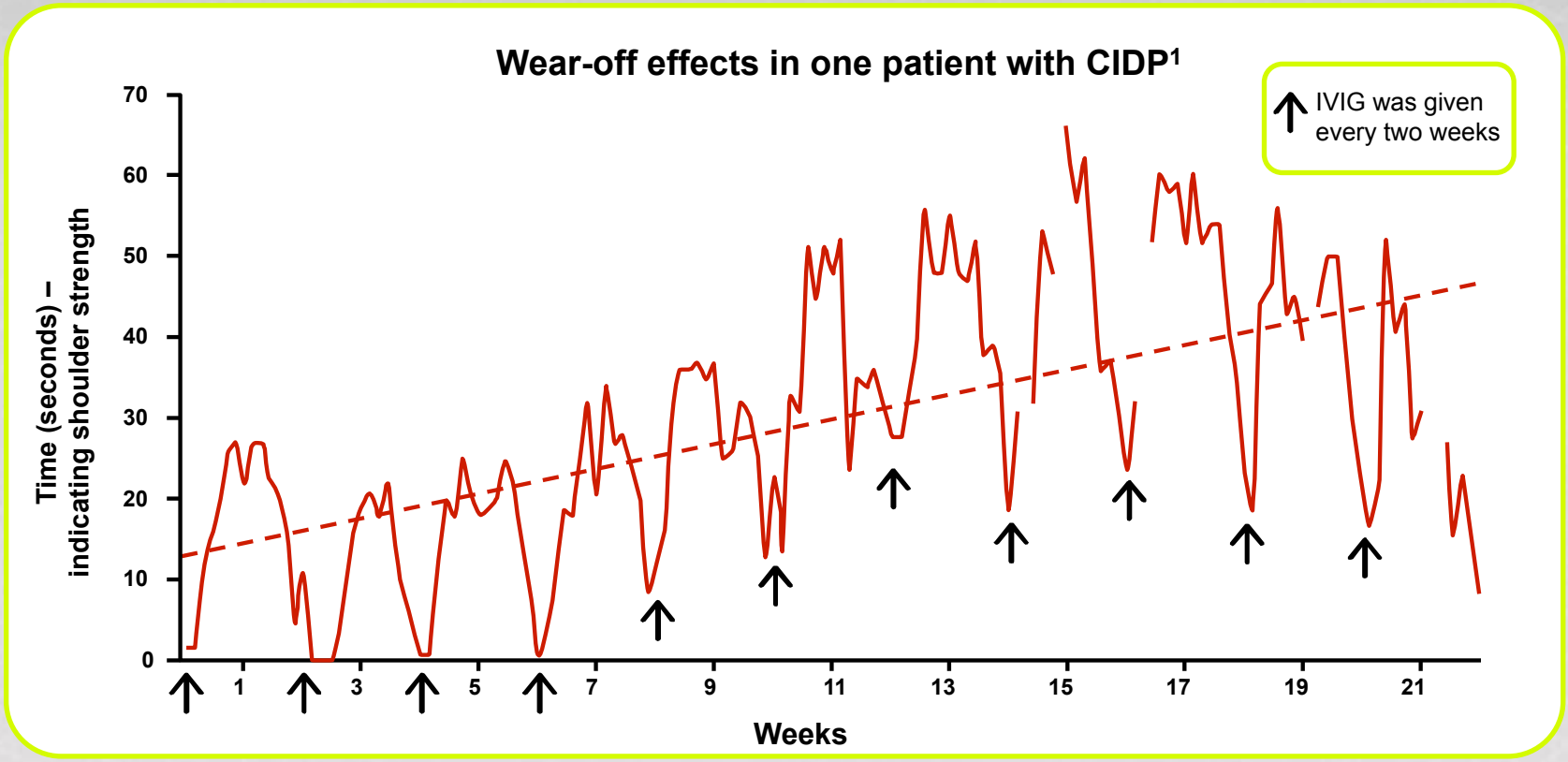
EFNS: European Federation of Neurological Societies, IVIG: intravenous immunoglobulin, PNS: Peripheral Nerve Society

1. Hughes RAC *et al.* Lancet Neurol. 2008;7(2):136–144.
2. EFNS Task force. Eur J Neurol. 2010;17(3):356–363.

IVIG treatment-related fluctuations: Wear-off

Wear-off:

Cyclic or periodic occurrence of clinical deterioration at an interval following an IVIG infusion

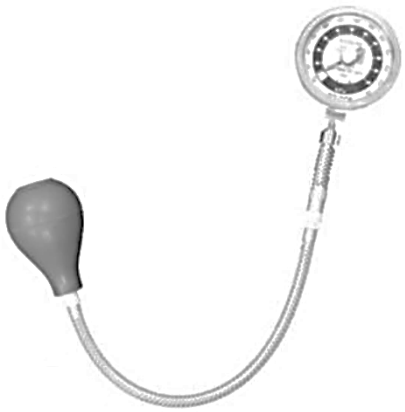


IVIG: intravenous immunoglobulin

1. "Wear-off in one patient with CIDP" by Allen JA, *et al.* J Periph Nerv Syst 2018;[Epub ahead of print]. DOI: 10.1111/jns.12262. is licensed under CC BY-NC-ND 4.0.

Grip strength as an outcome in CIDP[1–3]

Martin Vigorimeter[4]



Jamar Dynamometer[4]

- 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[3]
- 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

1. Vanhoutte EK *et al.* Eur J Neurol. 2013;20(5):748–755.
2. Draak TH *et al.* Neurology. 2014;83(23):2124–2132.
3. Rajabally YA, Narasimhan M. J Neurol Sci. 2013;325(1–2):36–38.
4. Reprinted from J Hand Ther, vol . 23, Irwin CB and Sesto ME. Reliability and validity of the multiaxis profile dynamometer with younger and older participants. pp. 281–288. Copyright (2010), with permission from Elsevier. https://www.sciencedirect.com/journal/journal-of-hand-therapy.

GRIPPER: Study objectives and hypothesis

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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GRIPPER: Eligibility criteria

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)

CDAS: CIDP disease activity status, CIDP: chronic inflammatory demyelinating polyneuropathy, EFNS: European Federation of Neurological Societies, IVIG: intravenous immunoglobulin, MMN: multifocal motor neuropathy, PNS: Peripheral Nerve Society, SCIG: subcutaneous immunoglobulin

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GRIPPER: Participants

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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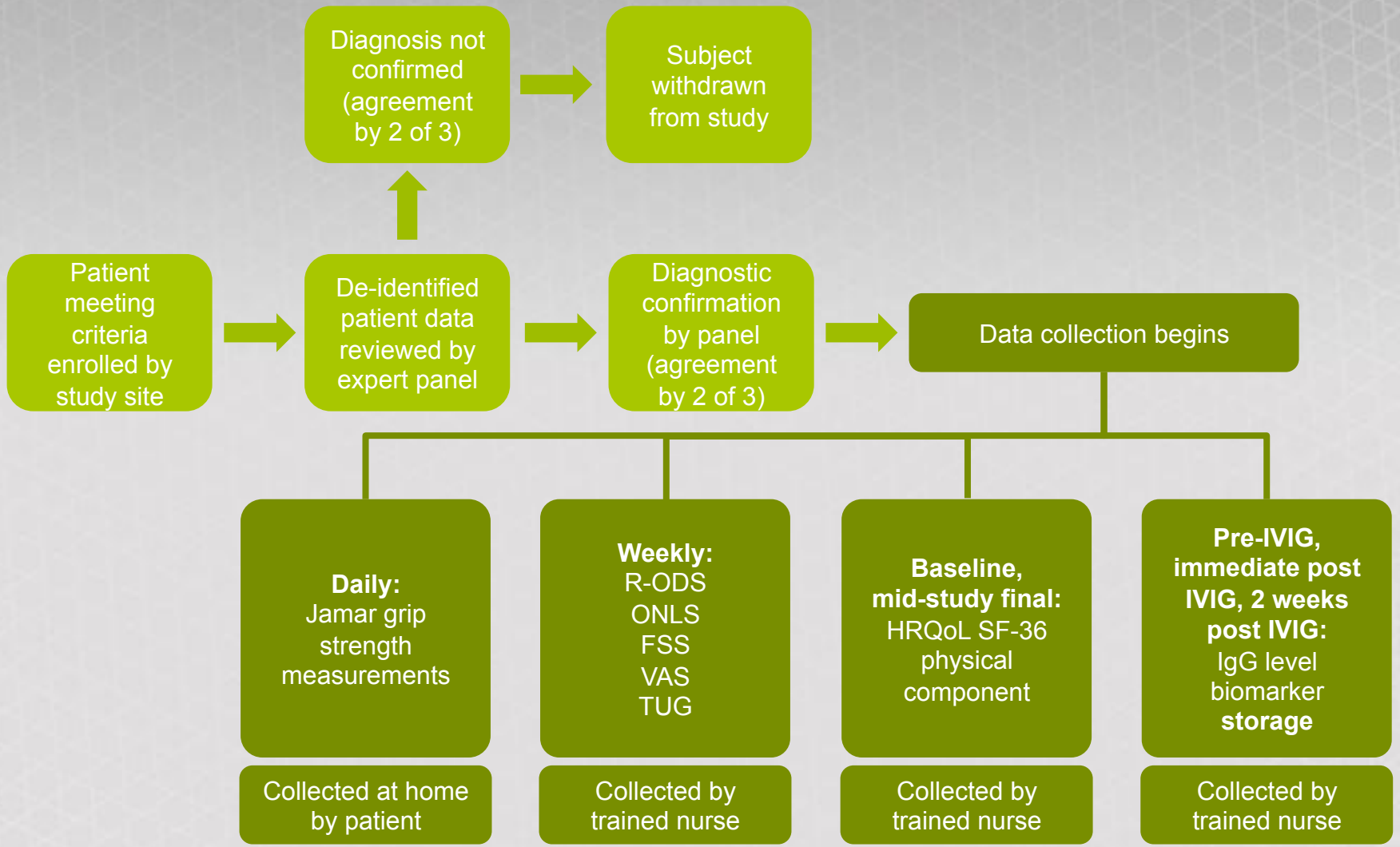
GRIPPER: Study methods



FSS: functional system score, HRQoL: health-related quality of life, IgG: immunoglobulin G, IVIG: intravenous immunoglobulin, ONLS: overall neuropathy limitations score, R-ODS: Rasch-built overall disability scale, SF-36: short-form 36, TUG: timed up and go, VAS: visual analog scale

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Results: Enrollment

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

	Number
Screened	30
Screen fail	3
Total Enrolled	**27**

	Number
Completed study	24
Active in study	3

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

IVIG: intravenous immunoglobulin
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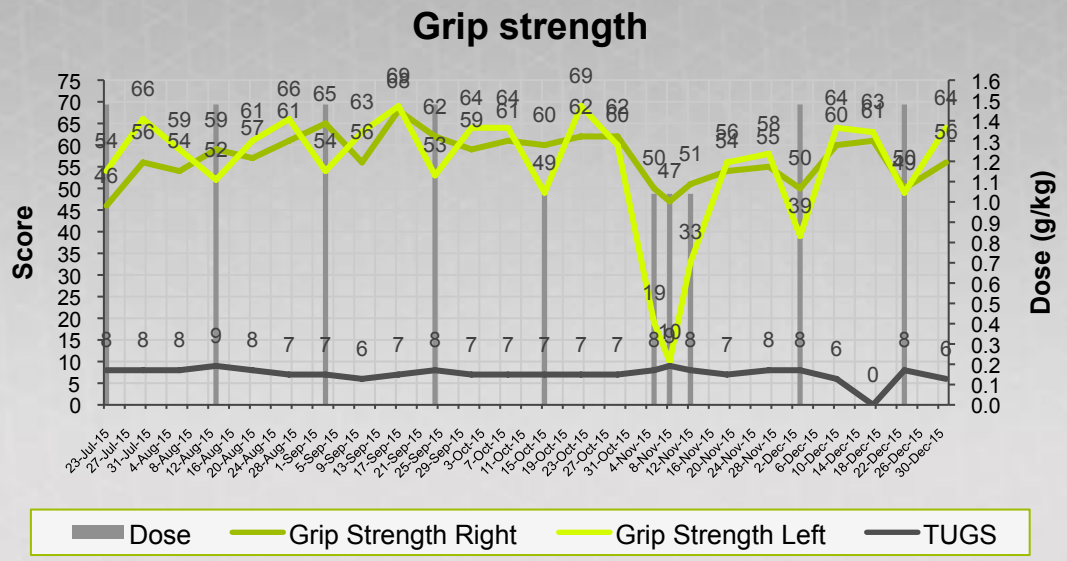
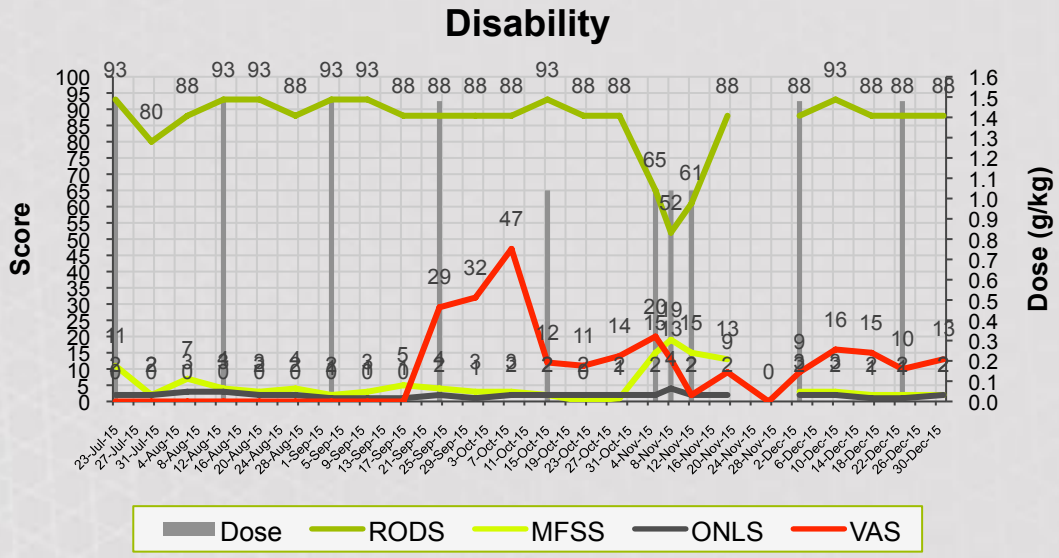
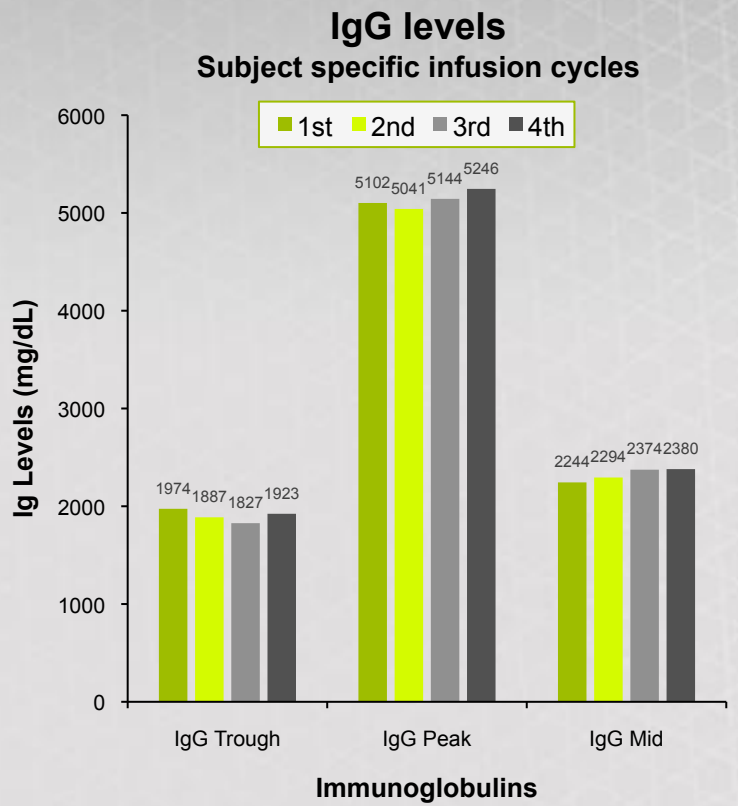
Results: Representative case 1

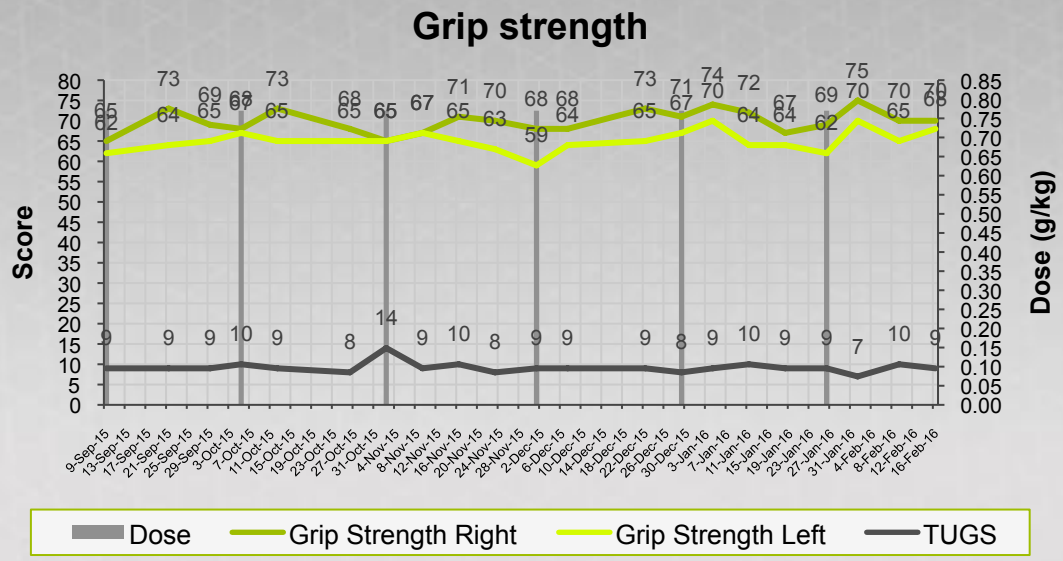


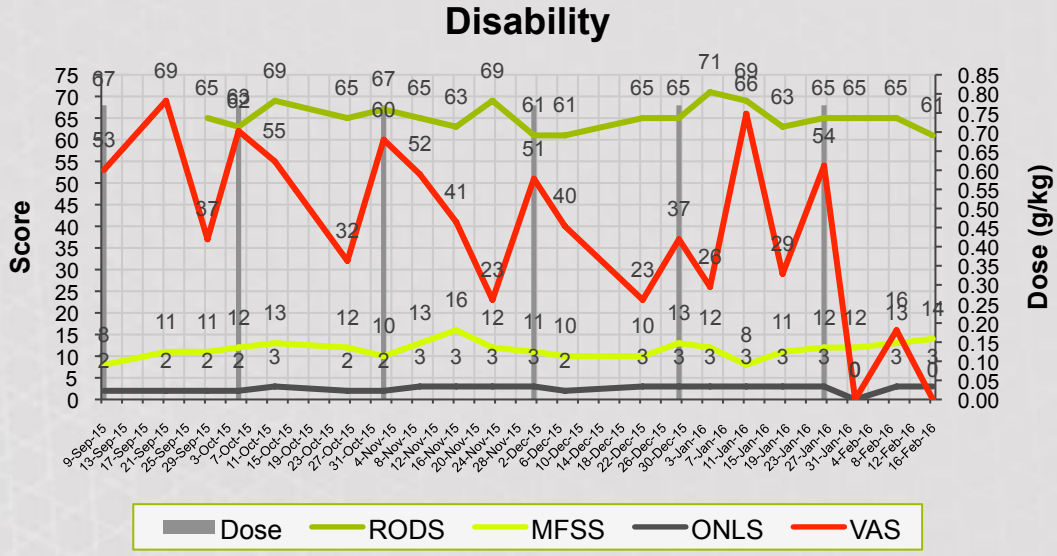


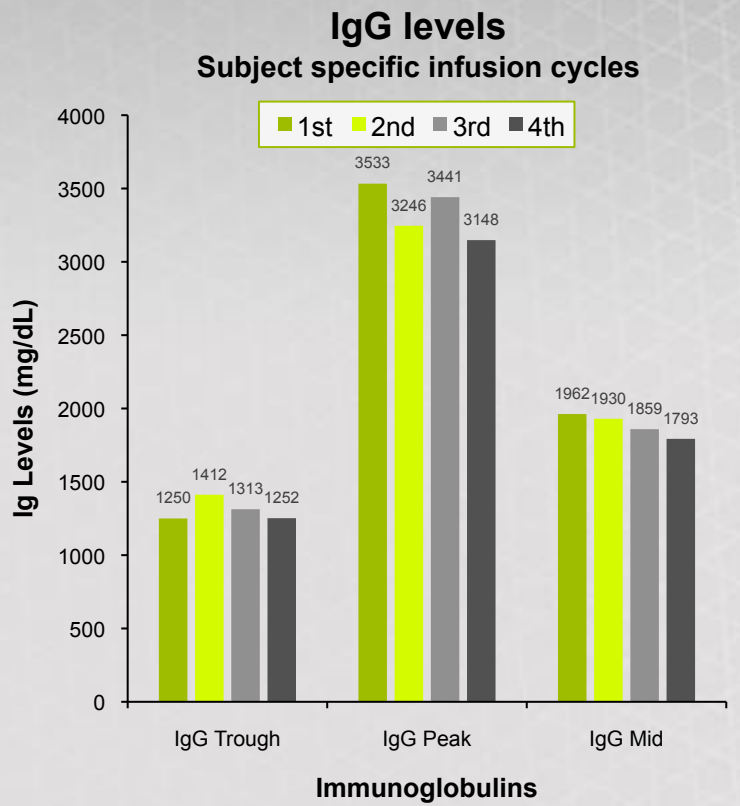


IgG: immunoglobulin G, MFSS: modified fatigue severity scale, ONLS: overall neuropathy limitations score, RODS: Rasch-built overall disability scale, TUG: timed up and go score, VAS: visual analog scale

Results: Representative case 2







IgG: 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)

IVIG: intravenous immunoglobulin
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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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