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# The Clinical Evidence in Support of HIZENTRA for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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# About Chronic Inflammatory Demyelinating Polyneuropathy

## WHAT IS IT?

- A neurological disorder characterized by symmetrical progressive weakness and impaired sensory function in the legs and arms[1,2]
- Progression: slowly progressive, relapsing-remitting, or monophasic[3]

## DISEASE OVERVIEW

- Personal/professional limitations: needing help with activities of daily living and decreased capacity for work, school, and leisure activities[4,5]
- ~30% of untreated patients progress to wheelchair dependence[6]

## EPIDEMIOLOGY

- Incidence: ~0.33 per 100,000 individuals per year[7]
- Prevalence: ~2.81 per 100,000 individuals[7]

**1**. Mathey EK et al. *J Neurol Neurosurg Psych*. 2015;86:973-985. **2.** Ohyama K et al. *Eur J Neurol*. 2014;21:1002-1010. **3.** Ripellino et al. *Autoimmune Dis*. 2014; 2014:201657. **4.** Santos PL et al. *Arq Neuropsiquiatr*. 2014;72:179-183. **5.** Merkies ISJ et al. *J Peripher Nerv Syst*. 2010;15:208-215. **6.** https://www.gbs-cidp.org/cidp/. Accessed August 5, 2020. **7**. Broers et al. *Neuroepidemiology*. 2019;52(3-4):161-172.





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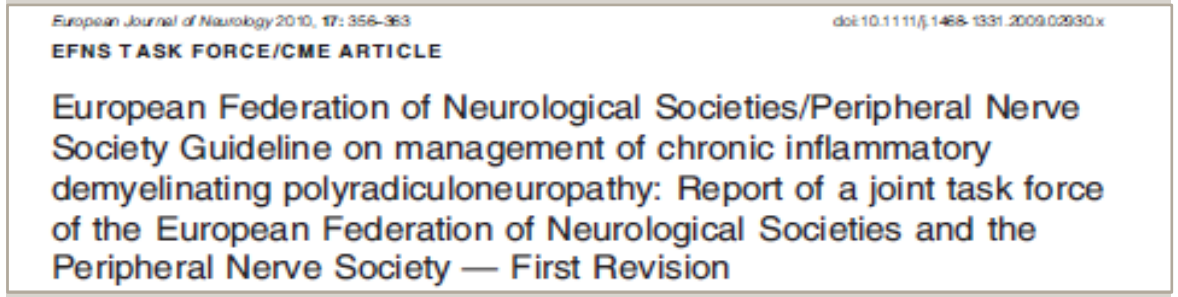
# Current guidelines recommend IVIg as a first-line treatment option

## 2010 EFNS/PNS Guidelines[1]


European Journal of Neurology 2010, 17: 356–363 doi:10.1111/j.1468-1331.2009.02930.x

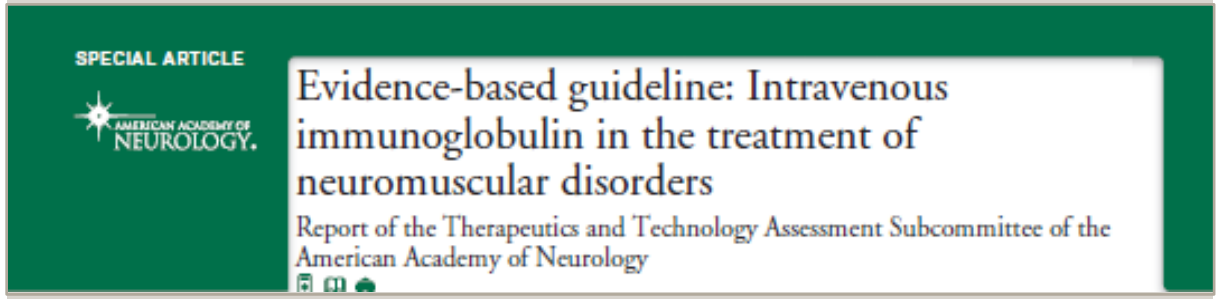
EFNS TASK FORCE/CME ARTICLE

European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society — First Revision

### Recommendations[1]

- IVIg or corticosteroids should be considered in sensory and motor CIDP
- IVIg should be considered as the initial treatment in pure motor CIDP
- Plasma exchange should be considered if IVIg and corticosteroids are ineffective
- Combination therapy or addition of an immunosuppressant/ immunomodulatory drug should be considered if the response is inadequate or the maintenance doses of the initial treatment are high or result in adverse events

## 2012 AAN Guidelines[2]


SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

Evidence-based guideline: Intravenous immunoglobulin in the treatment of neuromuscular disorders

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

### Recommendations[2]

- IVIg should be offered in the long-term treatment of CIDP

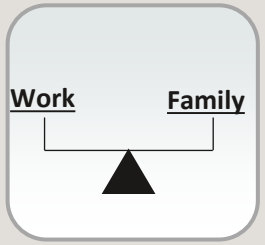
IVIg: intravenous immunoglobulin.

**1.** Van den Bergh PYK et al. *Eur J Neurol*. 2010;17:356-363. **2.** Patwa HS et al. *Neurology*. 2012;78:1009-1015

# While IVIg Treatment Helps Control CIDP Symptoms, Challenges Still Remain for Many Patients

**Venous access issues may limit the utility of IVIg in some patients[1]**

**More patients may experience systemic adverse reactions with IVIg than SCIg[1,2]**




**Patient lifestyle may require more freedom and flexibility[2]**

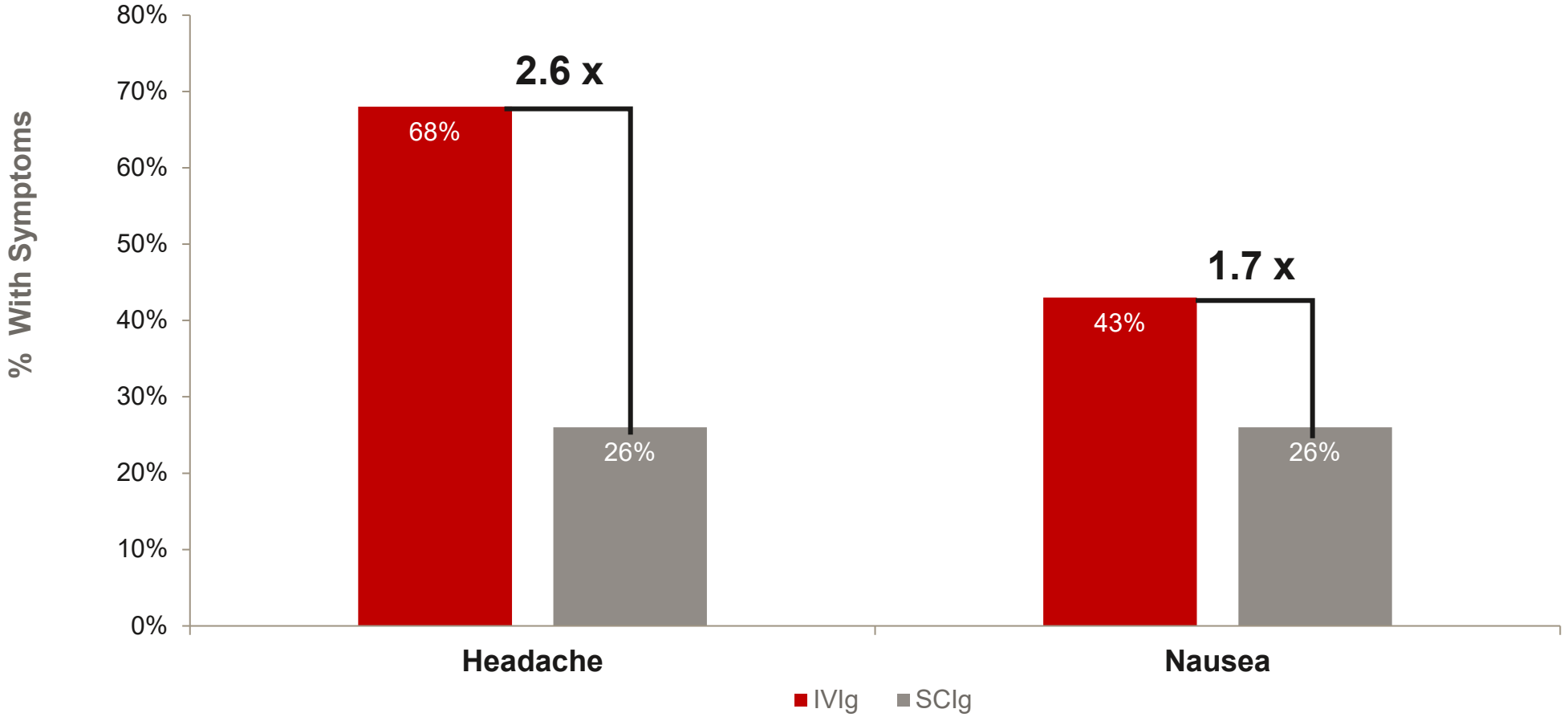
**Some patients may require more frequent IVIg infusions to manage their disease[3-5]**

**Getting to IVIg infusions or arranging home care can be inconvenient[1]**

**SCIg treatment may favorably impact patients' treatment experience**

**1.** Salameh JS et al. *J Clin Neuromusc Dis*. 2016;17:110-119. **2**. Jolles S et al. *Clin Exp Immunol.* 2015;179(2):146-160. **3**. Rajabally YA et al. *J Neurol*. 2013;260:2052-2056. **4.** Broyles R et al. *Postgrad Med*. 2013;125:65-72. **5.** Kuitwaard K et al. *J Neurol Neurosurg Psych*. 2013;84:859-861.

# Neurologic patients* with headache and nausea after treatment with subcutaneous Ig (SCIg) vs IVIg




*Based on a study of 59 patients treated with IVIg and 27 patients treated with SCIg. Diagnoses in the IVIg group were are follows (n): post-polio syndrome (28), CIDP or multifocal motor neuropathy (MMN) (26), myasthenia gravis (2), myositis (2), and stiff-person syndrome (1). Diagnoses in the SCIg group were as follows (n): CIDP or MMN (24), myositis (2), and stiff-person syndrome (1). Patients treated with SCIg received either Hizentra or Gammanorm (16.5% human Ig). Hizentra is not indicated for MMN, stiff-person syndrome, post-polio syndrome, myasthenia gravis, or myositis. Patients did not receive antihistamines, corticosteroids, or analgesic medication prior to IVIg or SCIg therapy.

Markvardsen LH et al. *Basic Clin Pharmacol Toxicol*. 2015;117(6):409-412.





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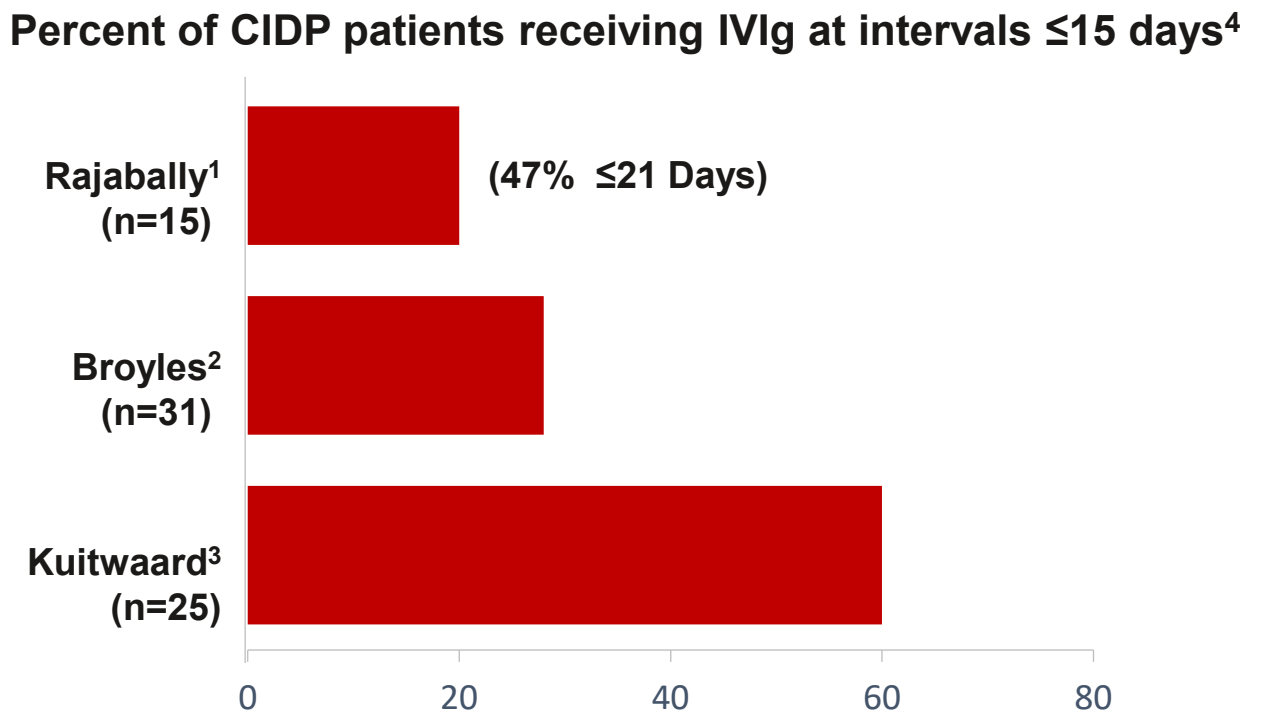
# In practice, IVIg dosing frequency is often increased to manage patients' disease

- More frequent dosing intervals are often used to manage patients' disease[1-3]
- More frequent, smaller doses of IVIg may be associated with fewer, less severe adverse effects[4]




Reprinted with permission from Berger M, Allen JA. *Muscle Nerve*. 2015;51:315-325.

**1**. Rajabally YA et al. *J Neurol*. 2013;260:2052-2060. **2.** Broyles R et al. *Postgrad Med*. 2013;125:65-72. **3.** Kuitwaard K et al. *J Neurol Neurosurg Psych*. 2013;84:859-861. **4.** Berger M, Allen JA. *Muscle Nerve*. 2015;51:315-325.





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# Features of IVIg and SCIg Therapy

| Infusion | SCIg | IVIg |
|---|---|---|
| **Administration** | Infused **subcutaneously** | Infused **intravenously** |
| **Volume*** | Generally **lower** volumes | Generally **higher** volumes |
| **Frequency** | **1-2 infusions** over **1-2 consecutive days weekly**† | Typically every **3–4 weeks** |
| **IgG Levels** | **Relatively stable** IgG levels | Wider **fluctuation** in IgG levels |
| **By Whom** | Can be **self-administered** after proper training | Requires administration by a trained **HCP** |
| **Duration** | Infusion usually lasts **1–2 hours**‡ | Infusion usually lasts **3–4 hours**§ |

No difference in the clinical benefit of SCIg and IVIg serum profiles has been demonstrated by substantial clinical evidence or experience. *Based on an equivalent dose in grams. †Dependent upon patient's clinical needs, tolerance for infusion volume and rate. ‡Based on previously approved infusion parameters. §Depending on product. HCP, health care provider.

Younger ME et al. IDF *Guide for Nurses Immunoglobulin Therapy for Primary Immunodeficiency Diseases*. 3rd ed. Towson, MD: Immune Deficiency Foundation; 2012:1-54.

# Important Safety Information

# Hizentra: Important Safety Information

Hizentra is indicated for:

- Treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years and older.
- Maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to prevent relapse of neuromuscular disability and impairment.
    - Limitation of use: maintenance therapy in CIDP has been systematically studied for 6 months and for a further 12 months in a follow-up study. Continued maintenance beyond these periods should be individualized based on patient response and need for continued therapy.

**For subcutaneous infusion only.**

**WARNING: Thrombosis may occur with immune globulin products, including Hizentra. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**

**For patients at risk of thrombosis, administer Hizentra at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.**

Hizentra is contraindicated in patients with a history of anaphylactic or severe systemic reaction to human immune globulin (Ig) or components of Hizentra (eg, polysorbate 80), as well as in patients with immunoglobulin A deficiency with antibodies against IgA and a history of hypersensitivity. Because Hizentra contains L-proline as stabilizer, use in patients with hyperprolinemia is contraindicated.

# Hizentra: Important Safety Information

IgA-deficient patients with anti-IgA antibodies are at greater risk of severe hypersensitivity and anaphylactic reactions. Thrombosis may occur following treatment with Ig products, including Hizentra.

Monitor patients for aseptic meningitis syndrome (AMS), which may occur following treatment with Ig products, including Hizentra. In patients at risk of acute renal failure, monitor renal function, including blood urea nitrogen, serum creatinine and urine output. In addition, monitor patients for clinical signs of hemolysis or pulmonary adverse reactions (eg, transfusion-related acute lung injury [TRALI]).

Hizentra is derived from human blood. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent and its variant (vCJD), cannot be completely eliminated.

The most common adverse reactions (observed in ≥5% of study subjects) were local infusion-site reactions, as well as headache, diarrhea, fatigue, back pain, nausea, extremity pain, cough, upper respiratory tract infection, rash, pruritus, vomiting, upper abdominal pain, migraine, arthralgia, pain, fall, and nasopharyngitis.

The passive transfer of antibodies can interfere with response to live virus vaccines and lead to misinterpretation of serologic test results.

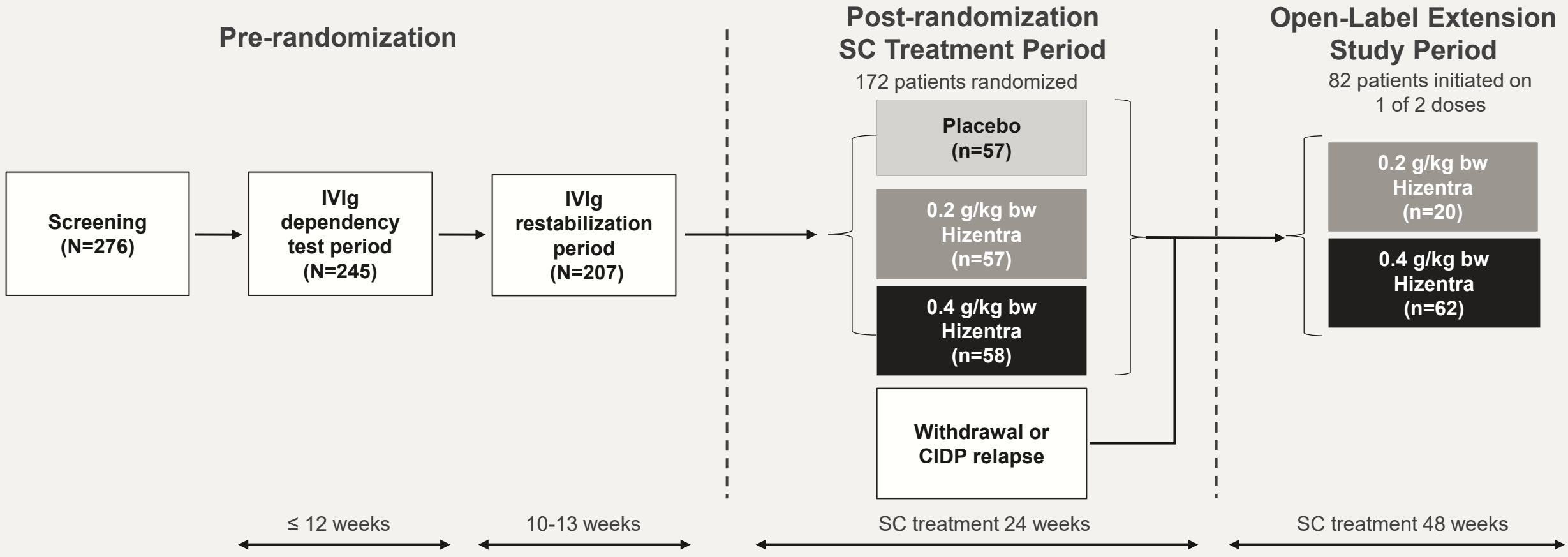
**Please see full prescribing information for Hizentra accompanying this presentation and at hizentra.com/prescribinginfo.**

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

# Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH)

## A randomised, double-blind, placebo-controlled, phase 3 trial

# PATH and Extension Study design[1-3]




bw: body weight.

**1**. van Schaik IN et al. *Lancet Neurol*. 2018;17:35-46. **2.** van Schaik IN et al; PATH study group. *Trials*. 2016;17(1):345. **3.** van Schaik IN et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):e590.





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# PATH: Efficacy endpoints

**PRIMARY ENDPOINT**

Proportion of patients who had a CIDP relapse* or withdrew from the study for any reason during the 24-week SCIg trial

**SECONDARY ENDPOINTS**

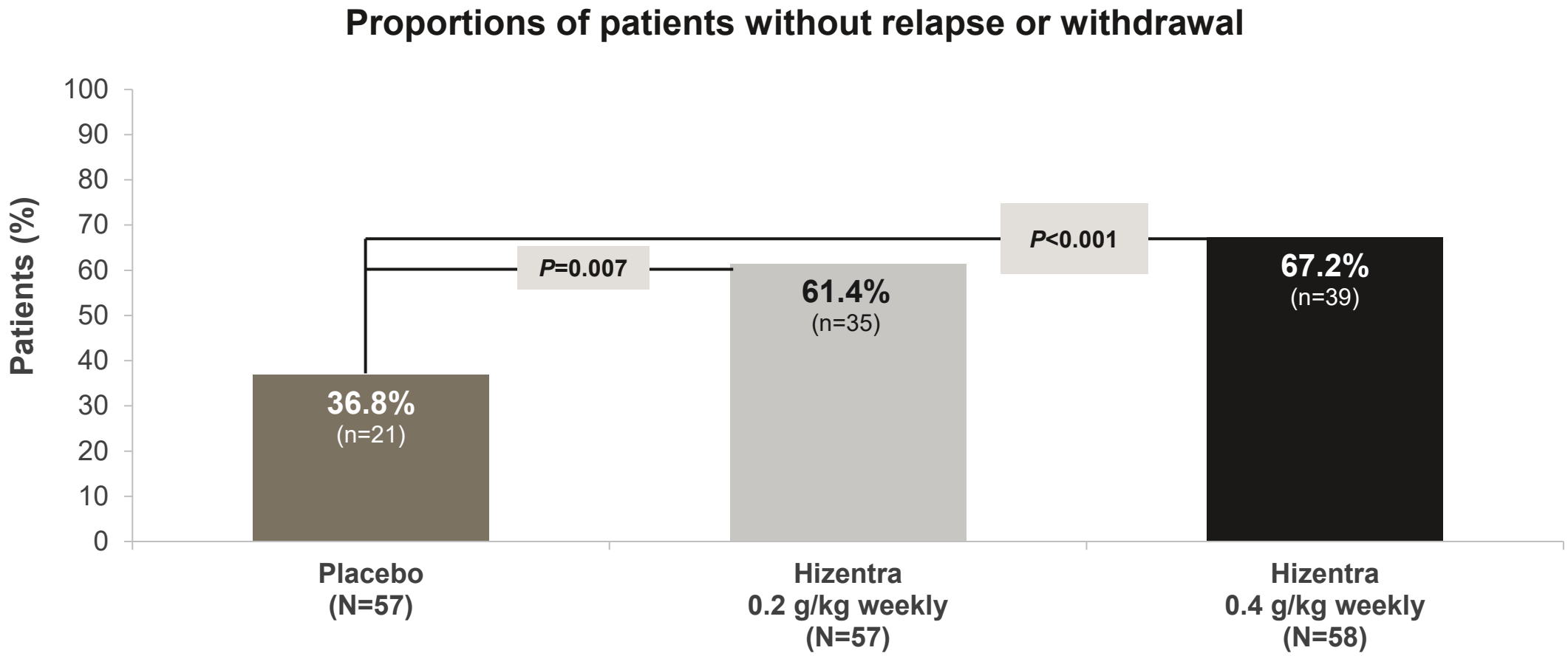
- Time to the primary endpoint
- INCAT score
- Mean grip strength for both hands
- MRC sum score
- I-RODS

*Relapse was defined as a deterioration (≥1 + point increase) in the total adjusted INCAT score at any SCIg treatment period visit vs baseline. Baseline was defined as the score at the end of the IVIg restabilization period.

INCAT=Inflammatory Neuropathy Cause and Treatment total score; MRC=Medical Research Council sum score; I-RODS=Inflammatory Neuropathy-Rasch-Built Overall Disability Score.

van Schaik IN et al. *Lancet Neurol*. 2018;17:35-46.

# PATH: Hizentra prevented relapse or withdrawal in higher proportions of patients (primary endpoint)




van Schaik IN et al. *Lancet Neurol*. 2018;17:35-46.





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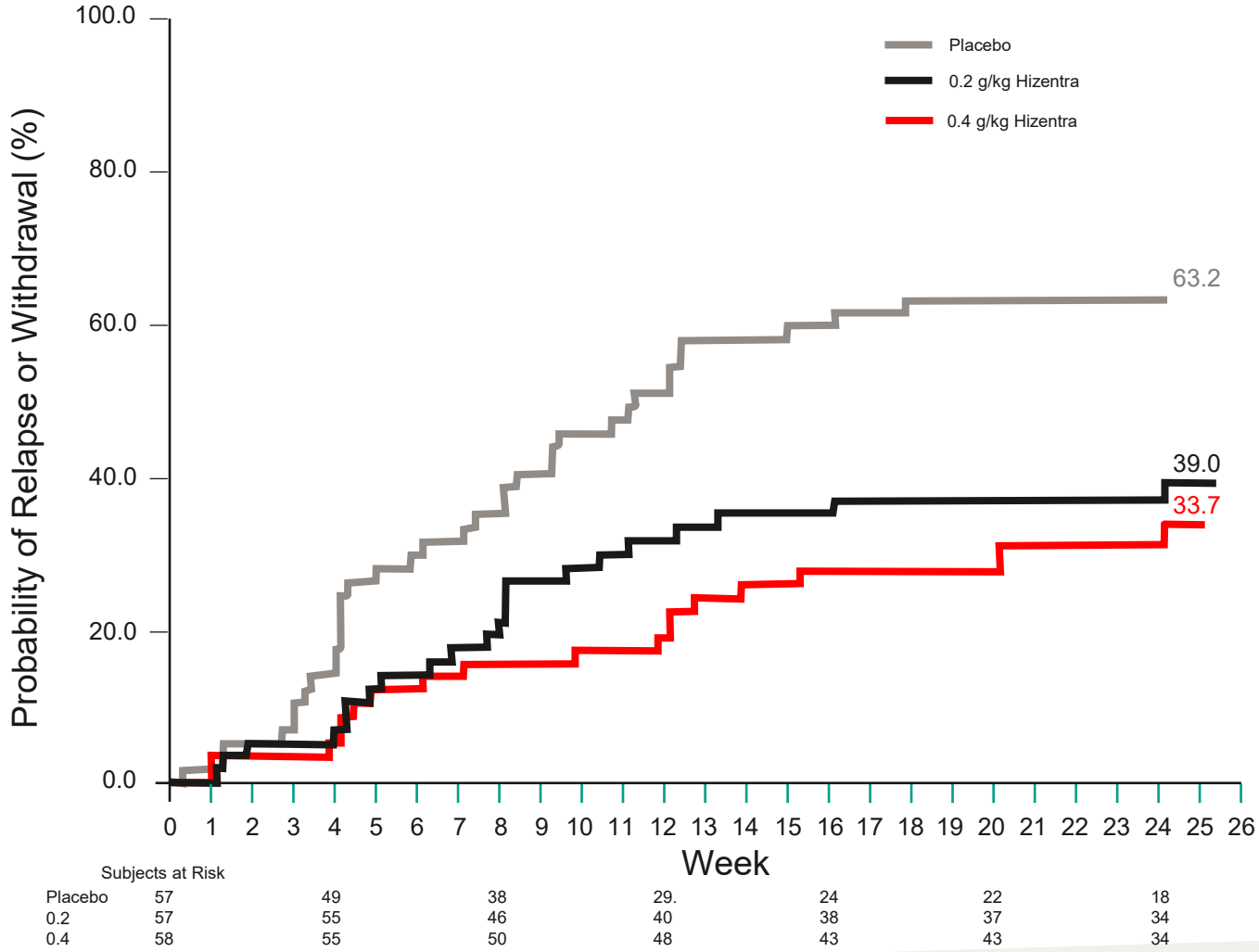
# PATH: Time to CIDP relapse or withdrawal for any other reason





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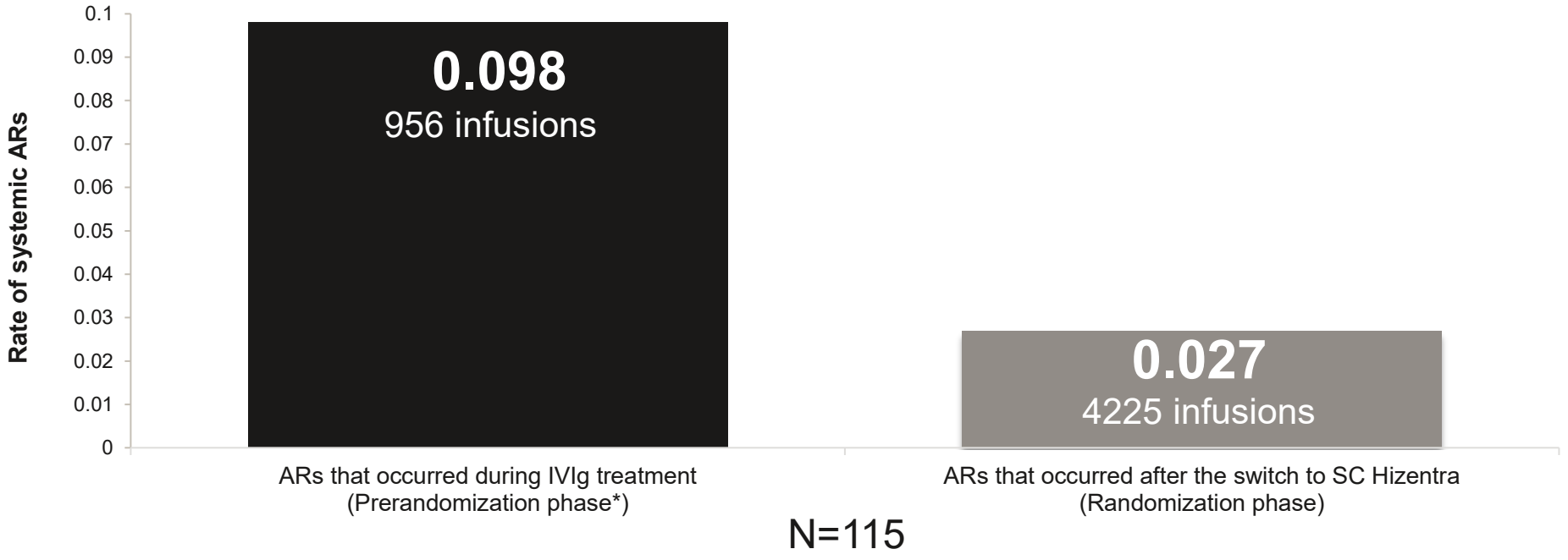
# PATH: Hizentra maintained functional status across multiple measures[1,2]

| Functional Measure | Median Change From Baseline | Overall *P* value |
|---|---|---|
| Stable MRC Score | 0.0 | 0.0026 |
| Stable Grip Strength | <5% | 0.0223 |
| Stable INCAT Score (total score) | 0.0 | <0.0001 |

**1.** van Schaik IN et al. *Lancet Neurol*. 2018;17:35-46. **2.** van Schaik IN et al; PATH study group. *Trials*. 2016;17(1):345.

# PATH safety: Patients stabilized on IVIg reported a 3.6-fold lower rate of systemic adverse reactions per infusion when they switched to Hizentra




**93% of 4225 total Hizentra infusions were free of any adverse reactions**

# PATH: Hizentra is safe and effective for preventing relapse and maintaining stability in CIDP subjects on maintenance therapy

**PRIMARY ENDPOINT[1]**

Significantly lower percentage of patients treated with Hizentra had CIDP relapse and/or withdrawal for other reasons compared with patients receiving placebo

**SECONDARY ENDPOINTS[1]**

Median INCAT, grip strength, and MRC scores remained stable in both Hizentra groups and deteriorated in the placebo group

**SAFETY[1,2]**

Adverse reaction rates were similar in both Hizentra groups

3.6-fold lower rate of systemic ARs per infusion reported during SCIg treatment vs previous IVIg treatment

No correlation of adverse reactions with infusion volume or rate

No hemolysis or thrombotic events occurred during the SCIg treatment period*

*Thrombosis or hemolysis may occur with Ig products, including Hizentra. Please see the boxed warning and section 5 of the full prescribing information for more details.

**1.** van Schaik IN et al. *Lancet Neurol*. 2018;17:35-46. **2.** van Schaik IN et al. *Lancet Neurol*. 2017; Supplementary Appendix. http://dx.doi.org/10.1016/S1474-4422(17)30378-2.





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# Long-term safety and efficacy of subcutaneous immunoglobulin IgPro20 in CIDP

## PATH extension study

# Extension Study: Efficacy and safety assessments

## Efficacy

- INCAT score
- Mean grip strength
- MRC sum score
- I-RODS score

## Safety

- During each visit subjects reported their AEs
- AEs were graded for severity and causal/temporal relationship

AE: adverse event; INCAT: Inflammatory Neuropathy Cause and Treatment; I-RODS: Inflammatory Rasch-built Overall Disability Scale; MRC: Medical Research Council.

van Schaik IN et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):e590.

# Extension Study: Methodology

- 48-week multicenter, open-label, prospective extension study
- Of the 172 PATH study patients, 82 subjects (48%) enrolled in the PATH extension study
- 62 patients initiated on 0.4 g/kg (high dose) and 20 patients on 0.2 g/kg (low dose)*
  - Patients initiated on high dose were switched to low dose after 24 weeks if no relapse occurred
  - Patients with a relapse on low dose were switched to high dose
  - Patients with a relapse on high dose could remain on high dose or discontinue
    - Patients who remained on high dose had to successfully recover from relapse within 4 weeks or were discontinued

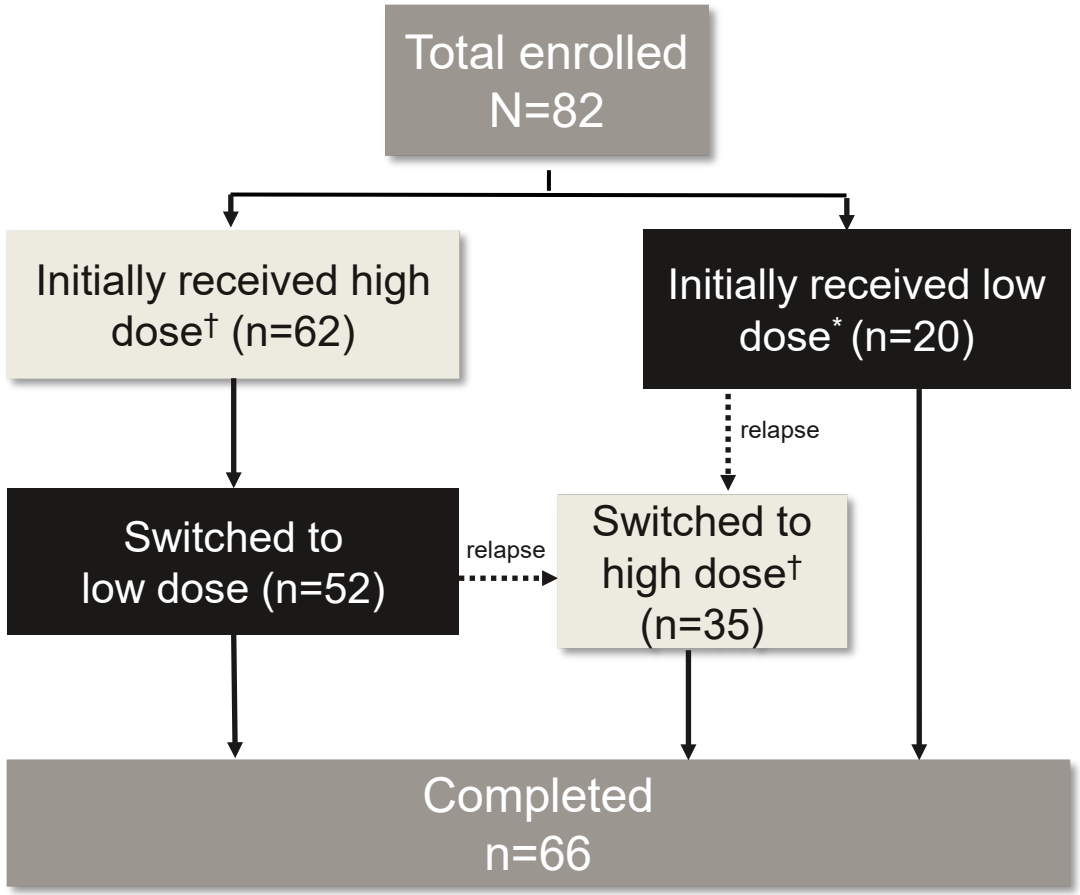
**Relapse:** a deterioration by ≥1 point in the total adjusted INCAT score compared with baseline

**Recovery after relapse:** a return to (or better than) the baseline adjusted INCAT score within 4 weeks

*Two patients under the original protocol and one patient after amendment 1 received a different dose than intended due to error or protocol deviation.

van Schaik IN et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):e590.

# Extension Study: Patient disposition[1]



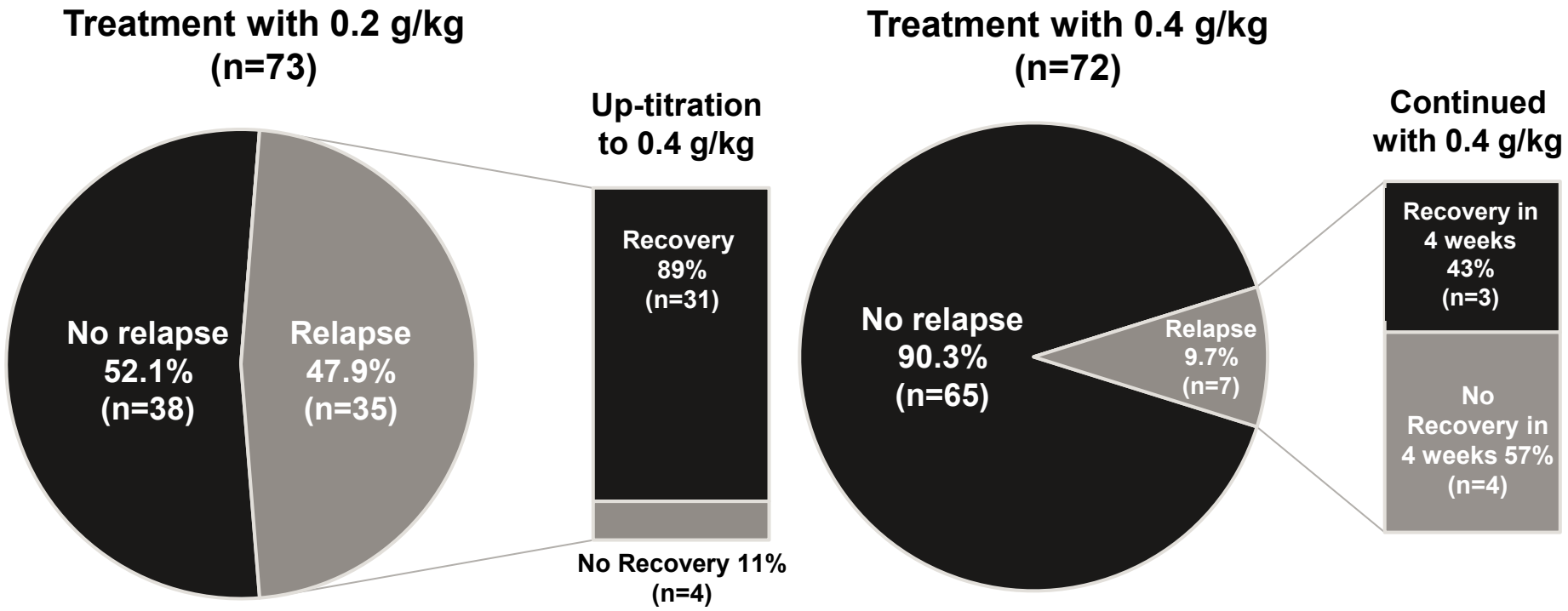

Per protocol, IVIg was not used to restabilize patients who relapsed.[2]

Low dose=0.2 g/kg/wk
High dose=0.4 g/kg/wk

*Protocol amendment allowed some patients to start on 0.2 g/kg/week.
†Patients with a relapse on high dose could remain on high dose or discontinue.

**1.** van Schaik IN et al. Long-term safety and efficacy of subcutaneous immunoglobulin IgPro20 in CIPD; the PATH extension study. Presented at the 143rd Annual Meeting of the American Neurological Association (ANA), Atlanta, GA, USA; October 21-23, 2018. **2.** van Schaik IN et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):e590.

# Extension Study: Relapse and recovery rates[1,2]




- More patients remained relapse-free while being treated with high dose (90%) than low dose (52%)
- Following a relapse on 0.2 g/kg dose, most patients (89%) recovered within 4 weeks when up-titrated to 0.4 g/kg
- 3 of the 7 patients who relapsed while on high dose improved spontaneously within 4 weeks of continued treatment on high dose, without further intervention

**1.** van Schaik IN et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):e590. **2.** van Schaik IN et al. 143rd Annual Meeting of the American Neurological Association (ANA), Atlanta, GA, USA; October 21−23, 2018.

# Adverse events in PATH Extension Study

| | 0.2 g/kg Hizentra | | 0.4 g/kg Hizentra | | Overall | |
|---|---|---|---|---|---|---|
| | Number (%) of patients with an event | Number of events (rate/infusion)* | Number (%) of patients with an event | Number of events (rate/infusion)* | Number (%) of patients with an event | Number of events (rate/infusion)* |
| **Category** | N=73 | n=1408 | N=72 | n=4145 | N=82 | n=5553 |
| **Any AE (treatment emergent)** | 33 (45.2) | 77 (0.055) | 46 (63.9) | 103 (0.025) | 62 (75.6) | 180 (0.032) |
| **General disorders and administration site conditions** | 8 (11.0) | 25 (0.018) | 18 (25.0) | 23 (0.006) | 22 (26.8) | 48 (0.009) |
| Fatigue | 1 (1.4%) | 1 (<0.001) | 3 (4.2) | 3 (<0.001) | 4 (4.9) | 4 (<0.001) |
| **Local reactions** | 7 (9.6) | 24 (0.017) | 13 (18.1) | 16 (0.004) | 18 (22.0) | 40 (0.007) |
| **Headache** | 0 | 0 | 4 (5.6) | 5 (0.001) | 4 (4.9) | 5 (<0.001) |
| **Nausea** | 0 | 0 | 2 (2.8) | 2 (<0.001) | 2 (2.4) | 2 (<0.001) |
| **Nasopharyngitis** | 6 (8.2) | 7 (0.005) | 6 (8.3) | 6 (0.001) | 11 (13.4) | 13 (0.002) |

*The rate per infusion is calculated as number of events divided by the overall number of infusions in the respective groups.
†Local reactions included all AEs reported within the MedDRA high level terms “Administration Site Reactions not elsewhere classified”, “Infusion Site Reactions” and “Injection Site Reactions”.
N = total number of patients ; n = total number of infusions.

van Schaik IN et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):e590.

# Extension Study: Safety findings consistent with PATH and known Hizentra profile

| | |
|---|---|
| **AE rate** | 62 patients (76%) experienced a total of 180 AEs |
| **AE severity** | The majority of events (91%) were mild or moderate |
| **Withdrawal due to AEs** | A total of 3 patients withdrew due to AEs: 2 on low dose and 1 on high dose Hizentra |

AE: adverse event

van Schaik IN et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):e590.





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# Management of Hizentra Therapy

# Hizentra dosing for CIDP

Initiate therapy with Hizentra 1 week after the last IVIg infusion

Recommended subcutaneous dose is 0.2 g/kg (1 mL/kg) body weight per week, administered in 1 or 2 sessions over 1 or 2 consecutive days

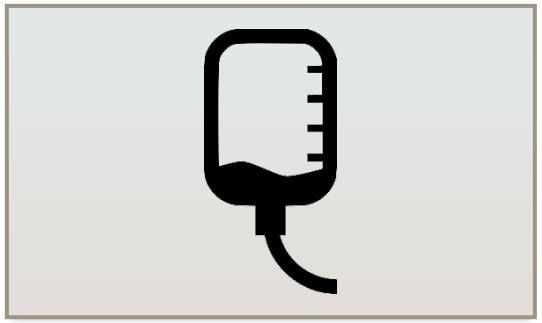
- In the clinical study, after transitioning from IVIg to Hizentra treatment, a dose of 0.4 g/kg (2 mL/kg) body weight per week was also safe and effective to prevent CIDP relapse

If CIDP symptoms worsen on 0.2 g/kg (1 mL/kg) body weight per week, consider increasing the HIZENTRA dose from 0.2 g/kg (1 mL/kg) to 0.4 g/kg (2 mL/kg) body weight per week, administered in 2 sessions per week over 1 or 2 consecutive days.

- If CIDP symptoms worsen on the 0.4 g/kg body weight per week dose, consider re-initiating therapy with an IVIg product approved for treatment of CIDP, while discontinuing Hizentra

Monitor the patient's clinical response and adjust the duration of therapy based on patient need

# Hizentra infusion parameters for CIDP



**Infusion Volume***

- Initial infusion **≤20 mL/site**
- Subsequent infusions **≤50 mL/site** as tolerated

**Infusion Rate***

- Initial infusion **≤20 mL/hr/site**
- Subsequent infusions **≤50 mL/hr/site** as tolerated

**Infusion Sites**

- Up to 8 sites simultaneously
- At least 2 inches between sites

**Infusion Time**

- Weekly dosing†
- About 1 hour/session‡

- Rate adjustments§, as tolerated, could decrease or increase total infusion time
- Site volume adjustments§, as tolerated, could reduce infusion sites and needle sticks

*As tolerated

†Patients can infuse in 1 or 2 sessions over 1 or 2 consecutive days.

‡Recommended subcutaneous dose is 0.2 g/kg (1 mL/kg) of body weight per week. Administered dose volumes will therefore vary with patient body weight, and will impact the duration of the infusion.

§Only adjust 1 parameter at a time.

# Example dose

**169 lb (77 kg)**

**Hizentra 0.4 g/kg dosed one week after last IVIg treatment**

**Dose: 31 g (1 g/5 mL) = 155 mL**

| **1st Infusion as tolerated: 0.4 g/kg** |
| --- |
| **Infusion Sites:** 8<br>**Volume per Site:** ~19 mL per site (as tolerated)<br>**Time per Infusion:** ~1 hour<br>**Infusion Sessions:** 1 |

| **Subsequent Dosing Regimen as tolerated: 0.4 g/kg** |
| --- |
| **Infusion Sites:** 4<br>**Volume per Site:** ~39 mL per site (as tolerated)<br>**Time per Infusion:** ~1 hour<br>**Infusion Sessions:** 1 |

*Rounded to the nearest vial.

# Dosing examples for subsequent* dosing regimens

| Weekly dose | Weight | | Total weekly volume | Total g | # sites | Time per infusion |
|---|---|---|---|---|---|---|
| | Lbs | Kg | | | | |
| 0.2 g/kg | 132 lb | 60 kg | 60 mL | 12 | 2 | ~1 hour |
| 0.4 g/kg | | | 120 mL | 24 | 3 | |
| 0.2 g/kg | 165 lb | 75 kg | 75 mL | 15 | 2 | |
| 0.4 g/kg | | | 150 mL | 30 | 3 | |
| 0.2 g/kg | 198 lb | 90 kg | 90 mL | 18 | 2 | |
| 0.4 g/kg | | | 180 mL | 36 | 4 | |


Patients can self-infuse Hizentra more frequently and in smaller doses than IVIg

- The recommended subcutaneous dose is 0.2 g/kg (1 mL/kg) body weight per week. In the clinical study, after transitioning from IVIg to Hizentra, 0.4 g/kg body weight per week was also safe and effective to prevent CIDP relapse
- In the PATH Study, subjects achieved sustained trough levels over a period of 24 weeks when receiving weekly doses

**With convenient weekly dosing, patients can fit Hizentra into their normal routine**

*For the first infusion of Hizentra do not exceed 20 mL per infusion site per hour. Subsequent infusions can be adjusted to up to 50 mL per infusion site per hour.

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# Summary

| Disease | IVIg Treatment | PATH and Extension |
| --- | --- | --- |
| CIDP is chronic with variable neurologic symptoms | CIDP treatment with IVIg presents unique challenges | Largest CIDP trial; first to study 2 doses of SCIg and dose titration in maintenance therapy for up to 72 weeks |

| SCIg Efficacy | Safety | Dosing |
| --- | --- | --- |
| Hizentra was shown to be efficacious for maintenance therapy for CIDP in adults | Similar safety results seen in PATH and PATH extension studies | Initiate Hizentra 1 week after the last IVIg infusion; volume, rate, and duration of therapy should be adjusted based on the patient's clinical response and tolerability |