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

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Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

About Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

WHAT IS IT?

- An immune-mediated chronic neurological disorder characterized by symmetrical progressive weakness and impaired sensory function in the legs and arms[1,2]
- Progression: slowly progressive usually over an 8-week period, relapsing-remitting, or monophasic[1,3]

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 February 24, 2023. **7**. Broers et al. *Neuroepidemiology*. 2019;52(3-4):161-172.

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Hizentra: Important Safety Information

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.

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.

Hizentra: Important Safety Information

Indications

Hizentra®, Immune Globulin Subcutaneous (Human), 20% Liquid, 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. o 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.

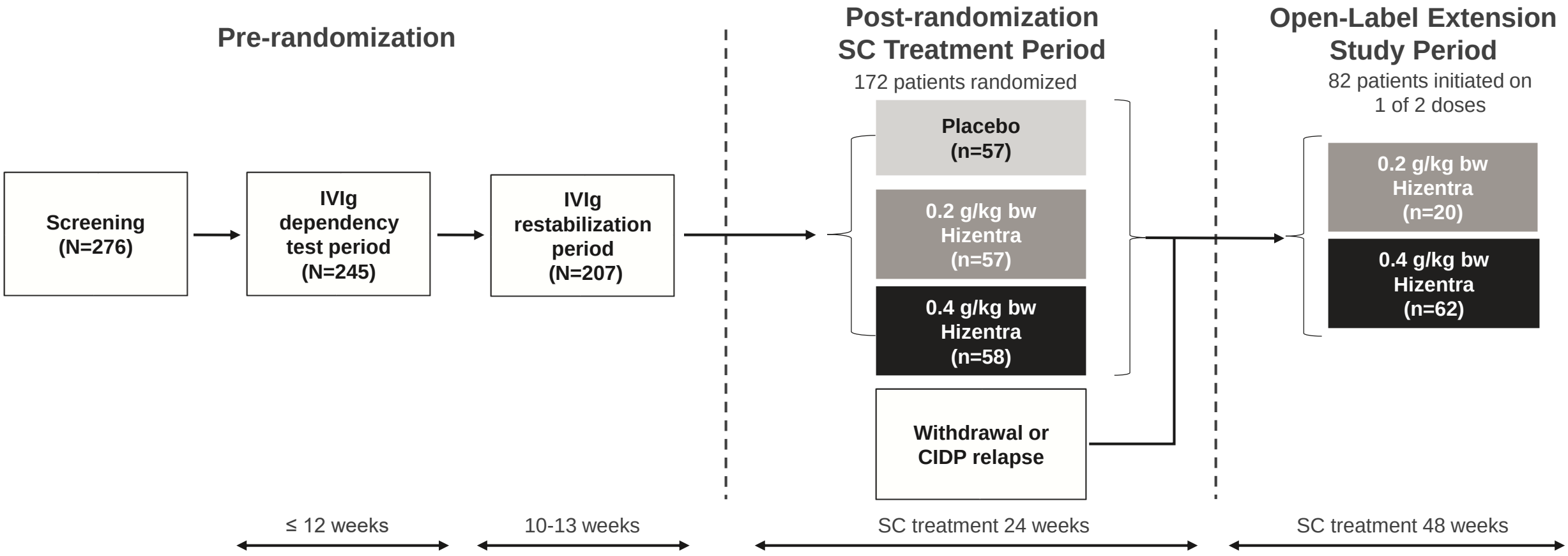
Please see full prescribing information for Hizentra including boxed warning.

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 randomized, 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: Inclusion Criteria

Age ≥ 18 years of age

Diagnosed with definite or probable CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria (these criteria were checked by a central medical monitor)

Received last IVIg treatment at least within 8 weeks before enrollment

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

PATH: Exclusion Criteria

Any polyneuropathy of other causes

Any other disease that could cause neurological symptoms and signs or could interfere with treatment or outcome assessments

Severe conditions that could interfere with satisfactory conduct of the study

History of thrombotic episodes within 2 years before enrollment

Known allergic or other sever reactions to blood products, including intolerance to previous IVIg, history of hemolysis after IVIg infusion, aseptic meningitis, recurrent severe headache, hypersensitivity, or severe generalized skin reaction

Use of prohibited medication

A serum IgA concentration of less than 5% of the lower limit of normal

HIV or hepatitis B or C

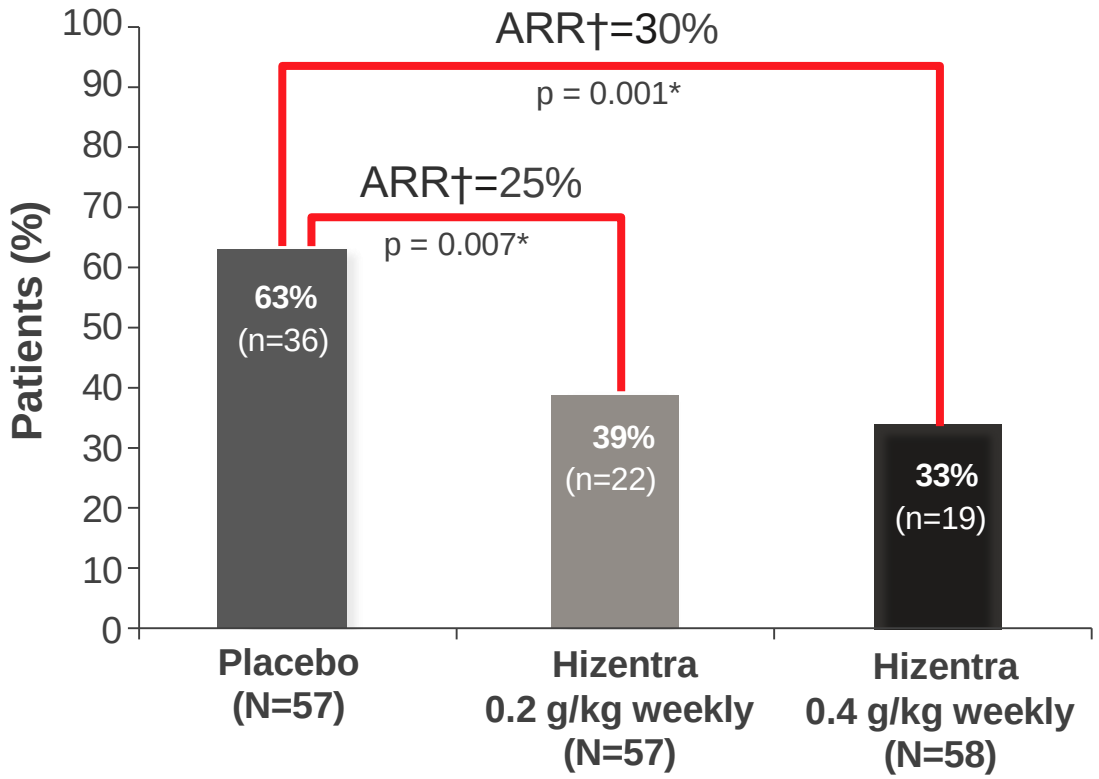
Abnormal laboratory variables

Pregnancy or being a nursing mother; intention of becoming pregnant during the course of the study; and being a female patient of childbearing potential either not using or not willing to use a medically reliable method of contraception for the duration of the study

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

PATH: Primary Endpoint

Percentage of subjects who had a CIDP relapse during SCIg treatment or were withdrawn from the study during SCIg treatment for any reason



†ARR=absolute risk reduction compared to placebo *p values determined by Fisher's exact test.

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

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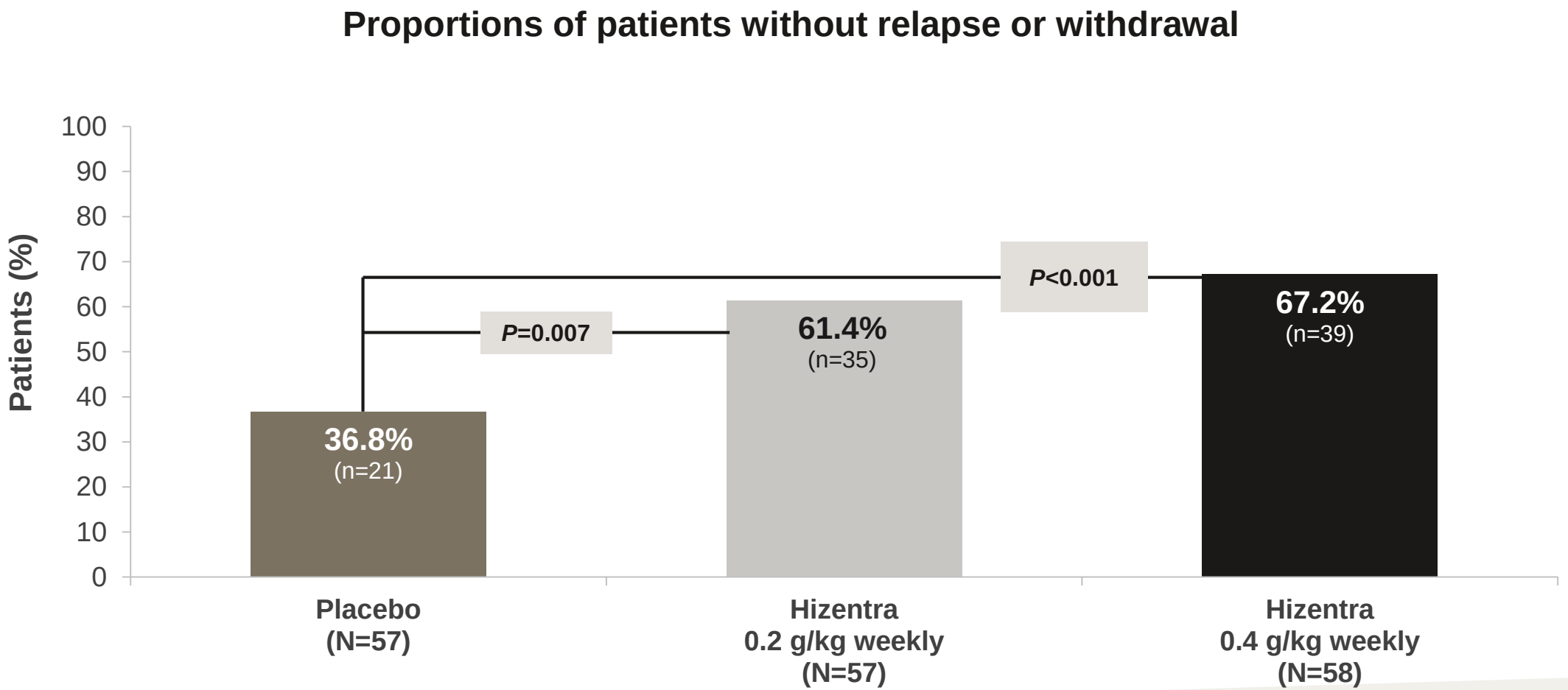
PATH: Primary Endpoint



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

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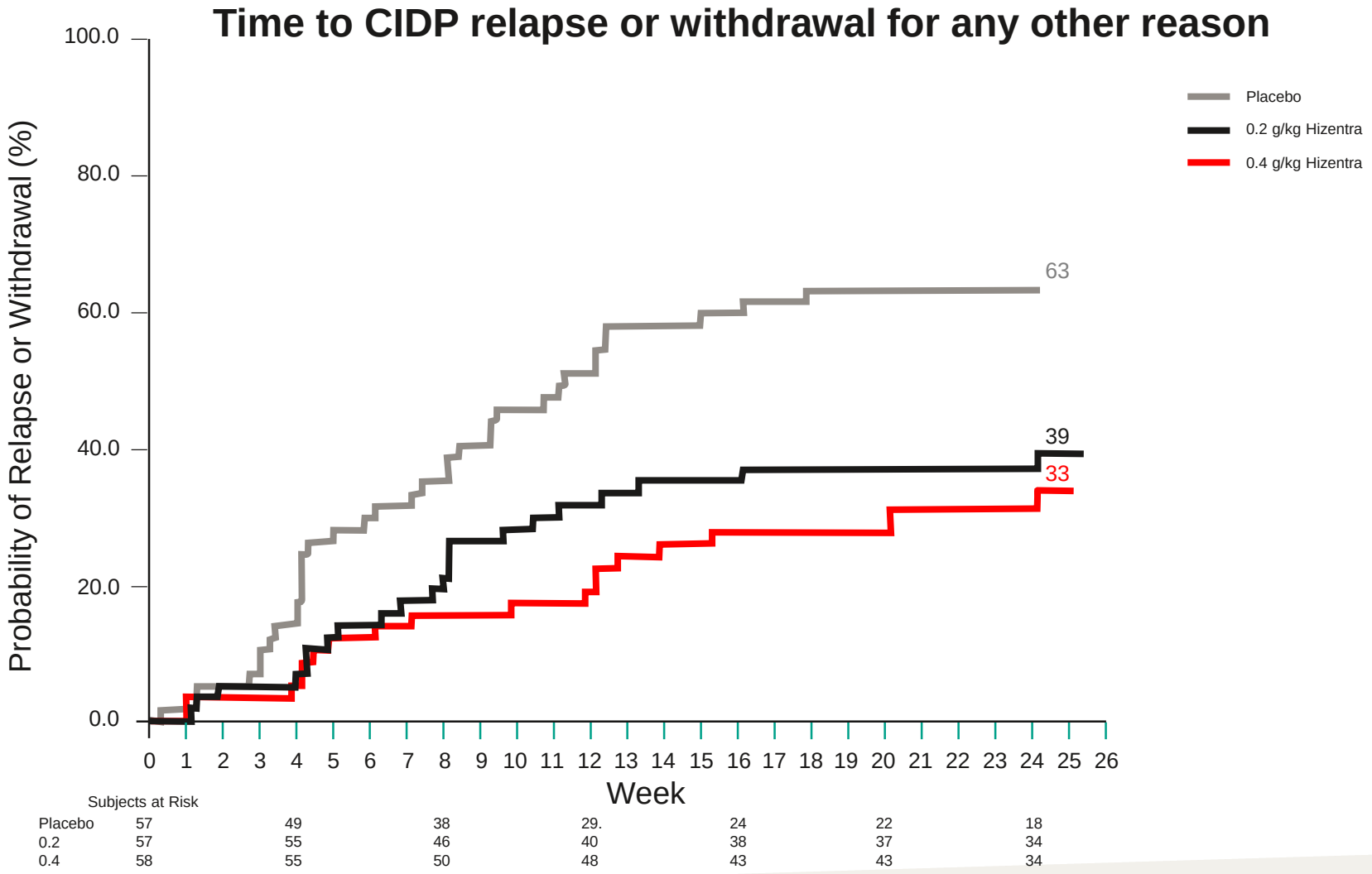
PATH: Secondary Endpoint



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PATH: Secondary Endpoint

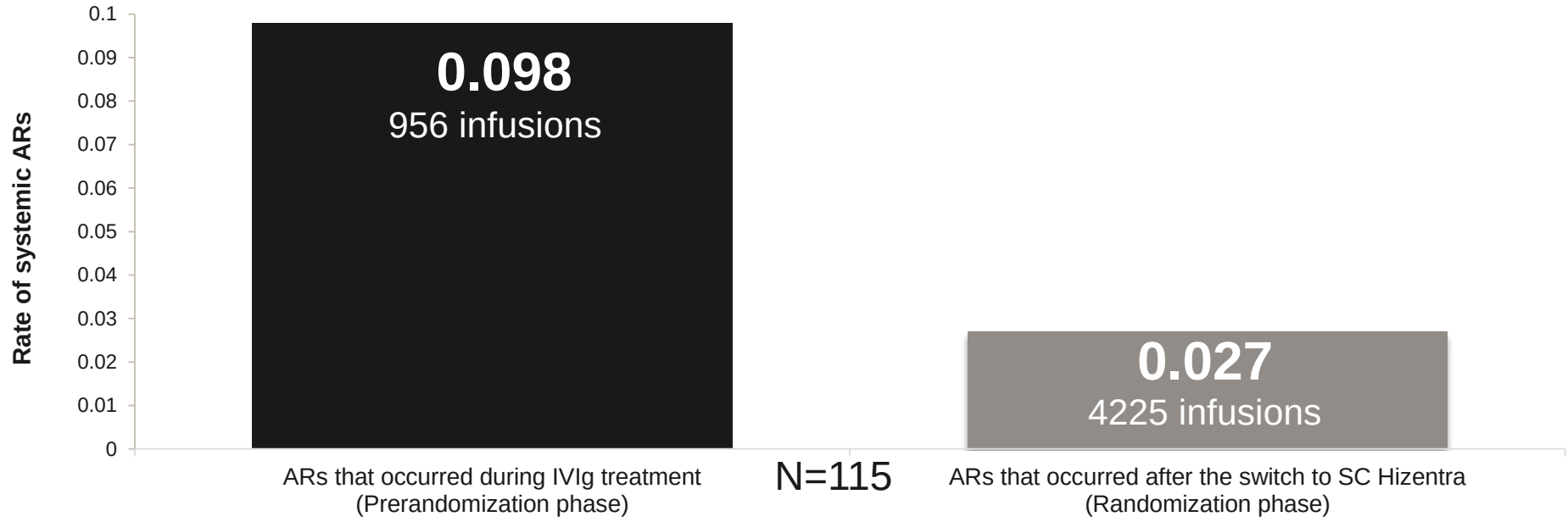
Median changes from baseline for INCAT score, I-RODS, grip strength (for both hands), Medical Research Council sum score

Functional Measure	Placebo (n=57)	Low-dose SCIg (n=58)	High-dose SCIg (n=58)	Overall P value*
INCAT (total score)	1.0 (0.0 to 2.0)	0.0 (0.0 to 1.0)	0.0 (0.0 to 0.0)	<0.0001
I-RODS (centile score)	-3.0 (-16.0 to 0.0)	-2.0 (-7.0 to 2.0)	0.0 (-2.0 to 3.5)	0.0002
Grip Strength (dominant hand [kPa])	-6.6 (-21.6 to 0.3)	-0.6 (-8.9 to 7.0)	-2.7 (-6.6 to 2.0)	0.0223
Grip Strength (non-dominant hand [kPa])	-8.3 (-24.7 to 1.7)	-0.4 (-10.3 to 7.0)	-1.7 (-6.0 to 4.6)	0.0026
MRC (sum score)	-2.0 (-6.0 to 0.0)	0.0 (-2.0 to 2.0)	0.0 (-2.0 to 1.0)	0.0026

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

PATH: Safety

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



*Data represent systemic side effects reported during the 13-week single-arm restabilization phase compared to those reported in the 2 Hizentra groups during the 24-week postrandomized phase. However, there was no parallel group of subjects receiving placebo in the IVIg restabilization phase.

PATH: Safety

Adverse Reactions Occurring in ≥5% of Subjects Treated with HIZENTRA and at a Higher Frequency than Placebo-Treated Subjects

	Placebo		0.2 g/kg HIZENTRA		0.4 g/kg HIZENTRA	
	Number (%) of Subjects n=57	Number of Events (Rate/Infusion) N=1514*	Number (%) of Subjects n=57	Number of Events (Rate/Infusion) n=2007*	Number (%) of Subjects n=58	Number of Events (Rate/Infusion) n=2218*
Local Reactions+	4 (7.0)	7 (0.005)	11 (19.3)	54 (0.027)	17 (29.3)	49 (0.022)
Headache	2 (3.5)	2 (0.001)	4 (7.0)	5 (0.002)	4 (6.9)	4 (0.002)
Nasopharyngitis	1 (1.8)	1 (<0.001)	4 (7.0)	6 (0.003)	2 (3.4)	2 (<0.001)
Fatigue	1 (1.8)	1 (<0.001)	5 (8.8)	5 (0.002)	0	0
Upper respiratory tract infection	2 (3.5)	2 (0.001)	3 (5.3)	3 (0.001)	2 (3.4)	2 (<0.001)
Fall	0	0	3 (5.3)	8 (0.004)	1 (1.7)	1 (<0.001)
Back Pain	1 (1.8)	1 (<0.001)	3 (5.3)	4 (0.002)	1 (1.7)	1 (<0.001)
Arthralgia	1 (1.8)	1 (<0.001)	3 (5.3)	4 (0.002)	1 (1.7)	1 (<0.001)
Pain in Extremity	0	0	1 (1.8)	1 (<0.001)	3 (5.2)	3 (0.001)

*Number of infusions

+Includes infusion-site erythema, infusion-site swelling, infusion-site pain, infusion-site induration, infusion-site warmth, infusion-site hematoma, and infusion-site pruritis

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

PATH extension study

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.

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Extension Study: Efficacy and Safety Assessments

Efficacy

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

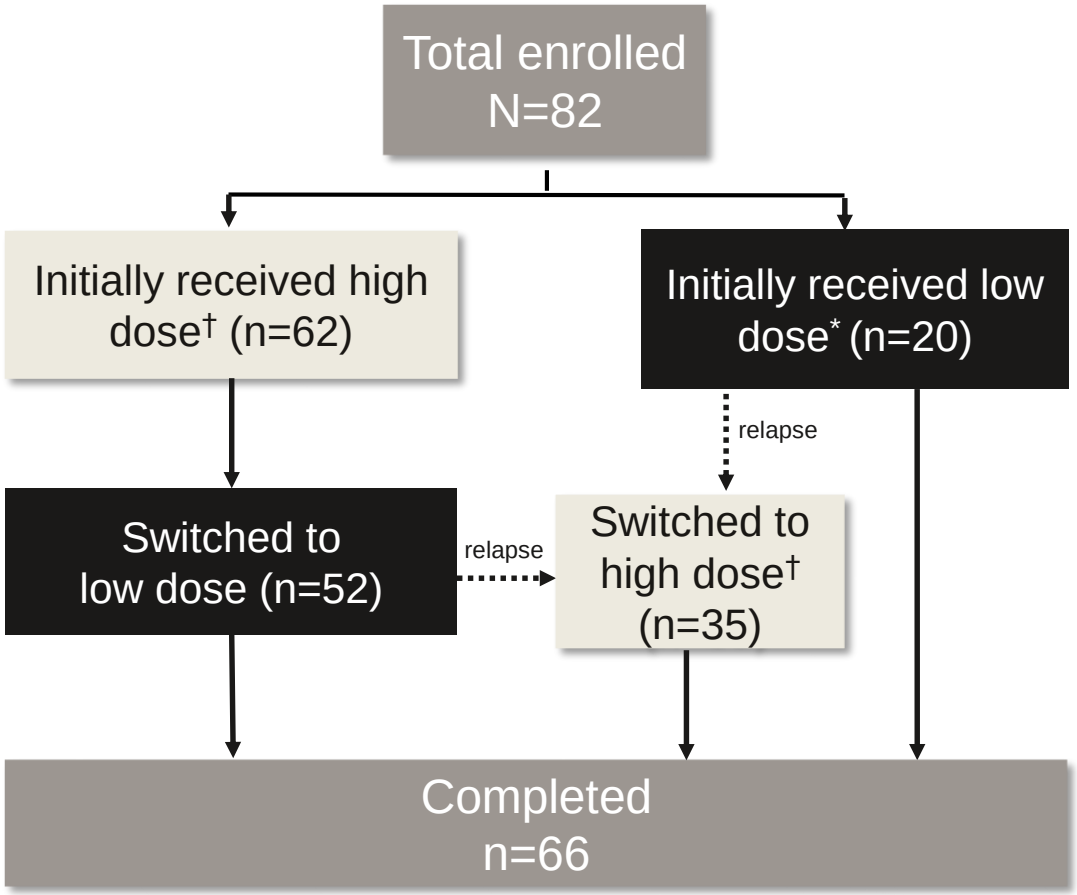
Safety

- 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: Patient Disposition[1]



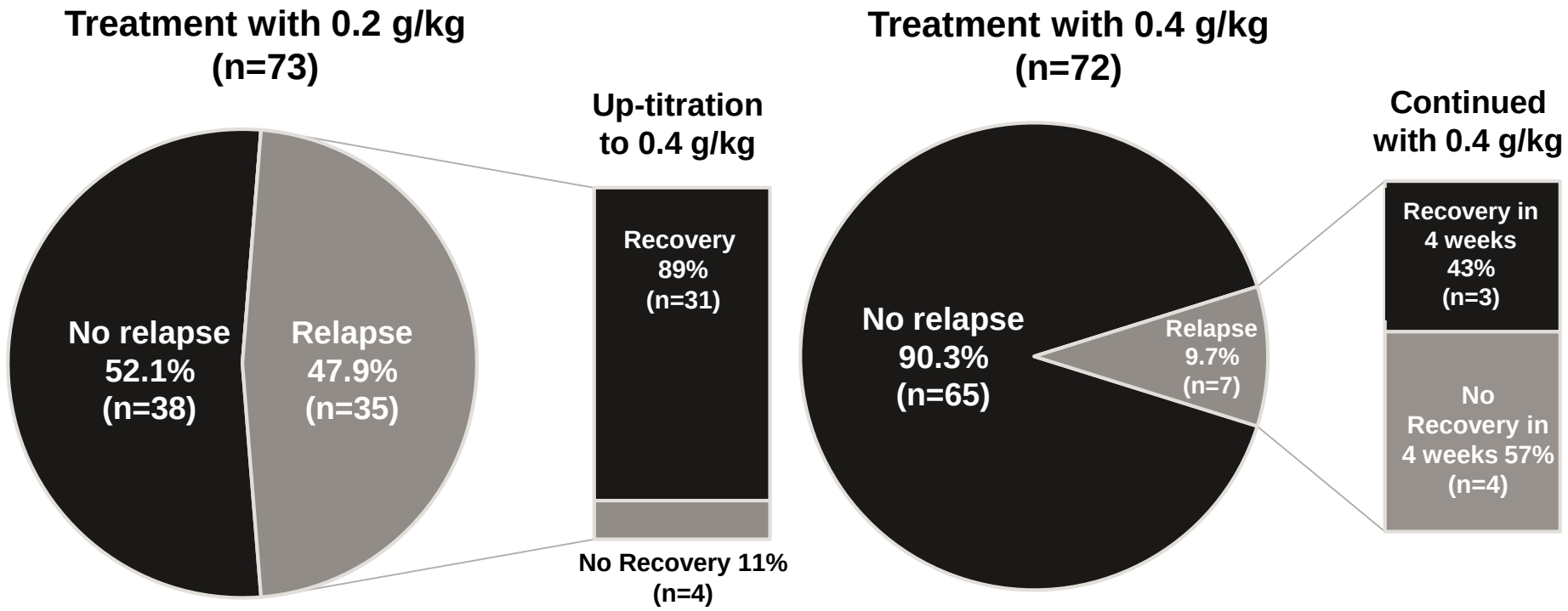
Per protocol, IVIg was not used to restabilize patients who relapsed.[2]

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 CIDP; 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

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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Hizentra Overview

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

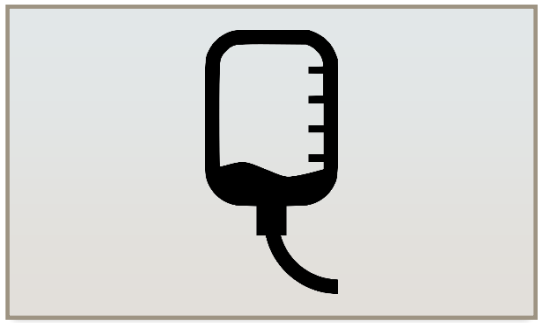
Hizentra: Additional Information

HIZENTRA is supplied in a prefilled syringe or a tamper-evident vial containing 0.2 grams of protein per mL of preservative-free liquid. The HIZENTRA packaging components are not made with natural rubber latex.

Storage and Handling

- Store the HIZENTRA prefilled syringe or vial in its original carton to protect it from light.
- Each prefilled syringe or vial label contains a peel-off strip with the prefilled syringe or vial size and product lot number for use in recording doses in a patient treatment record.
- When stored at room temperature (up to 25°C [77°F]), HIZENTRA is stable for up to 30 months, as indicated by the expiration date printed on the outer carton of the prefilled syringe or vial label.
- Do not shake the HIZENTRA prefilled syringe or vial.
- Do not freeze. Do not use product that has been frozen.
- Discard any unused product and all used disposable supplies after each infusion.

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
- Change the site of infusion with each administration

Infusion Time

- Weekly dosing†
- About 1 hour/session‡

*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.

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Hizentra in CIDP - 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