CIDP

AMBASSADOR PROGRAM

Treatment of CIDP

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Goals

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- Review the different therapies available to treat patients with CIDP
- Review the strong evidence base supporting the use of IVIG as a first-line therapy
- Review the impact that clinical presentation might have on therapy choice and response
- Discuss how to assess outcomes and incorporate these assessments into our therapeutic decisions
- Discuss long-term management, including practical suggestions on how to taper treatment options

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2021 EAN/PNS CIDP Guidelines Treatment Recommendations

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- IVIG or corticosteroids are strongly recommended as initial treatment in typical CIDP and CIDP variants
- IVIG should be considered as first-line treatment in motor CIDP (good practice point)
- Plasma exchange is strongly recommended if IVIG and corticosteroids are ineffective
- IVIG, SCIG, or corticosteroids are recommended for maintenance treatment
- If the maintenance dose of any of these is high, consider either combination treatments or adding an immunosuppressant or immunomodulatory drug (good practice point)
- If pain is present, consider drugs against neuropathic pain and multidisciplinary management (good practice point)

EAN, European Academy of Neurology; PNS, Peripheral Nerve Society.
Reference: van den Bergh PYK. *J Peripher Nerv Syst*. 2021;26(3):242-268.

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How to Choose a Therapy

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- When choosing to treat, a therapeutic goal should be outlined before therapy begins. If the disease burden is minimal, assessment of effect will be difficult
- Be familiar with the level of evidence supporting the treatment you are considering administering
- Therapies with level 1 evidence are supported by well-designed, placebo-controlled, randomized studies

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Plasma Exchange in CIDP

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- Double-blind study of 18 CIDP patients (9 with progressive neuropathy and 9 with relapsing course)
- Over 4 weeks, patients received 10 plasma exchange treatments or 10 sham plasma exchange treatments, with a wash-out period and a crossover
- ITT analysis of clinical and electrodiagnostic outcomes
- 15 patients completed the trial: 12/15 improved with plasma exchange
- 8/12 relapsed, most within 1-2 weeks of stopping plasma exchange
- All patients who relapsed subsequently improved with open-label plasma exchange ± prednisone

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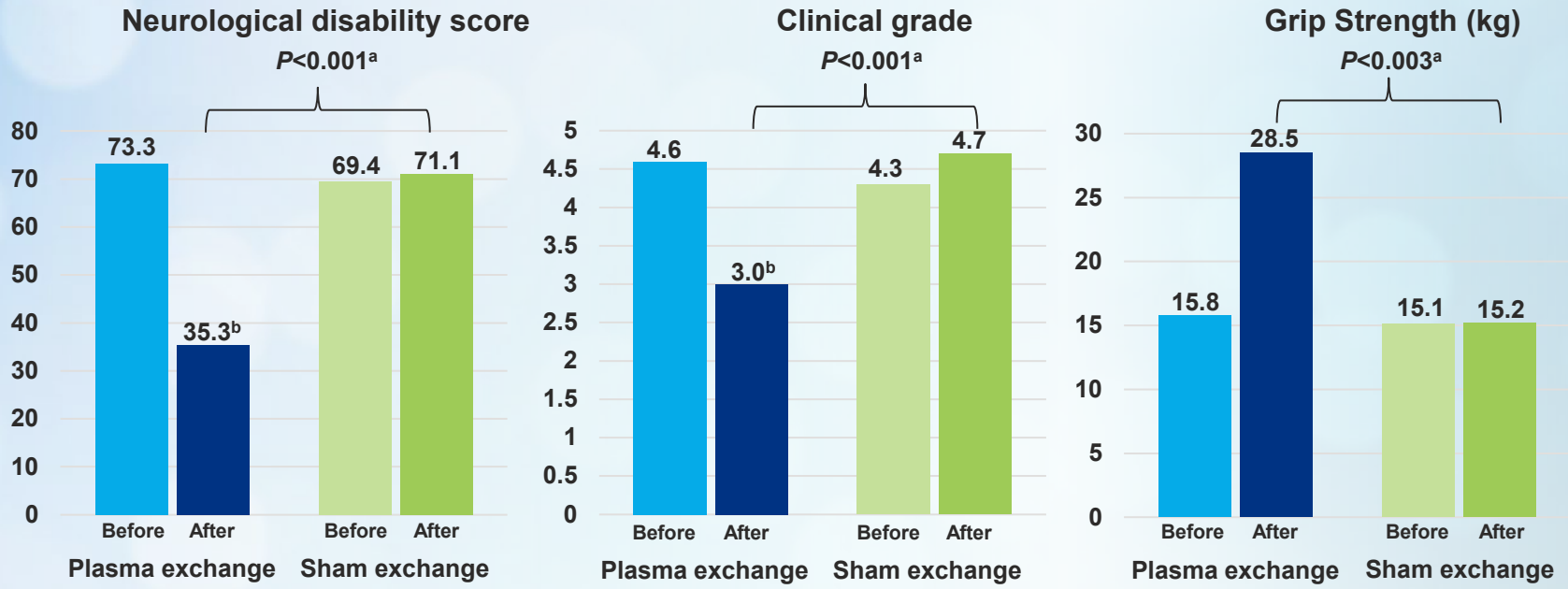
ITT, intention to treat.

Reference: Hahn AF. *Brain*. 1996;119(pt 4):1055-1066.

Plasma Exchange in CIDP: Clinical Outcome Measures



[a] *P* values were obtained from ANOVAs, repeated measures option, and refer to the differences between the effects of plasma exchange and sham plasma exchange treatments.
[b] Decreasing values for neurological disability score and clinical grade signify improvement.

Patients were randomly assigned to plasma exchange or sham plasma exchange and received 10 treatments over 4 weeks

- 4 in week 1, 3 in week 2, 2 in week 3, and 1 in week 4

ANOVA, analysis of variance.

Reference: Hahn AF. *Brain.* 1996;119(pt 4):1055-1066.

Open-Label Trial of Prednisone

- 59 treated patients
- >90% response rate to prednisone
- Mean time to any improvement: ~2 months
- Mean time to maximum improvement: ~6 months

Reference: Barohn RJ. *Arch Neurol.* 1989;46(8):878-884.

Corticosteroids

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- First therapy for patients with CIDP; though not strictly level 1 evidence, the vast clinical experience is important in the classification of evidence in this case[1-2]
- Many studies exist showing the efficacy of steroids for inducing clinical improvement in various scenarios, including nonrandomized, retrospective, and noncontrolled studies[1]
  - However, the consensus of experts is that glucocorticoid therapy produces a significant improvement in clinical syndrome and disability
- Delivery is deemed effective using oral and intravenous delivery protocols[1,3,4]

References: 1. Press R. *Acta Neurol Scand.* 2016;133(4):228-238. **2.** van den Bergh PYK. *J Peripher Nerv Syst*. 2021;26(3):242-268. **3.** Barohn RJ. *Arch Neurol.* 1989;46(8):878-884. **4.** Lopate G. *Arch Neurol.* 2005;62(2):249-254.

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Corticosteroids (cont.)

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- Example: Oral prednisone protocol
  - 1 mg/kg (100 mg max) for 2 months followed by slow tapering of 10 mg per month.[1] Tapering too fast often triggers relapse requiring a return to previous levels.[2] Improvement in disability may be seen in 2 months (one study showed 2 weeks); may not be observed for up to 6 months[2-3]
- Example: Intravenous therapy protocol
  - 1 g for 3 consecutive days; then 1 g weekly for 4 weeks; then slowly decreasing interval from weekly to every 12 weeks[4]

References: 1. Dimachkie MM. *Curr Treat Options Neurol.* 2013;15(3):350-366. **2.** Gorson KC. *Ther Adv Neurol Disord.* 2012;5(6):359-373. **3.** Barohn RJ. *Arch Neurol.* 1989;46(8):878-884. **4.** Lopate G. *Arch Neurol.* 2005;62(2):249-254.

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Randomized Controlled Trials of IVIG in CIDP Before 2008

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Reference	Year	Therapy	N	Design/duration	Efficacy summary
van Doorn et al[1]	1990	IVIG	7	Double-blind, placebo-controlled, crossover; single-dose comparison	Improvement in all patients
Vermeulen et al[2]	1993	IVIG	28	Double-blind, placebo-controlled, parallel-group comparison of 5 consecutive daily doses	No significant difference between groups
Hahn et al[3]	1996	IVIG	30	Double-blind, placebo-controlled, crossover; 4 weeks	Improvement in 63% of patients
Thompson et al[4]	1996	IVIG	7	Double-blind, placebo-controlled, crossover; 24 weeks (stopped early)	Improvement in 43% of patients
Mendell et al[5]	2001	IVIG	53	Double-blind, placebo-controlled; 6 weeks	Improvement in 76% of patients
Hughes et al[6]	2001	IVIG vs prednisolone	32	Double-blind, placebo-controlled, crossover; 6 weeks	Improvement but no significant difference between groups
Dyck et al[7]	1994	IVIG vs plasma exchange	15	Randomized, observer-blinded, crossover; 6 weeks	Improvement but no significant difference between groups

References: 1. van Doorn PA. *Neurology.* 1990;40(2):209-212. **2.** Vermeulen M. *J Neurol Neurosurg Psych.* 1993;56(1):36-39. **3.** Hahn AF. *Brain.* 1996;119(pt 4):1067-1077. **4.** Thompson N. *J Neurol.* 1996;243(3):280-285. **5.** Mendell J. *Neurology.* 2001;56(4):445-449. **6.** Hughes R. *Ann Neurol.* 2001;50(2):195-201. **7.** Dyck PJ. *Ann Neurol.* 1994;36(6):838-845.

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Randomized Controlled Trials of IVIG in CIDP 2008 and Later

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Reference	Year	Therapy	N	Design/duration	Efficacy summary
Hughes et al[1]	2008	IVIG-C vs placebo	117	Double-blind, placebo-controlled with crossover for nonresponders during initial 24-week efficacy period; re-randomization of IVIG responders after 24 weeks for continued therapy or withdrawal (placebo arm); total of 48 weeks	Significantly higher proportion of adjusted-INCAT responders with IVIG vs placebo in initial treatment period (54% vs 21%, *P*=0.0002) Significantly longer time to relapse with IVIG vs placebo during maintenance period (*P*=0.011)
Kuitwaard et al[2]	2010	Freeze-dried IVIG vs liquid IVIG	27	Active-controlled, double-blind, parallel-group; total of 10 infusions	No significant difference on primary outcome (overall disability sum score)
Nobile-Orazio et al[3]	2012	IVIG vs IV methylpred-nisolone	46	Double-blind, placebo-controlled, parallel-group; 6 months	Significantly fewer IVIG patients discontinued therapy vs IV methylprednisolone (13% vs 52%, *P*=0.0085) at 6 months
Kuitwaard et al[4]	2021	High-frequency, low-dose IVIG vs low-frequency, high-dose IVIG	22	Randomized, placebo-controlled, crossover	No significant differences between groups
Cornblath et al[5]	2022	3 maintenance doses of IVIG	142	Randomized, double-blind, parallel-group	Primary and secondary endpoints showed dose-dependent response

INCAT, inflammatory neuropathy cause and treatment.

References: 1. Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144. **2.** Kuitwaard K. *J Neurol Neurosurg Psych*. 2010;81(12):1374-1379. **3.** Nobile-Orazio E. *Lancet Neurol.* 2012;11(6):493-502. **4.** Kuitwaard K. *Eur J Neurol*. 2021;28(1):286-296. **5.** Cornblath DR. *BRAIN*. 2022;145(3):887-896.

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PATH Study Only Enrolled CIDP Patients Who Were IVIG Dependent[1-2]…

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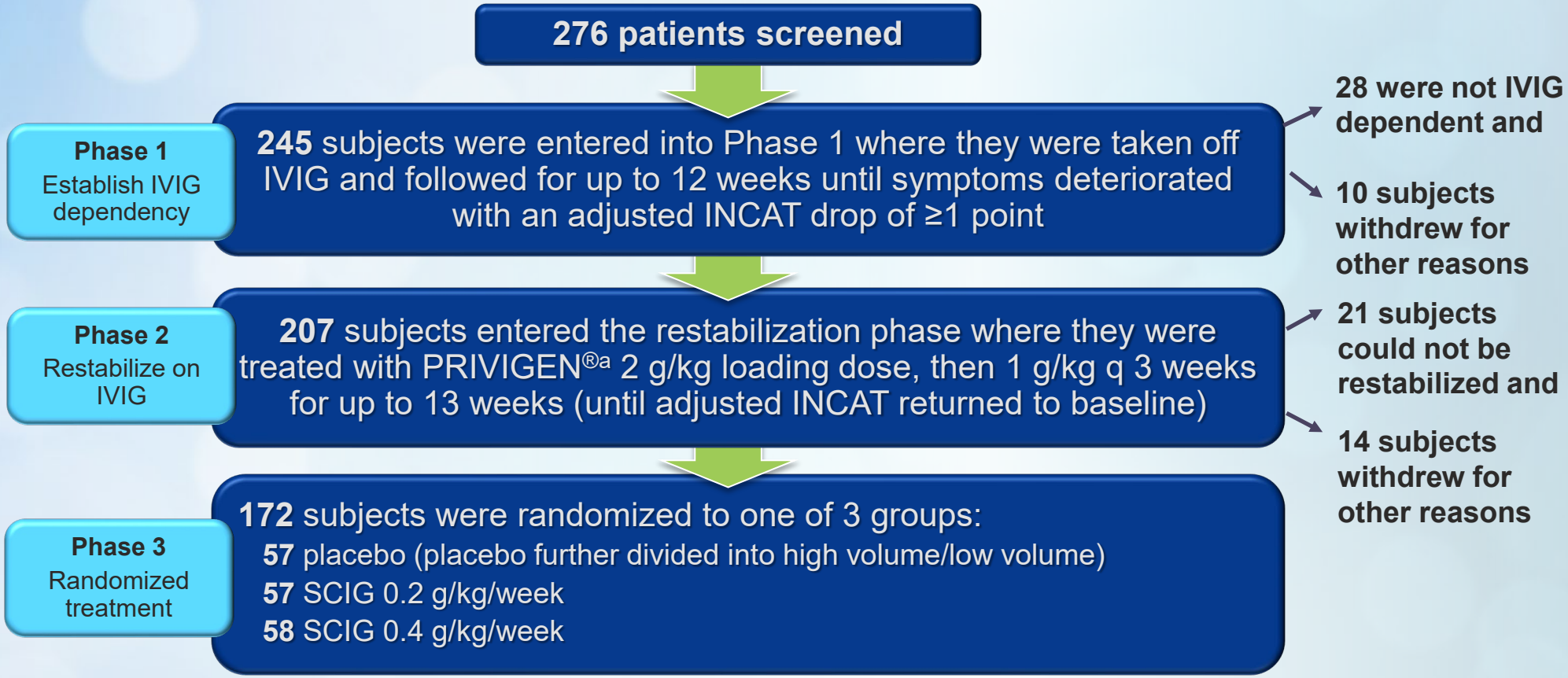

[a]PRIVIGEN® is a registered trademark of CSL Behring LLC.

INCAT, inflammatory neuropathy cause and treatment.

References: 1. van Schaik IN. *Lancet Neurol*. 2018;17(1):35-46.
2. van Schaik IN. *Trials*. 2016;17(1):345.

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PATH Study: Predetermined Outcome Measures[1-2]

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Primary Outcome Measure	**% relapse or withdrawal in SCIG treatment period (≥1 point increase in INCAT)**
Secondary Outcome Measures	Between-group differences of median changes from baseline to completion visits in INCAT, grip strength, MRC, I-RODS
	Time to relapse or withdrawal in SCIG period
	Time to improvement on SCIG restabilization therapy in INCAT, I-RODS, grip strength
	Median changes before and at end of SCIG restabilization or rescue in INCAT disability score, I-RODS, grip strength, MRC
	Time to improvement after relapse in SCIG period with SCIG rescue (INCAT back to or below baseline)
Exploratory Outcome Measures	Quality of life (EuroQOL-5)
	Treatment Satisfaction Questionnaire for Medication (TSQM)
	Work Productivity and Activity Impairment Questionnaire for General Health (WPAI-GH)

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References: 1. van Schaik IN. *Lancet Neurol*. 2018;17(1):35-46.
2. van Schaik IN. *Trials*. 2016;17(1):345.

PATH Results: Primary Endpoint

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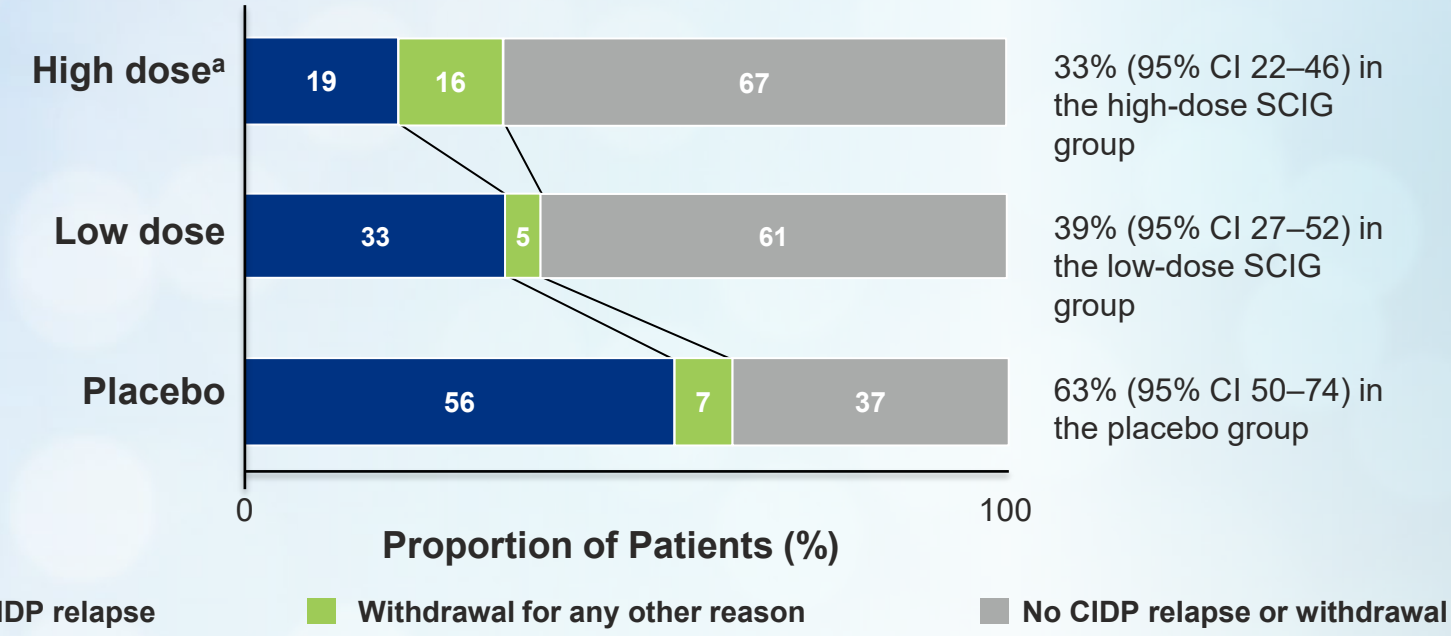
Percentage of Patients Who Withdrew From SCIG or Relapsed



- **All patients who withdrew from the study for reasons other than relapse were assumed not to have had a relapse**
- There was no significant difference between the 2 SCIG dose groups

[a] One patient relapsed at the end of study visit but was discontinued due to an AE. This patient is therefore counted as relapsed and as withdrawn for any other reason.

Reference: van Schaik IN. *Lancet Neurol*. 2018;17(1):35-46.

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SCIG Relapse and IVIG Rescue

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- 36% of patients relapsed after randomization:
  - 56% in the placebo group
  - 33% in the low-dose SCIG group
  - 19% in the high-dose SCIG group
- 90% of patients who relapsed were treated with rescue PRIVIGEN®[a] (induction dose and up to 4 maintenance doses) **3 Months**
- **70%** of those who received more than one rescue dose of PRIVIGEN®[a] recovered (returned to at least baseline INCAT score; assessed at last study visit)
- **1/3 of patients did not return to baseline**

[a]PRIVIGEN® is a registered trademark of CSL Behring AG.
INCAT, inflammatory neuropathy cause and treatment.
Reference: van Schaik IN. *Lancet Neurol*. 2018;17(1):35-46.

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Responder Analysis During Randomized Withdrawal Phase: PATH

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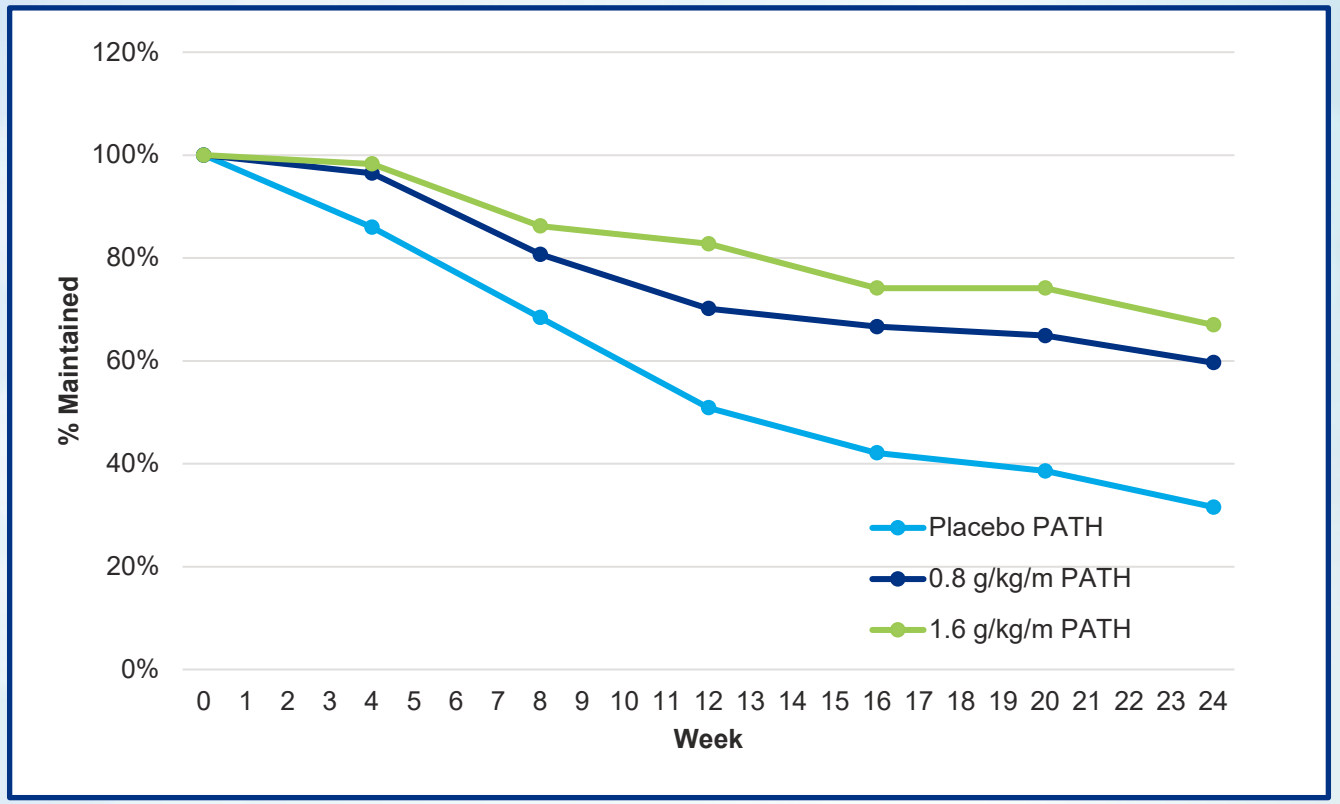
Responder Analysis: Subjects-at-Risk Plots



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Reference: van Schaik IN. *Lancet Neurol*. 2018;17(1):35-46.

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The Clinical Rationale for IVIG-C in Chronic Inflammatory Demyelinating Polyneuropathy

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IGIV-C CIDP Efficacy (ICE) Study: Objectives and Design

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- Assess long-term efficacy and safety of IVIG-C in treatment of CIDP[1]
  - Phase 3, 48-week, randomized, double-blind, placebo-controlled, multinational study (N=117)
- Longest randomized study of IVIG in the treatment of CIDP (48 weeks total)[1]
  - 24-week study + 24-week extension
- The ICE study led to the first FDA indication for IVIG-C in CIDP and established IVIG as a level A recommendation in the 2010 EFNS/PNS CIDP guidelines[2]

ADVERSE REACTIONS IN CIDP STUDY
In CIDP, the most common adverse reactions with IVIG-C were headache, pyrexia, hypertension, chills, rash, nausea, arthralgia, and asthenia. The most serious adverse reaction was pulmonary embolism (PE) in 1 subject with a history of PE.

EFNS, European Federation of Neurological Societies; PNS, Peripheral Nerve Society.

Reference: 1. Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144. **2.** van den Bergh PYK. *Eur J Neurol.* 2010;17(3):356-363.

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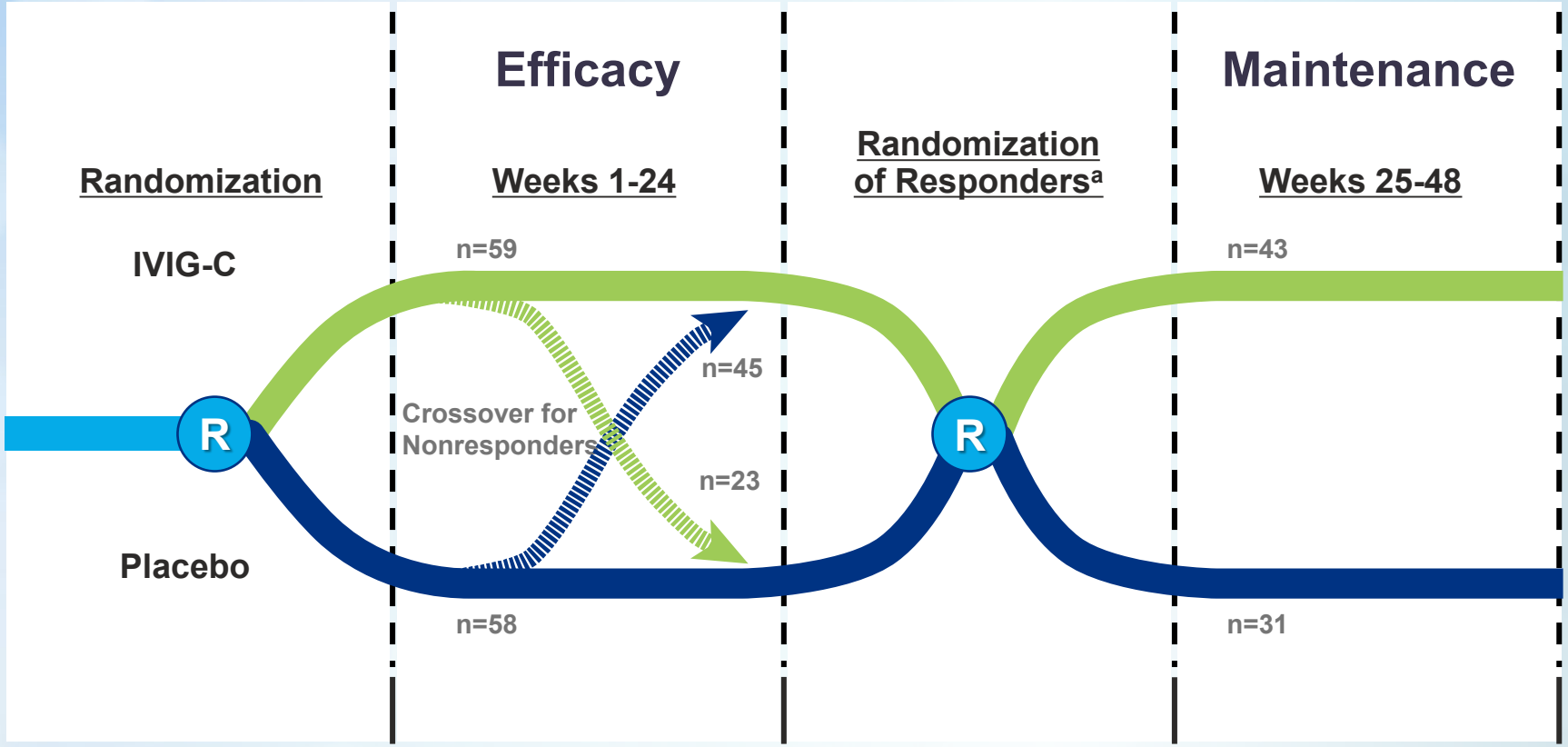
ICE Study: Study Treatment Periods



[a] First-period nonresponders were those whose adjusted INCAT disability score deteriorated by ≥1 point at any time after first infusion; those whose score was stable until week 6; and those whose score had improved but then returned to baseline (or lower) from week 6 to week 24.

INCAT, inflammatory neuropathy cause and treatment.

Reference: Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

ICE Study: Loading and Maintenance Dosing

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	Loading dose[1,2] (first dose at week 0 or crossover)	Maintenance dose[1,2] (weeks 3 to 21)
IVIG-C	2 g/kg (20 mL/kg) over 2-4 days[a] (up to 80 g/day)	1 g/kg (10 mL/kg) over 1-2 days[b] (up to 80 g)
Placebo	0.1% albumin (20 mL/kg) over 2-4 days[a] (up to 80 g equivalent volume/day)	0.1% albumin (10 mL/kg) over 1-2 days[b] (up to 80 g equivalent volume)

The dosing was by actual body weight up to 80 kg, and for those weighing more than 80 kg, the dose was capped at the dose for an 80 kg person.[2]

[a] Maximum of 4 days if 2-day or 3-day treatment not well tolerated.

[b] Maximum of 2 days if 1-day treatment not well tolerated.

References: 1. Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144. 2. Data on file, Grifols.

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ICE Study: Clinical Endpoints

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Primary	• Percentage of adjusted-INCAT responders who completed initial treatment phase (by week 6) without crossing over and maintained improvement ≥1 point through week 24[1]
Key Secondary	• Maximum grip strength[1]
	• Time to relapse among responders to IVIG-C who entered extension phase[1]
	• MRC sum score and ISS[1]
	• Health-related quality of life (SF-36 and RHS)[2]

INCAT, inflammatory neuropathy cause and treatment; ISS, INCAT sensory score; MRC, Medical Research Council; RHS, Rotterdam Handicap Scale; SF-36, short form 36.

References: 1. Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.
2. Merkies ISJ. *Neurology.* 2009;72(15):1337-1344.

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ICE Study: Definition of INCAT Disability Scale

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Score	Arm disability	Score	Leg disability
0	No upper limb problems	0	Walking not affected
1	Symptoms not affecting ability to perform: doing all zippers and buttons, washing or brushing hair, using knife and fork together, handling small coins	1	Walking affected, but walks independently outdoors
2	Symptoms affecting but not preventing functions listed above	2	Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors
3	Symptoms preventing 1 or 2 functions listed above	3	Usually uses bilateral support (sticks, crutches, frame, 2 arms) to walk outdoors
4	Symptoms preventing 3 or all functions listed above, but some purposeful movements still possible	4	Usually uses wheelchair to travel outdoors, but able to stand and walk few steps
5	Inability to use either arm for any purposeful movement	5	Restricted to wheelchair, unable to stand and walk a few steps with help

INCAT, inflammatory neuropathy cause and treatment.

Reference: Hughes RAC. *Ann Neurol.* 2001;50(2):195-201.

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What Does a 1-Point INCAT Change Mean for the Patient?

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Score	Arm disability	Score	Leg disability
0	No upper limb problems	0	Walking not affected
1	Symptoms not affecting ability to perform: doing all zippers and buttons, washing or brushing hair, using knife and fork together, handling small coins	1	Walking affected, but walks independently outdoors
2	Symptoms affecting but not preventing functions listed above	2	Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors
3	Symptoms preventing 1 or 2 functions listed above	3	Usually uses bilateral support (sticks, crutches, frame, 2 arms) to walk outdoors
4	Symptoms preventing 3 or all functions listed above, but some purposeful movements still possible	4	Usually uses wheelchair to travel outdoors, but able to stand and walk few steps
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INCAT, inflammatory neuropathy cause and treatment.

Reference: Hughes RAC. *Ann Neurol.* 2001;50(2):195-201.

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ICE Study: Baseline Characteristics

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Parameter	IVIG-C (n=59)	Placebo (n=58)	*P* value
Male:Female, n	31:28	46:12	0.002
Age,[a] y	50 ± 17	53 ± 16	NS
Race, n (%) **White** **Other**	 55 (93) 4 (7)	 52 (90) 6 (10)	NS
Time since first CIDP symptoms,[a] y	5.8 ± 7.4	4.8 ± 4.9	NS
Time since CIDP diagnosis,[a] y	2.4 ± 3.7	1.8 ± 2.9	0.043
Baseline INCAT score[a]	4.2 ± 1.4	4.1 ± 1.5	NS

[a]Mean ± standard deviation.
INCAT, inflammatory neuropathy cause and treatment.
Reference: Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

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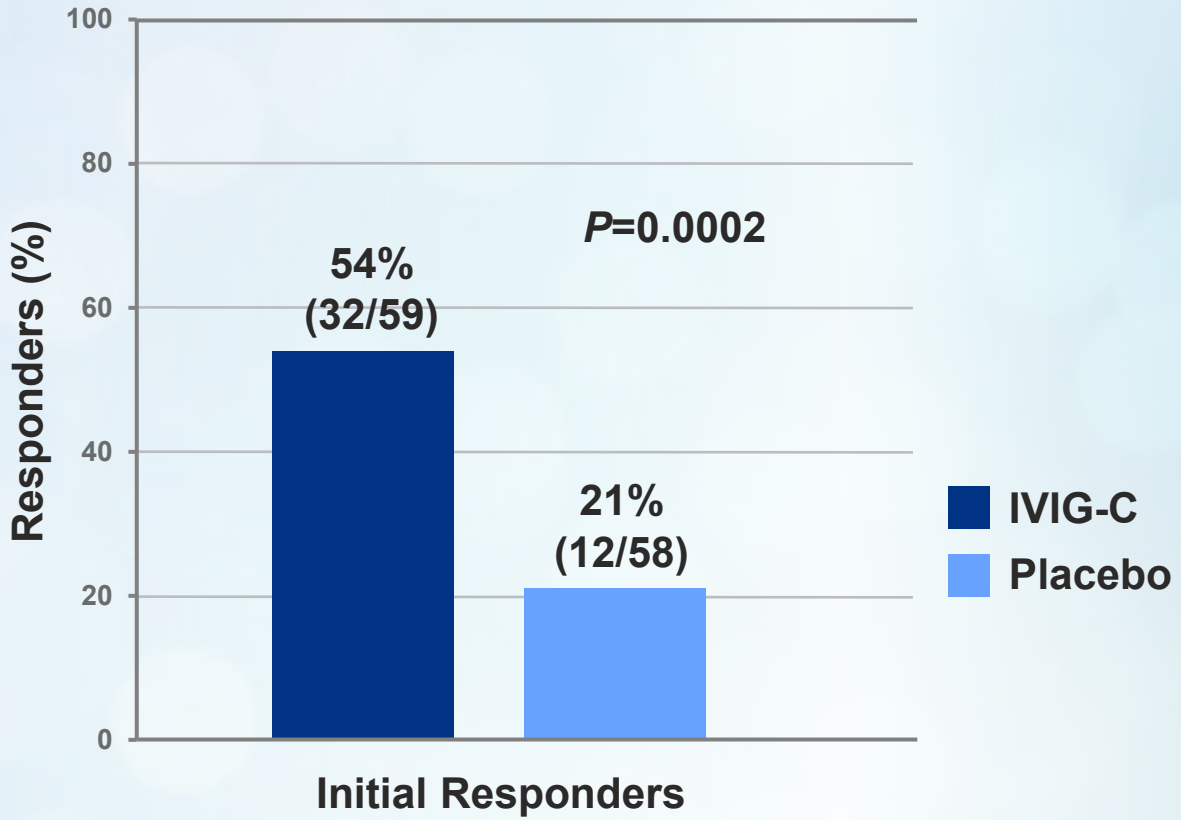
ICE Study: Significantly Higher Response Rate by Week 6 and Maintained Through Week 24



Primary endpoint: Percentage of adjusted-INCAT responders who completed the initial treatment period without crossing over and maintained ≥1 point through week 24.

INCAT, inflammatory neuropathy cause and treatment.

Reference: Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

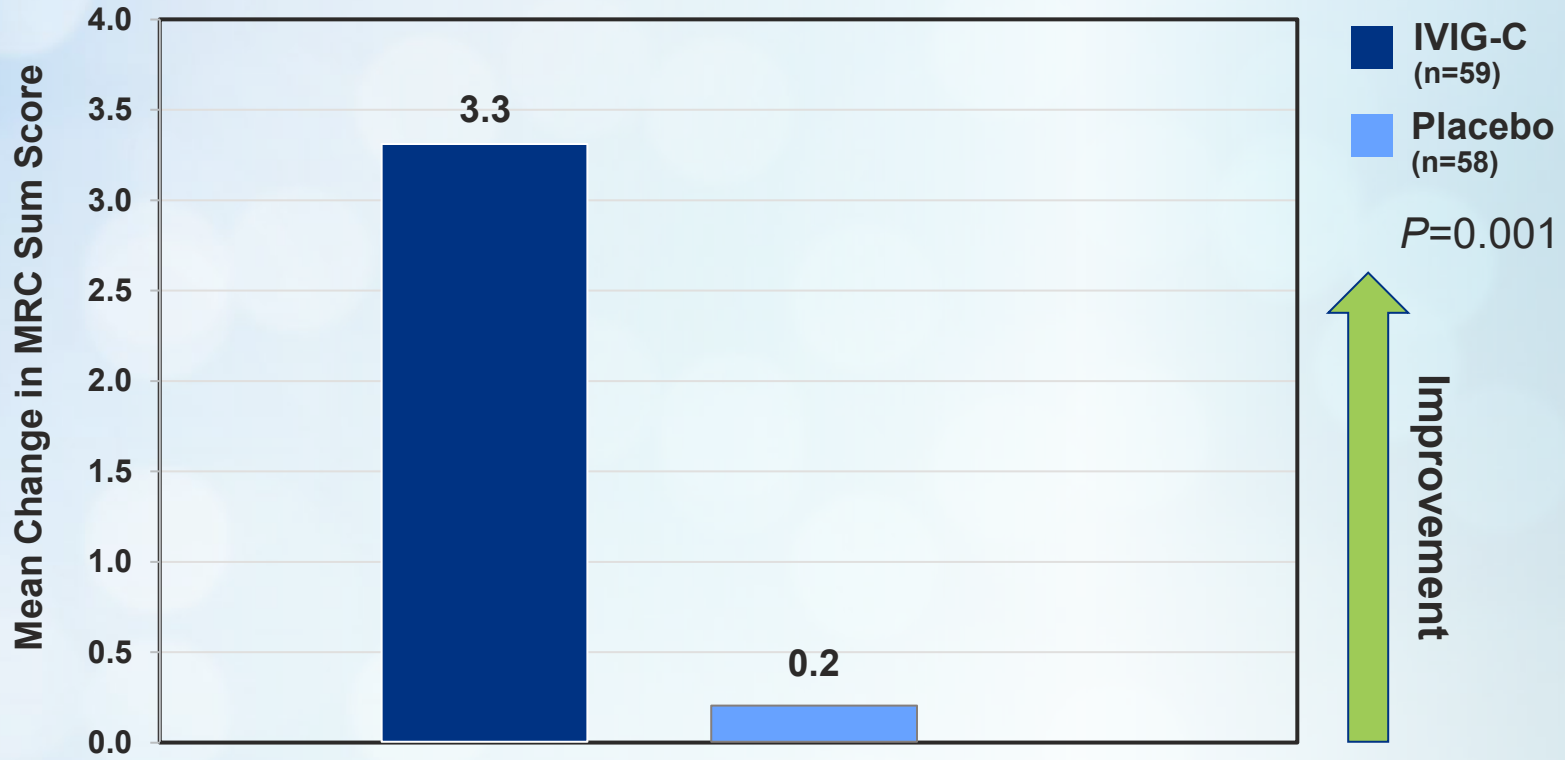
ICE Study: Short Duration of Infusion Time

- Most loading-dose infusions[a] given over 2 days
  - 79% (179/227 infusions) with IVIG-C
  - 73% (133/182 infusions) with placebo
- Maintenance-dose infusions every 3 weeks
  - 96% given within 5 hours
  - Mean: 2.7 hours

[a] Occurring at start of initial or crossover (rescue) phases.

Reference: Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

ICE Study: Significant Improvement in MRC Sum Scores at 24 Weeks

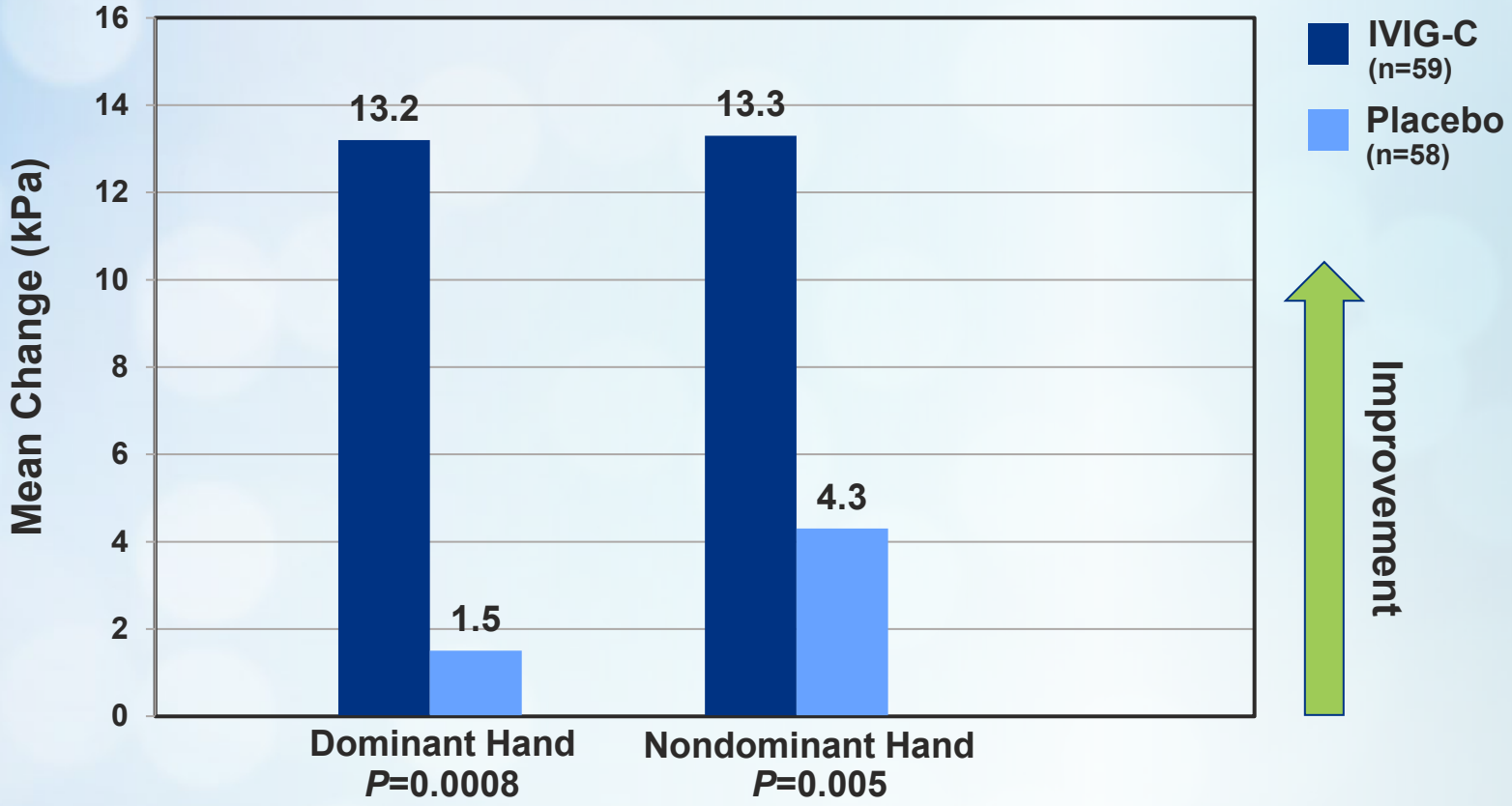


Exploratory endpoint: Mean change from baseline to final (week 24) measurement in the initial treatment period on the MRC sum score.

MRC, Medical Research Council.

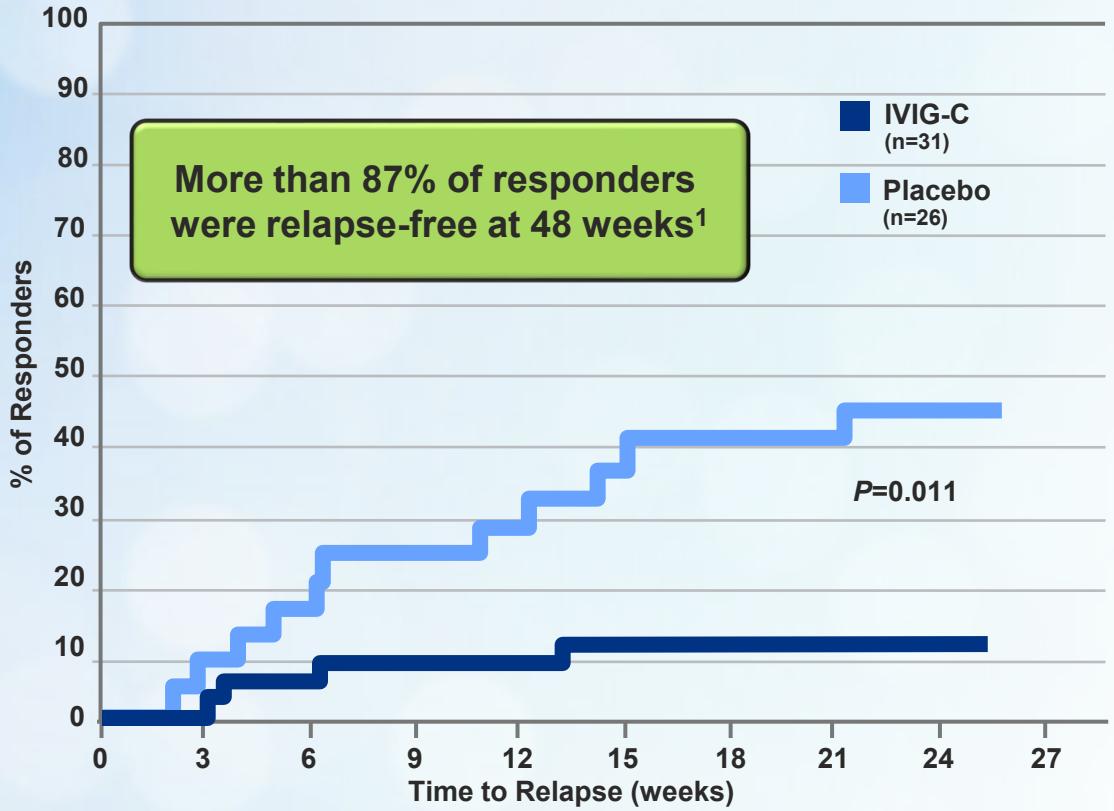
Reference: Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

ICE Study: Significant Improvement in Grip Strength at 24 Weeks



Reference: Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

ICE Study: Extended Time to Relapse[1,a]



ICE study demonstrated neuroprotective qualities by improvement of symptoms and prevention of relapse[1,2] to allow healing

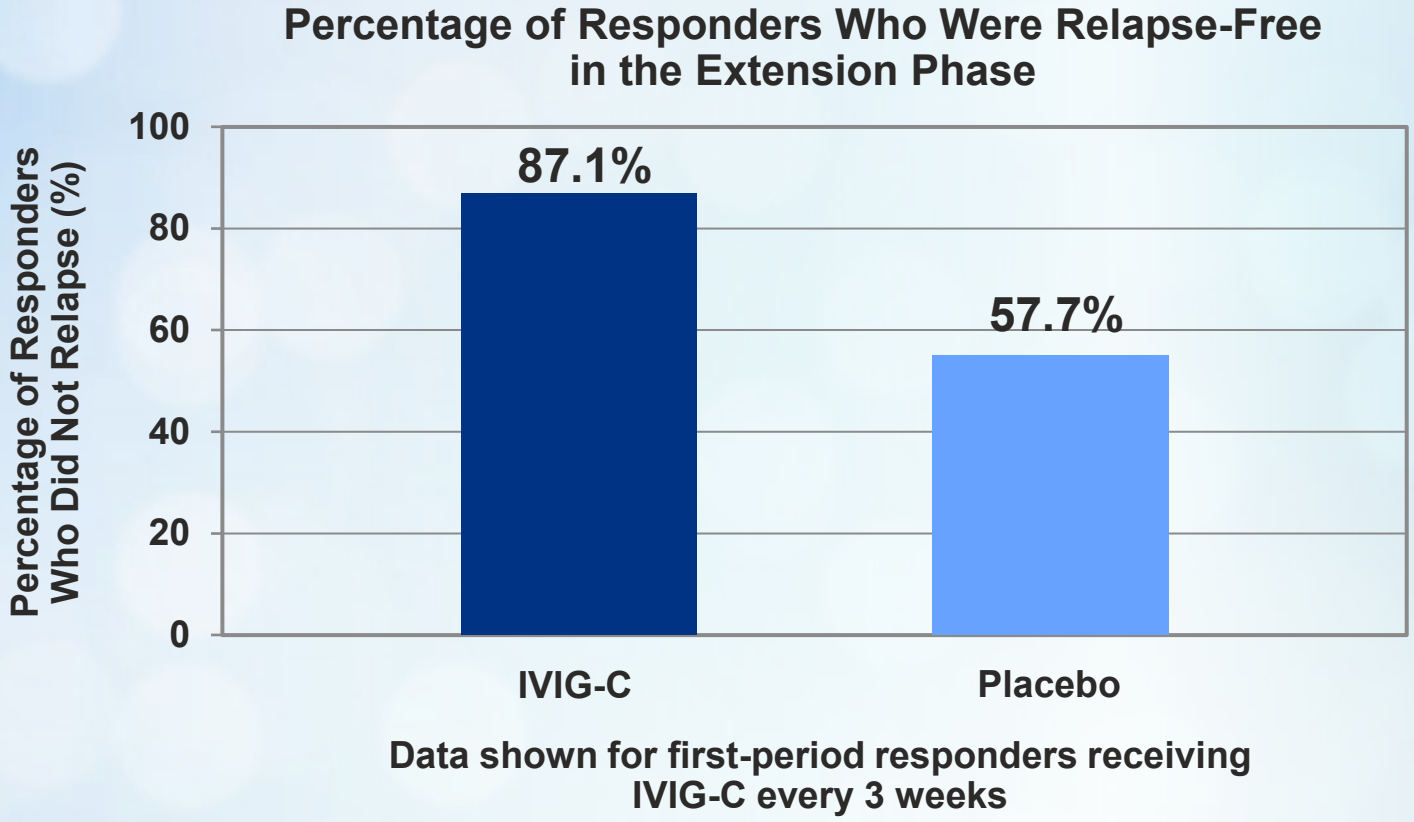
[a] Time to relapse among first-period adjusted-INCAT responders or crossover-period adjusted-INCAT responders to IVIG-C who were re-randomized to IVIG-C or placebo in the extension phase.[1]

The patient who was enrolled in the extension period in error was not included in this analysis.[1]

INCAT, inflammatory neuropathy cause and treatment.

References: 1. Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144. Copyright 2008, reprinted from The Lancet with permission from Elsevier. **2.** Data on file, Grifols.

ICE Study: >87% of Responders Were Relapse-Free at 48 Weeks[a]



[a] Percentage of responders who were relapse-free among first-period adjusted-INCAT responders or crossover-period adjusted-INCAT responders to IVIG-C who were re-randomized to IVIG-C or placebo in the extension phase.

INCAT, inflammatory neuropathy cause and treatment.

Reference: Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

ICE Study: Important and Sustained Improvements[1,2]

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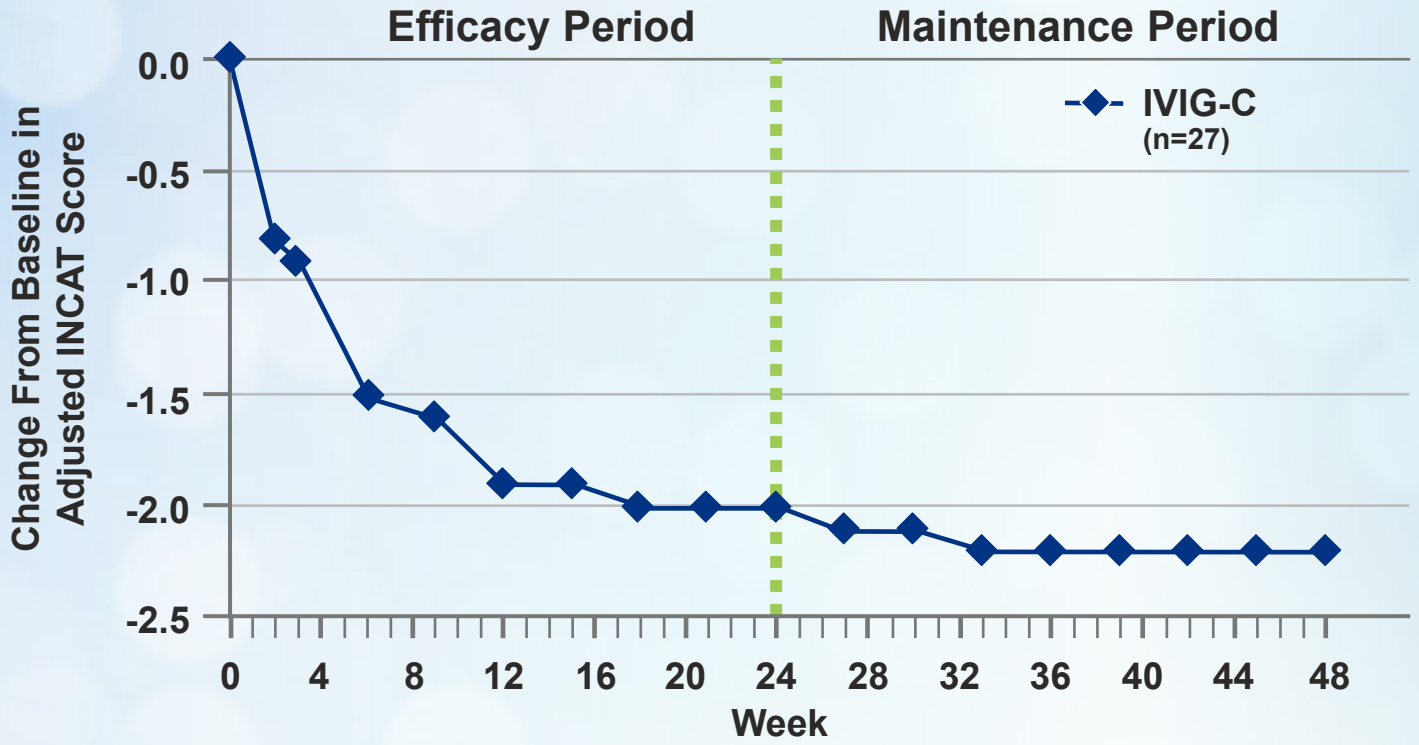

Among responders, maximal improvement achieved by weeks 12-24 and maintained through week 48

More than 87% of responders were relapse-free at 48 weeks[3]

INCAT, inflammatory neuropathy cause and treatment.

References: 1. Latov N. *Arch Neurol.* 2010;67(7):802-807. **2.** Data on file, Grifols.
3. Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

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ICE Study: 60% of Responders Achieved Maximal Response by Week 6

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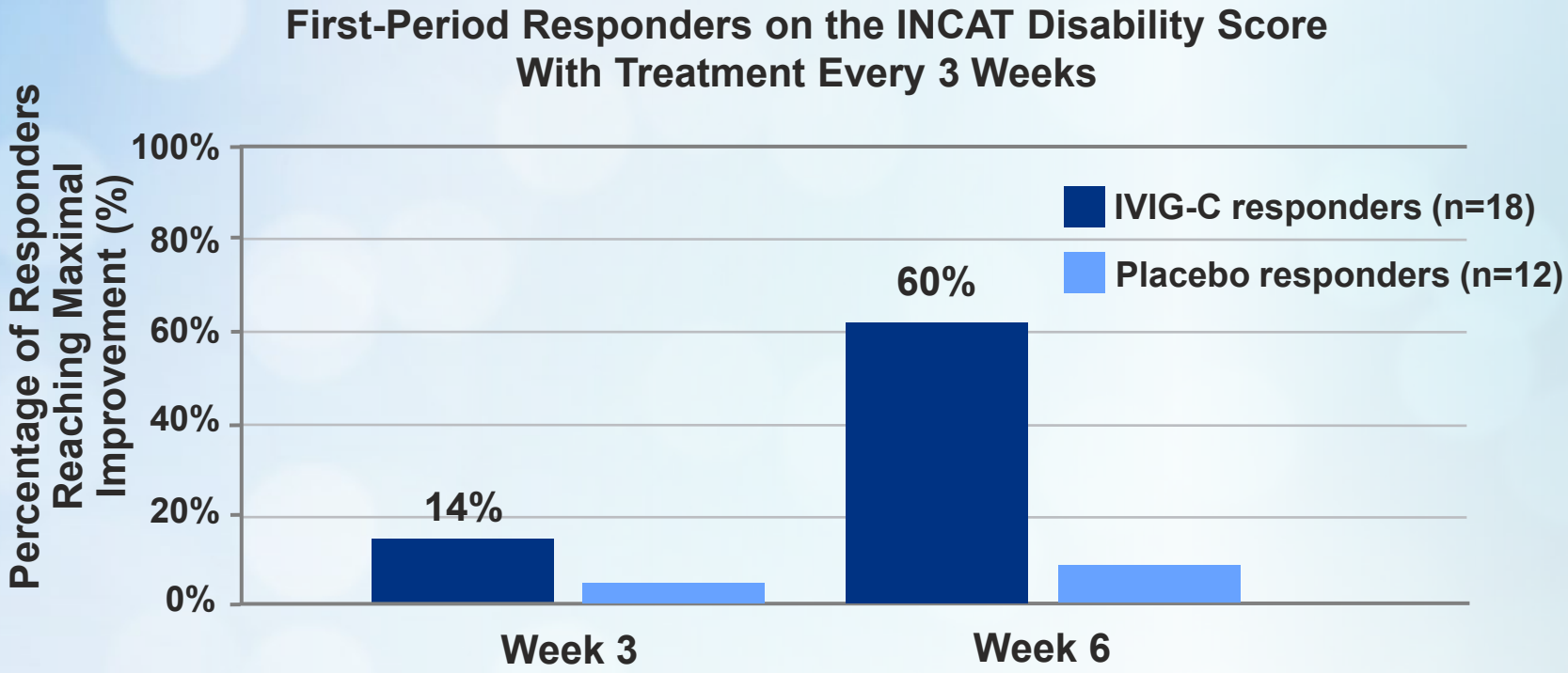

All 30 (100%) reached maximal improvement by week 24

INCAT, inflammatory neuropathy cause and treatment.

Reference: Latov N. *Arch Neurol.* 2010;67(7):802-807.

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ICE Study: ZERO Dropouts With IVIG-C in the Extension Phase due to AEs

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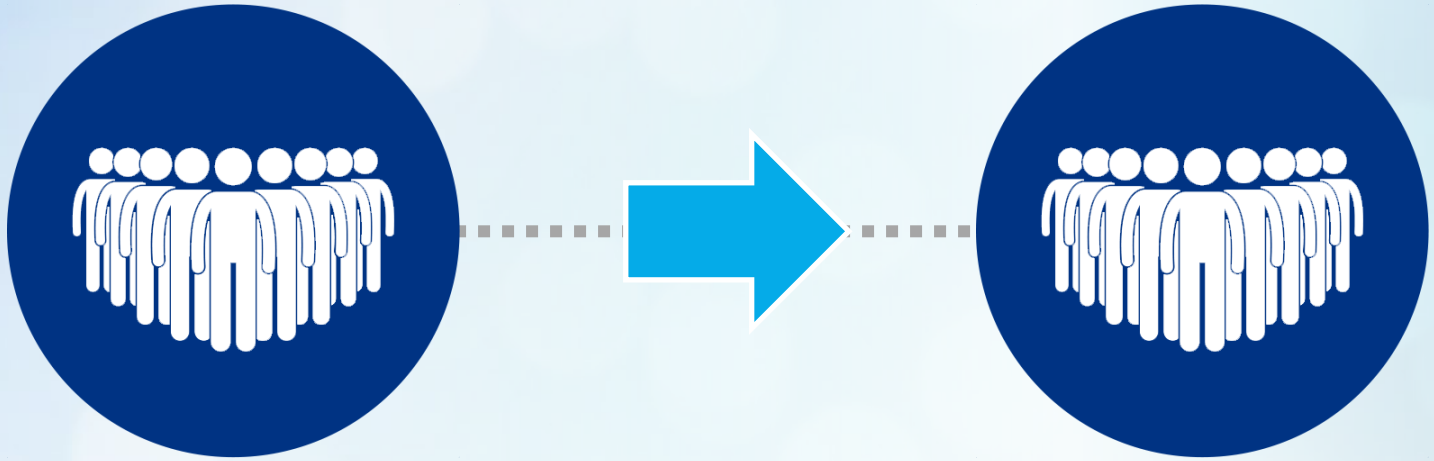

Week 24
Crossover period

Extension phase

Week 48
No dropouts[a]

[a] Patients treated with IVIG-C during the first period and then assigned to IVIG-C during the extension phase.

Reference: Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

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ICE Study: Time to Response Among Responders in the Efficacy Period

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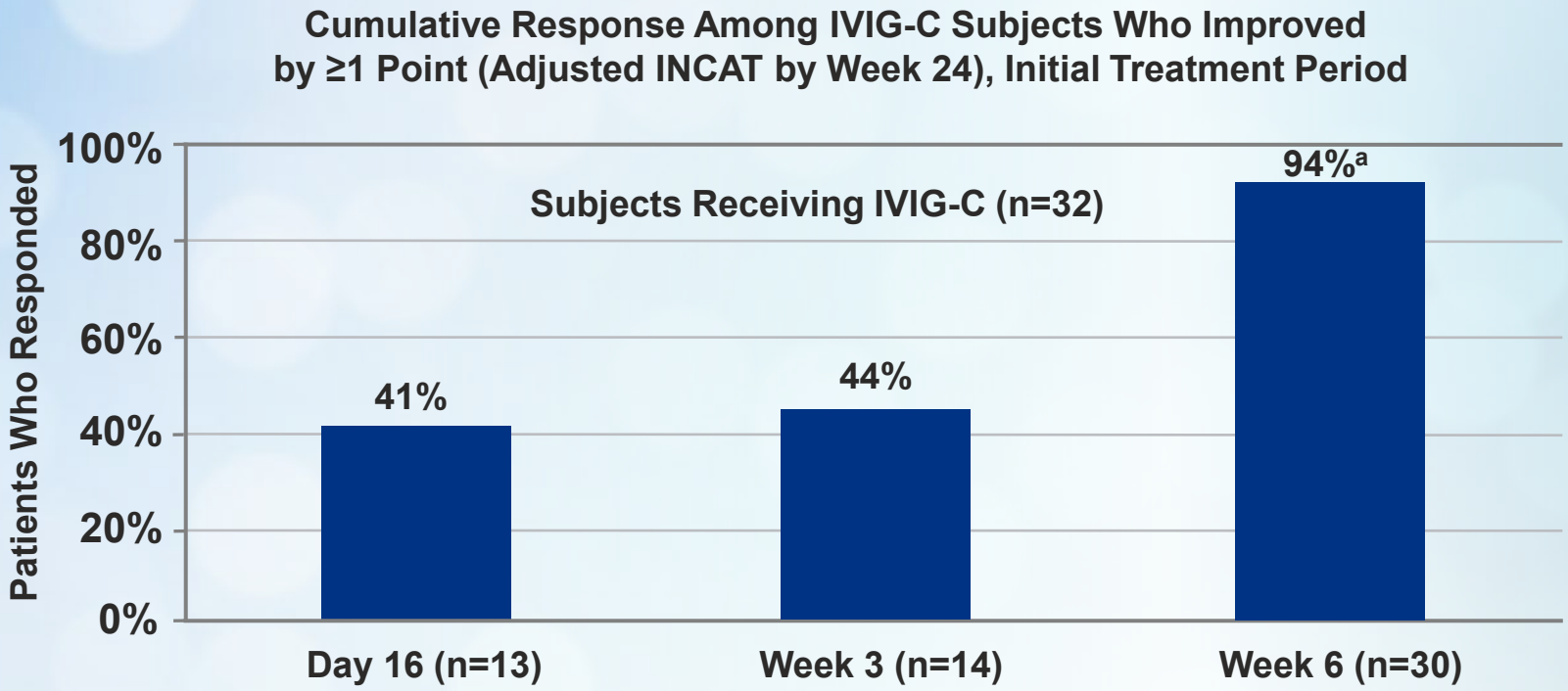

[a]Number reflects recalculation after 2 patients were found to have been misclassified as initial responders.

INCAT, inflammatory neuropathy cause and treatment.

Reference: Data on file, Grifols.

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ICE Study: Treated CIDP Patients' QOL Approached Norms for US Healthy Population Over Time

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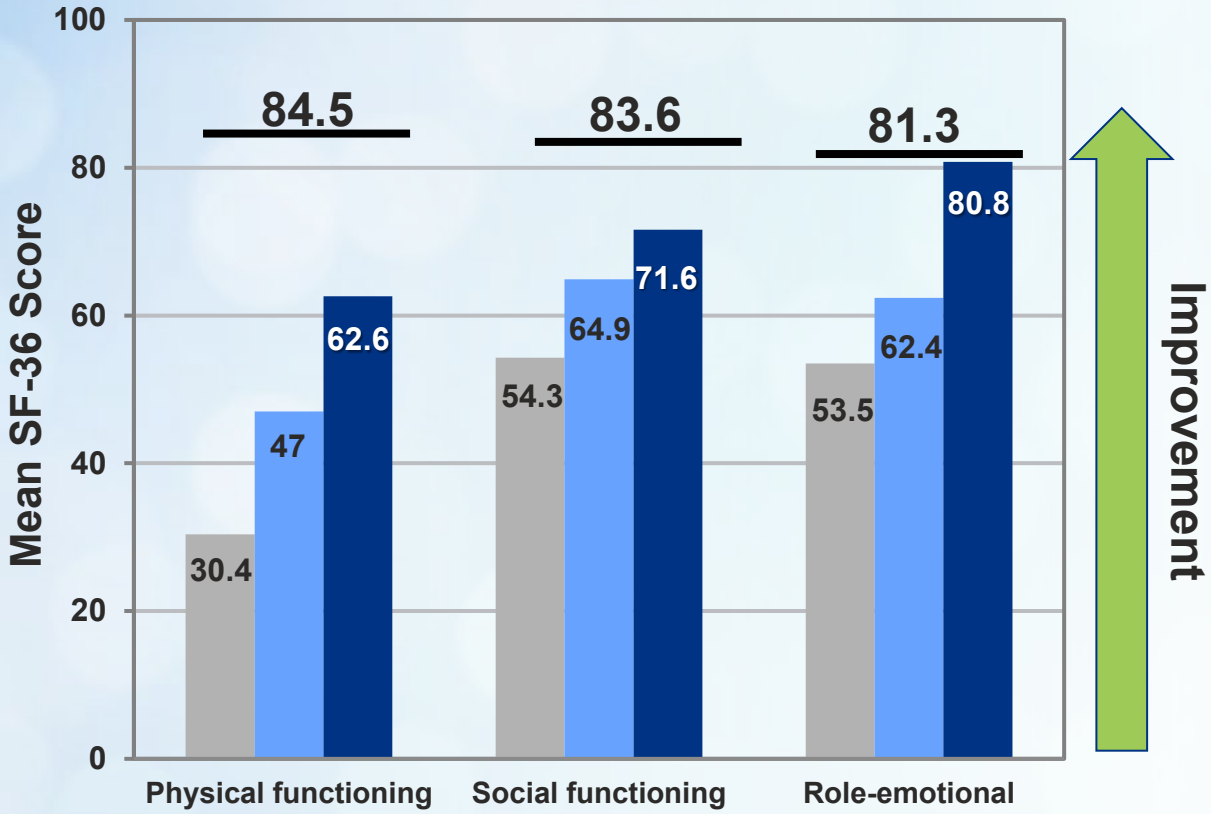
SF-36 scores approached those of the normal US healthy population with maintenance therapy every 3 weeks, for 48 weeks.



There was a gradual positive shift toward normal values for all domains.

Initial treatment/crossover period and extension phase. Data from 2474 healthy volunteers were used to calculate mean normal values.

- Normal US healthy population
- Baseline before IVIG-C
- After 24 weeks of IVIG-C
- After 48 weeks of IVIG-C

SF-36, short form 36.

Reference: Merkies ISJ. *Neurology.* 2009;72(15):1337-1344.

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ICE Study: Efficacy Summary

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- During the efficacy period[1]
  - 59 patients were randomized to IVIG, 58 to placebo
  - Dosing: 2 g/kg loading dose followed by 1 g/kg every 3 weeks
  - IVIG arm: 33 improved; 23 did not respond
  - Placebo arm: 12 improved; 45 did not respond
- 100% of responders achieved maximal clinical response at 24 weeks[2]
- Following ICE study dosing (2 g/kg induction maintained with 1 g/kg every 3 weeks), the neuroprotective qualities were demonstrated by improvement of symptoms and prevention from relapse[1,3]
- During the 24-week extension phase, 57 responders were analyzed for efficacy after re-randomization. Responders who received IVIG for the 48 weeks had a significantly lower relapse rate, with 87% in sustained remission without the need to increase maintenance IVIG dose[1]
- IVIG is effective for the treatment of CIDP. The maintenance dose of 1 g/kg every 3 weeks is effective in preventing relapse vs placebo[1]
- In ICE, the longest randomized clinical trial for CIDP, there were ZERO dropouts with IVIG-C in the extension phase due to AEs[1]

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References: 1. Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144. **2.** Latov N. *Arch Neurol.* 2010;67(7):802-807. **3.** Data on file, Grifols.

CIDP: Considerations for IVIG Therapy

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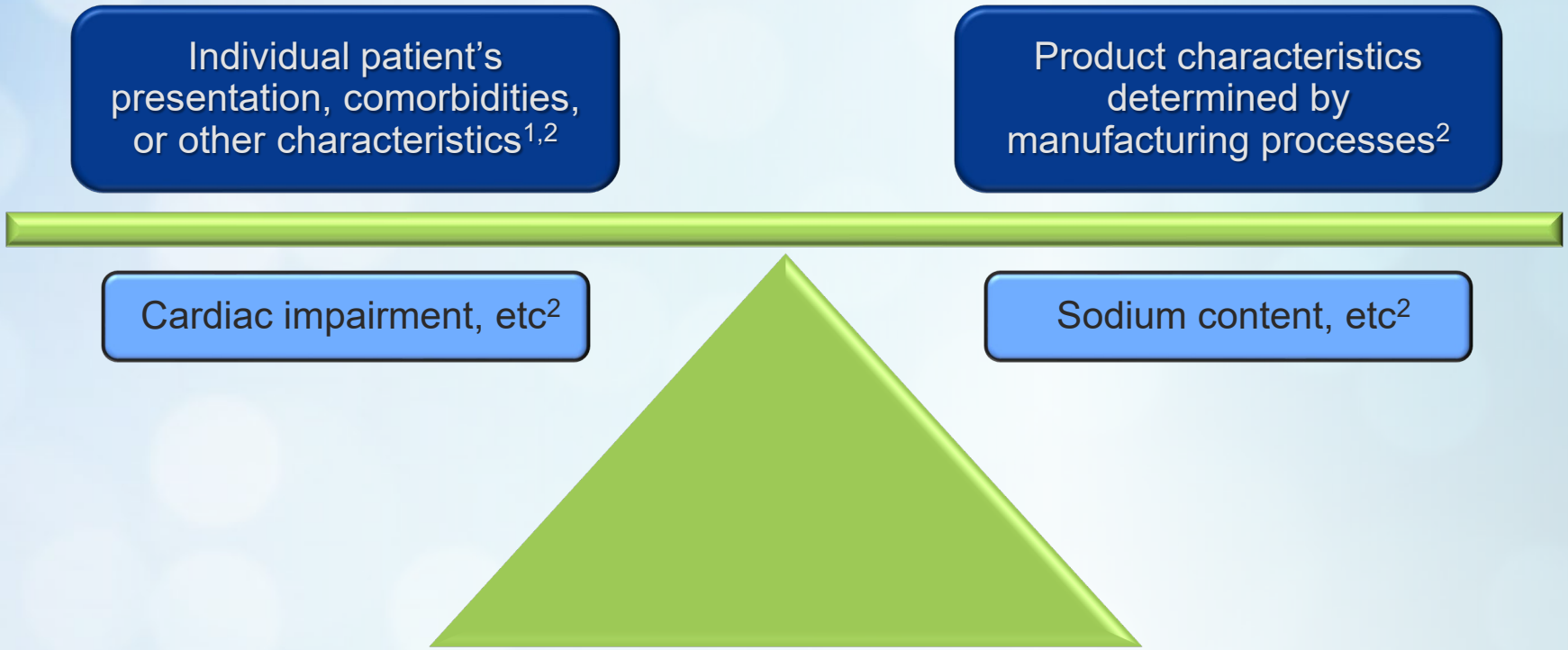

References: 1. van den Bergh PYK. *J Peripher Nerv Syst*. 2021;26(3):242-268.
2. Gelfand EW. *Int Immunopharmacol*. 2006;6(4):592-599.

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Select IVIG Therapy Based on Patient Profile[1-3]

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IVIG product characteristics	Patient risk factors				
	Cardiac impairment	Renal dysfunction	Thrombo-embolic risk	(Pre) Diabetes	Elderly patients
Sugar content[a]		✓		✓	✓
Sodium content	✓	✓	✓		✓
Osmolality	✓	✓	✓		✓
Volume load	✓	✓	✓		✓

[a]Sugars may include sucrose, maltose, and glucose. Up to 90% of IVIG-associated renal adverse events have been linked to sucrose-containing preparations.

References: 1. Chérin P. *BioDrugs.* 2010;24(4):211-223. **2.** Gürcan HM. *Autoimmun Rev.* 2010;9(8):553-559. **3.** Gelfand EW. *Int Immunopharmacol.* 2006;6(4):592-599.

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IV Administration Is Suitable for a Wide Variety of CIDP Patients

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Considerations for Selecting Best Route of Administration for Your Patients[1-2]

Consideration	Intravenous	Subcutaneous
Compliance concerns[2]		
Poor dexterity[2]		
Prefers fewer infusions[2]		
Needle phobia		
Health care requires professional oversight		
Poor venous access[2]		
Remote location		
Patient request		

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References: 1. Data on file, Grifols. **2.** Dalakas MC. *Lancet Neurol.* 2018;17(1):20-21.

How to Discuss Long-Term IG Treatment With Your Patients

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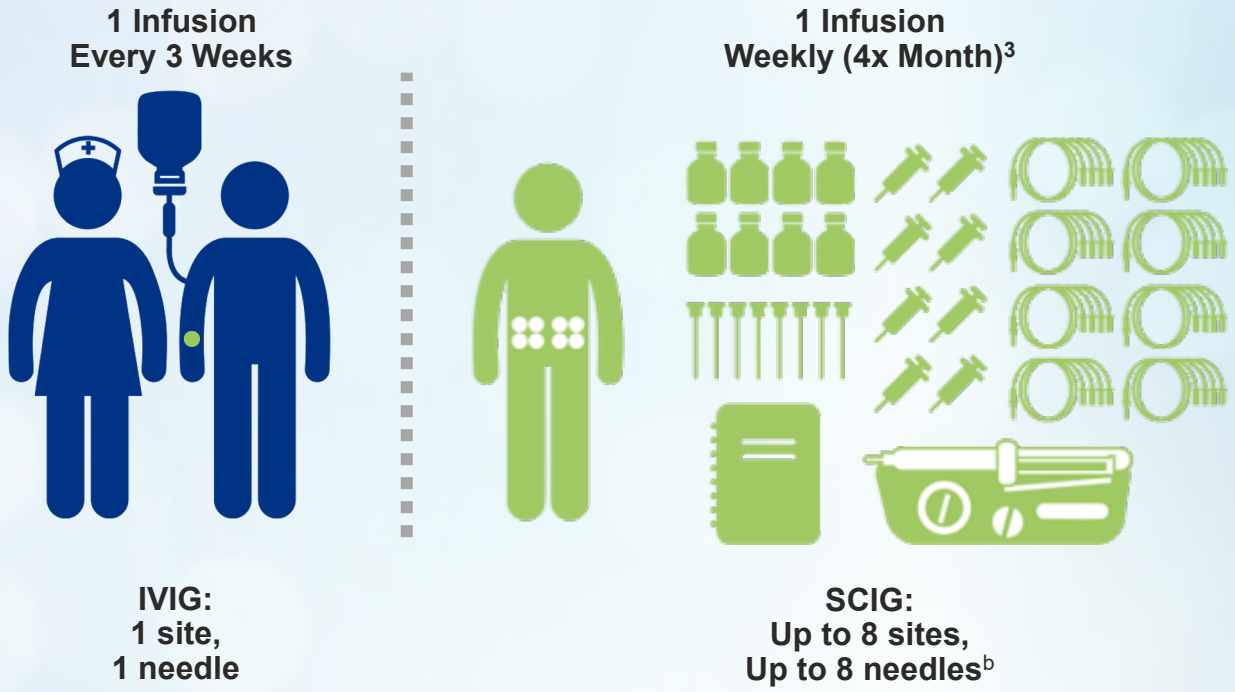
1 Site, 1 Needle, 1 Infusion Every 3 Weeks for Patients Receiving IVIG[a,1-2]



IVIG is always administered by an HCP

[a]Individual dosing may vary by patient.

[b]Subjects generally used 4 infusion sites in parallel (maximum: 8 sites in parallel)[3]

References: 1. Data on file, Grifols. **2.** van Schaik IN. *Lancet Neurol.* 2018;17(1):35-46. **3.** HIZENTRA Prescribing Information. CSL Behring LLC.

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The Process Is the Product

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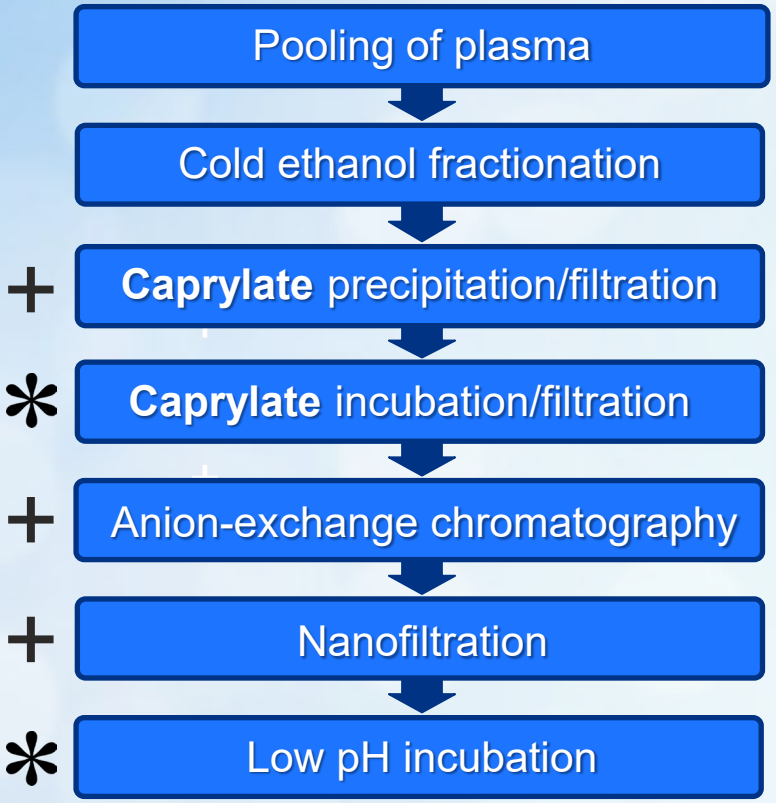
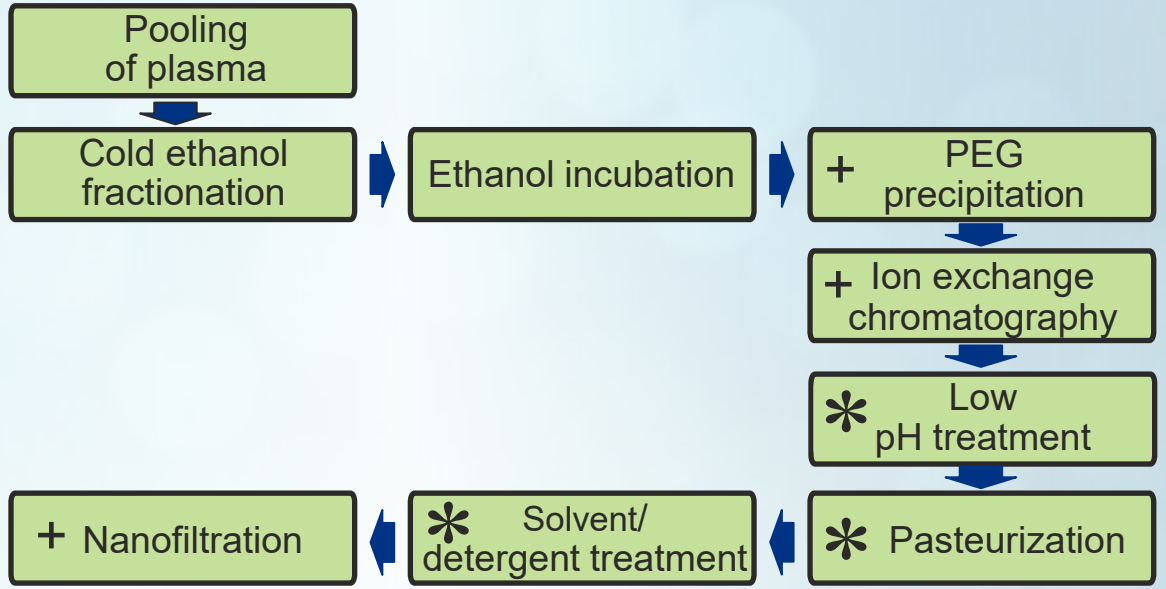
Different manufacturing processes may yield differences in IgG monomeric form and subclass distribution[1]

Caprylate/Chromatography Process[2]



Solvent/Detergent Process[2]



* Virus inactivation step[1,3] + Virus removal step[4]

PEG, polyethylene glycol.

References: 1. Shah S. *Am J Health Syst Pharm*. 2005;62(16 suppl 3):S5-S11. **2.** Data on file, Grifols. **3.** Korneyeva M. *Biologicals*. 2002;30(2):153-162. **4.** Burnouf T. *Curr Nanoscience*. 2005;1(3):189-201.

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ICE Study: Tolerability and Adverse Reaction Profile

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Adverse events	Comment
Most common adverse reactions (≥5% incidence)	Headache, pyrexia, hypertension, chills, rash, nausea, arthralgia, and asthenia[1]
Most serious adverse reaction	PE in 1 patient with history of PE who received IVIG-C[1]
Adverse events associated with treatment discontinuation	3 of 113 IVIG-C patients[1]; none in extension phase[1] 2 of 95 placebo patients[1]

- Most AEs were mild[2]
- Less than half the incidence of SAEs per infusion compared with placebo (0.8% vs 1.9%)[2]
- ZERO dropouts with IVIG-C in the extension phase of the ICE study due to AEs[2]

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SAE, serious adverse event.

References: 1. Data on file, Grifols. **2.** Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

ICE Study: Adverse Reactions Occurring in ≥5% of Subjects

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	IVIG-C (n=113)			Placebo (n=95)		
Adverse reaction[a]	No. of subjects (%)	No. of adverse reactions	Incidence density[b]	No. of subjects (%)	No. of adverse reactions	Incidence density[b]
Headache	35 (31.0)	50	0.046	7 (7.4)	9	0.016
Pyrexia	15 (13.3)	27	0.025	0	0	—
Hypertension	10 (8.8)	19	0.017	3 (3.2)	3	0.005
Chills	9 (8.0)	10	0.009	0	0	—
Nausea	7 (6.2)	9	0.008	3 (3.2)	3	0.005
Rash	7 (6.2)	10	0.009	1 (1.1)	1	0.002
Arthralgia	6 (5.3)	7	0.006	0	0	—
Asthenia	6 (5.3)	6	0.005	1 (1.1)	2	0.003

[a] An adverse reaction is an adverse event that meets any of the following 3 criteria: (a) that began during or within 72 hours of the end of product infusion, (b) that was considered at least possibly related by either the investigator or the applicant, and/or (c) whose causality assessment by the investigator was missing or indeterminate.

[b] Calculated by the total number of adverse reactions divided by the number of infusions received (1096 for IVIG-C and 575 for placebo).

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Reference: Data on file, Grifols.

ICE Study: Summary of Results

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Endpoints	Results vs placebo
Adjusted INCAT disability scores	Statistically significant improvement through week 24 (*P*=0.006)[1]
MRC sum scores	Significantly improved (*P*=0.001)[2]
Grip strength	Significantly improved[2] • Dominant hand (*P*=0.0008) • Nondominant hand (*P*=0.005)
Time to relapse	Significantly extended (*P*=0.011)[2] • 87% of responders in initial period and extension phases did not relapse over 48 weeks (HR=0.19)[2]
Health-related quality-of-life scores	Greatest improvements observed on domains most dramatically affected at baseline[1] • Physical functioning (*P*=0.013) • Role-physical (*P*=0.033)

HR, hazard ratio; INCAT, inflammatory neuropathy cause and treatment; MRC, Medical Research Council.

References: 1. Data on file, Grifols. **2.** Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144.

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ICE Study: Summary of Results (cont.)

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	Results
Safety	• Most common adverse reactions[1,a]: • Headache, pyrexia, hypertension, chills, rash, nausea, arthralgia, and asthenia • Most serious adverse reaction: PE in 1 subject with history of PE[1] • Frequency of adverse events per infusion did not differ greatly between IVIG-C and placebo[1] • Most AEs were mild[2] • Less than half the incidence of SAEs per infusion compared with placebo (0.8% vs 1.9%)[2] • ZERO dropouts with IVIG-C in the extension phase of the ICE study due to AEs[2]

Dosing and infusion time	• Loading dose: 2 g/kg (20 mL/kg)[2]
	  • 87% of IVIG-C loading dose courses given over 2 days[3]
	• Maintenance dose: 1 g/kg (10 mL/kg) every 3 weeks[2]
	  • 96% of overall infusions (IVIG-C and placebo) given within 5 hours (mean: 2.7 hours)[2]
	  • 89% of IVIG-C maintenance dose courses given over 1 day[3]

[a] ≥5% of subjects.

References: 1. Data on file, Grifols. **2.** Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144. **3.** Donofrio PD. *Arch Neurol.* 2010;67(9):1082-1088.

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IVIG Contraindications and Precautions

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Contraindications

- Individuals with acute hypersensitivity reactions to human immunoglobulin
- IgA-deficient patients with antibodies against IgA and a history of hypersensitivity

Warnings and Precautions

- Hypersensitivity
- Thrombotic events
  - Consider baseline assessment for blood viscosity in patients at risk for hyperviscosity
- Renal failure
  - Renal function and urine output should be monitored periodically in patients at risk
- Hyperproteinemia, increased serum viscosity, and hyponatremia
- Aseptic meningitis syndrome
- Hemolysis
  - If signs and/or symptoms of hemolysis are present after infusion, appropriate confirmatory tests should be done
- Transfusion-related acute lung injury
- Volume overload
- General—Risk of transmitting infectious agents, including the variant Creutzfeldt-Jacob disease (vCJD) agent and the Creutzfeldt-Jakob disease (CJD) agent
- Hematoma formation
- Interference with laboratory tests—After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation

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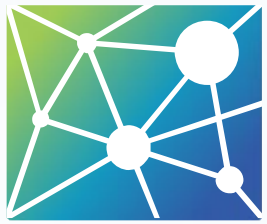
Reference: Data on file, Grifols.



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