

IgG Levels and Wear Off Reflect Administration and Outcome

#### 'Wear-off' of treatment effect towards the end of the dosing cycle

- Patients with primary immunodeficiencies have been treated with IVIG since the early 1980s
- Mechanisms of IVIG action reflect competition between therapeutic IgG and pathologic autoantibodies<sup>1</sup>
- Towards the end of the dosing cycle, patients with primary immunodeficiency are more susceptible to infection and their quality of life decreases<sup>2</sup>
- IVIG trough levels may be associated with wear-off effects



Illustration of potential wear-off occurrence in relation to IVIG dosing and IgG levels

Wear-off: "cyclic or periodic occurrence of clinical deterioration at an interval following an IVIG infusion"<sup>3</sup>

CIDP: chronic inflammatory demyelinating polyneuropathy,, IgG: immunoglobulin G, IVIG: intravenous immunoglobulin, MMN: multifocal motor neuropathy

1. Berger et al. J Peripher Nerv Syst. 2013:18;275-96.

- 2. Rojavin M, et al. J Clin Immunol. 2016;36:210-19.
- 3. Allen J et al. J Peripher Nerv Syst. 2018; [Epub ahead of print].

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# IVIG improves and maintains functionality in patients with CIDP<sup>1,2</sup>



IVIG is FDA approved for CIDP and MMN<sup>†4</sup> IVIG is effective in improving and maintaining functionality in these patients<sup>3,5</sup>

\*Patients had previously received IVIG. Error bars represent the standard error of the mean <sup>†</sup>Privigen, Gamunex and Gammaked are approved for CIDP, Gammagard Liquid is approved for MMN

CIDP: chronic inflammatory demyelinating polyneuropathy, FDA: US Food and Drug Administration, INCAT: inflammatory neuropathy cause and treatment, IVIG: intravenous immunoglobulin, MMN: multifocal motor neuropathy

1. Hughes RAC et al. Lancet Neurol. 2008;7(2):136-44.

2. Leger J-M et al. J Peripher Nerv Syst. 2013;18(2):130-40.

3. This work is a derivative of "Mean adjusted INCAT score over time by IVIG-pretreatment" by

Léger J-M et al. J Peripher Nerv Syst. 2013: 18(2):130–140. This figure is licensed under CC BY 3.0 by CSL Behring.

4. FDA Immune Globulin Intravenous Indications. Available at:

http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/

ucm133691.htm. Accessed Jun 2018.

5. van Schaik IN et al. Lancet Neurol. 2018;17(1):35-46.

## Close relationship between IgG dosing and patient response



A close relationship exists between the frequency of dosing and functional capability in some patients<sup>2</sup>

IgG: immunoglobulin G, IVIG: intravenous immunoglobulin, PK: Pharmacokinetics

1. Berger M and Allen JA. Muscle Nerve. 2015;51(3): 315-26.

2. Berger M, et al. Immunotherapy. 2018; [Epub ahead of print].

Figure "Cyclic response to IVIG from CIDP patient superimposed on typical pharmacokinetic curve of IVIG" by

Berger M and Allen JA. Muscle Nerve 2015:51:315–326 is licensed under <u>CC BY-NC-ND 4.0</u>. Reprinted from Immunol Allergy Clin

North Am, Vol. 28, Bonilla FA. "Pharmacokinetics of Immunoglobulin Administered via Intravenous or Subcutaneous Routes", pp.803– 819, Copyright (2008), with permission from Elsevier.

https://www.sciencedirect.com/journal/immunology-and-allergy-clinics-of-north-america and reprinted with permission from Pollard JD

and Armati PJ. CIDP - the relevance of recent advances in Schwann cell/axonal neurobiology.

J Peripher Nerv Syst 2011;16:15–23. John Wiley and Sons. © 2011 Peripheral Nerve Society.



# Individually optimized therapy may include more frequent dosing



Percentage of patients receiving IgG at intervals ≤14 days<sup>1</sup>

Patients who experience wear-off may do better when the IVIG dosing interval is less than the expected half-life of IgG<sup>1</sup>

\*Final or lowest dose per course IgG, immunoglobulin G

- 1. Allen J et al. J Peripher Nerv Syst. 2018; [Epub ahead of print].
- 2. Rajabally YA, et al. J Peripher Nerv Syst. 2006;11:325–29.
- 3. Lunn MP, *et al.* J Peripher Nerv Syst. 2016;21:33–7.
- 4. Broyles R, *et al.* Postgrad Med. 2013;125:65–72.
- 5. Kuitwaard K, et al. J Neurol Neurosurg Psychiatry. 2013;84:859-61.



#### Serum IgG levels vary with administration route





It is possible to achieve near constant steady-state serum IgG levels with frequent SCIG administration<sup>2</sup>

IgG: immunoglobulin G, IVIG: intravenous immunoglobulin, SCIG: subcutaneous immunoglobulin

1. Kanegane H, et al. J Clin Immunol 2014; 34(2):204–11.

2. Berger M, et al. Immunotherapy. 2018;[Epub ahead of print].

Figure "Study design" by Kanegane, H., Imai, K., Yamada, M. et al. J Clin Immunol (2014) 34: 204 is licensed under <u>CC BY 4.0</u>. Reprinted from J Clin Immunol, Vol. 34, Kanegane H et al. "Efficacy and Safety of IgPro20, a Subcutaneous Immunoglobulin, in Japanese Patients with Primary Immunodeficiency Diseases.", pp.204–211, <u>https://doi.org/10.1007/s10875-013-9985-z</u>. Copyright (2014), with permission from Springer.



## SCIG in patients with CIDP

 Randomized, double-blinded, placebo-controlled trial of the effect of SCIG on muscular performance in 30 patients with CIDP<sup>1,2</sup>



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1. Markvardsen LH, et al. Eur J Neurol. 2013;20:836-42.

### SCIG in patients with CIDP



SCIG significantly increases plasma IgG levels and improves muscle strength, walking performance and disability score as compared with treatment with placebo<sup>1</sup>

40-MWT: 40-mwalking test, 9-HPT, nine-hole-peg test, CIDP: chronic inflammatory demyelinating polyneuropathy, GS: grip strength, IVIG: intravenous immunoglobulin, MRC: Medical Research Council score, SCIG: subcutaneous immunoglobulin

1. Markvardsen LH, et al. Eur J Neurol. 2013;20:836–42.

Figure reprinted from Eur J Neurol. Vol. 20. Markvardsen LH et al. "Subcutaneous immunoglobulin in responders to intravenous therapy with chronic inflammatory demyelinating polyradiculoneuropathy.", pp.836–842, Copyright (2013), with permission from John Wiley and Sons.



Mechanisms of IVIG action reflect competition between therapeutic IgG and pathologic autoantibodies<sup>1,2</sup>

Insufficient levels of therapeutic IgG just prior to repeat IVIG treatments may lead to wear-off and loss of peripheral nerve function<sup>1,2</sup>

Wear-off may be avoided by shortening the dosing interval or by switching from IVIG to SCIG<sup>1,2</sup>

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

Allen J *et al.* J Peripher Nerv Syst. 2018; [Epub ahead of print].
Berger M and Allen JA. Muscle Nerve. 2015;51(3): 315–26.

