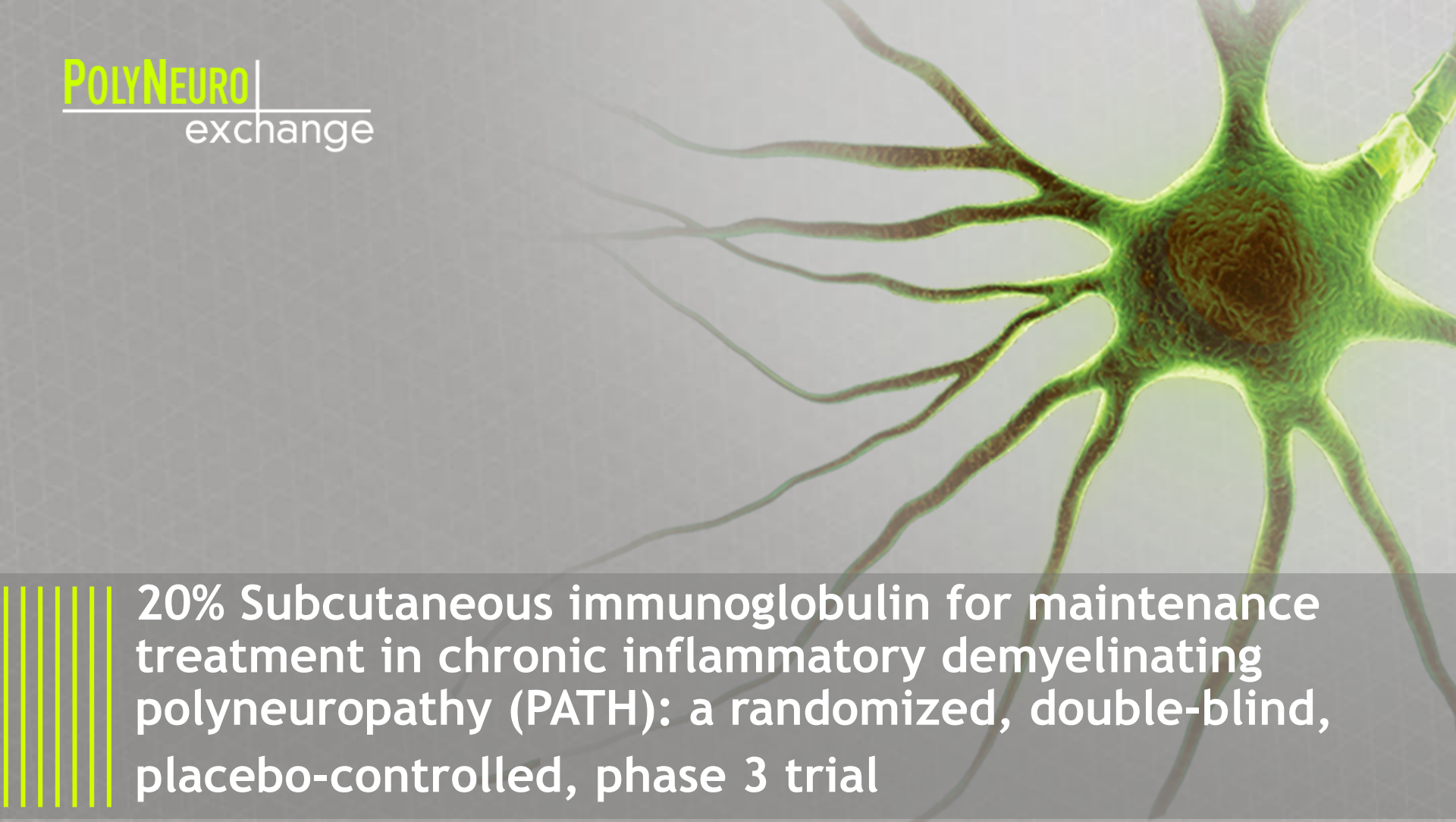
PolyNeuro exchange



20% Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomized, double-blind, placebo-controlled, phase 3 trial

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

- **Symmetric (motor and sensory) proximal and distal neuropathy**
- Follows a monophasic, progressive, or relapsing course
- Developing over 2 months or more[1,2]

- **1.6–8.9 cases per 100,000 adults**[3,4]
- Can occur in children and adults at any age, with a peak prevalence in adults aged 50 to 60[1]

First-line treatments include[5]

- **Intravenous immunoglobulins (IVIG)**
- **Corticosteroids**
- **Plasma exchange**

CIDP: chronic inflammatory demyelinating polyneuropathy; IVIG: intravenous immunoglobulin

1. Steinberg JS *et al*. A publication of the GBS/CIDP Foundation International 10th Edition, 2010. http://30g7el1b4b1n28kgpr414nuu-wpengine.netdna-ssl.com/wp-content/uploads/2012/01/OverviewENG.pdf. Accessed April 2014; 2. Vallat JM *et al*. Lancet Neurol. 2010;9(4):402-12; 3. Iijima M *et al*. J Neurol Neurosurg Psychiatry. 2008;79(9):1040-3; 4. Laughlin RS *et al*. Neurology. 2009;73(1):39-45; 5. Oaklander AI *et al*. Cochrane Database Syst Rev. 2017, Issue 1. Art. No.: CD010369

PATH: Background and Rationale

First large-scale, randomized, placebo-controlled, phase 3 clinical trial investigating SCIG for the treatment of CIDP, and the largest CIDP study to date

Rationale

- IVIG products have become an established treatment for CIDP[1]
- As compared to hospital-based IVIG, subcutaneous immunoglobulin (SCIG) offers self-administration at a time and place that suits patients resulting in increased autonomy, increased QoL, a lower rate of systemic reactions, potential cost savings, and more stable IgG levels which are associated with a reduction in wear-off effects[2-7]
- Small studies previously indicated potential benefits of SCIG for CIDP[8-10]
- Before PATH, no large-scale randomized clinical trials had unequivocally demonstrated the efficacy and safety of SCIG in CIDP

CIDP: chronic inflammatory demyelinating polyneuropathy; IgG: immunoglobulin G; IVIG: intravenous immunoglobulin; QoL: quality of life; SCIG: subcutaneous immunoglobulin

1. Van den Bergh PY *et al*. Eur J Neurol. 2010;17(3):356-63.
2. Nicolay U *et al*. J Clin Immunol. 2006;26(1):65-72.
3. Kittner JM *et al*. J Clin Immunol. 2006.;26(4):400-5.
4. Lee DH *et al*. Muscle Nerve, 2008;37(3):406-9.
5. Cocito D *et al*. J Neurol. 2014;261(11):2159-64.
6. Rojavin MA, Hubsch A, and Lawo JP. J Clin Immunol. 2016;36(3):210-9.
7. Berger M and Allen JA. Muscle Nerve. 2015;51(3):315-26.
8. Markvardsen LH *et al*. Eur J Neurol. 2017;24(2):412-418.
9. Markvardsen LH *et al*. Eur J Neurol. 2013;20(5):836-42.
10. Markvardsen LH *et al*. Basic Clin Pharmacol Toxicol. 2015;117(6):409-12.

PATH: Objectives and Endpoints[1]

PATH Study Objective: To determine the efficacy and safety of SCIG using 2 different doses of 20% SCIG 0.2 g/kg bw weekly and 0.4 g/kg bw weekly, in the maintenance treatment of CIDP in comparison with placebo

Primary Endpoint

The percentage of patients with a CIDP relapse (based on adjusted INCAT) or who were withdrawn for any other reason during 24 weeks of SCIG treatment

Secondary Endpoints

- **Time to CIDP relapse or withdrawal for any other reason (primary endpoint) in the SCIG treatment period**
- **Differences between groups of the median changes from baseline to completion visits in:**
  - **INCAT score**
  - **R-ODS**
  - **Mean grip strength (measured using a Martin Vigorimeter)**
  - **MRC sum score**
- **Safety**

- Exploratory endpoints include serum IgG levels and QoL assessments

bw: body weight; CIDP: chronic inflammatory demyelinating polyneuropathy; IgG: immunoglobulin G; INCAT: Inflammatory Neuropathy Cause and Treatment; IVIG: intravenous immunoglobulin; MRC: Medical Research Council; QoL: quality of life; R-ODS: Rasch-built Overall Disability Scale; SCIG: subcutaneous immunoglobulin

1. van Schaik IN *et al*. Trials. 2016;17:345.

PATH: Efficacy Assessments[1]

Primary Efficacy Endpoint

Adjusted INCAT Score*	10-point score assessing functionality of legs and arms • Arm disability: 0 “no upper limb problems” to 5 “inability to use either arm for any purposeful movement” • Leg disability: 0 “walking not affected” to 5 “restricted to wheelchair, unable to stand and walk a few steps with help”

Secondary Efficacy Endpoints

MRC Score	Sum of 8 muscle group scores • Grades muscle movement from 0 “no visible contraction” to 5 “normal”
Mean Grip Strength	Grip strength measured by Martin Vigorimeter
R-ODS Score	24-item questionnaire capturing activity and social participation

- Improvement = 1 point in adjusted INCAT score*, 3 points in the MRC sum score, 8 kPa in mean grip strength, or 4 points in R-ODS centile score

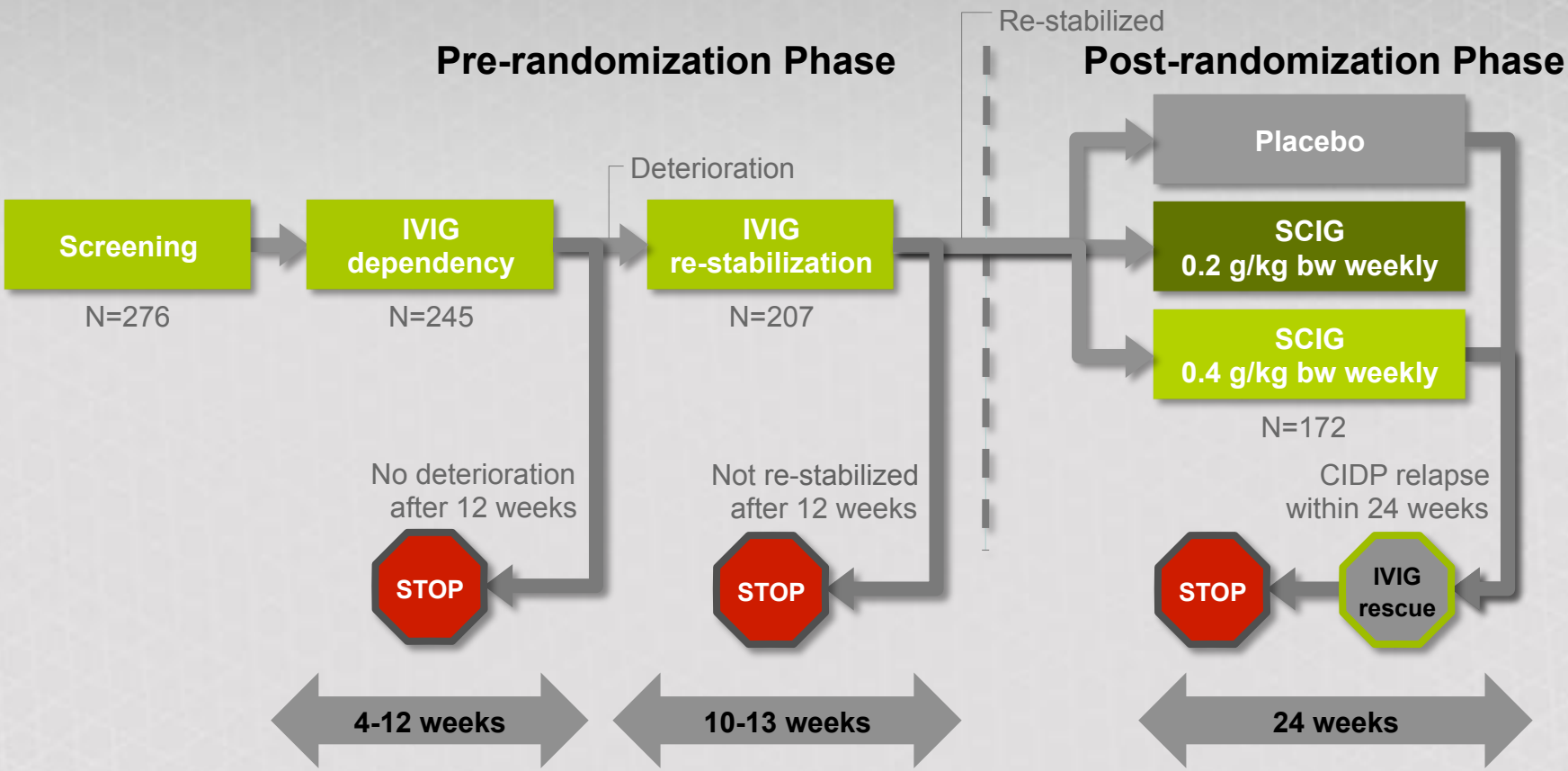
*Adjusted INCAT score: changes in upper limb function from 0 to 1 or 1 to 0 were not recorded as deterioration or improvement

INCAT: Inflammatory Neuropathy Cause and Treatment; MRC: Medical Research Council; R-ODS: Rasch-built Overall Disability Scale

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

PATH: Study Design[1]

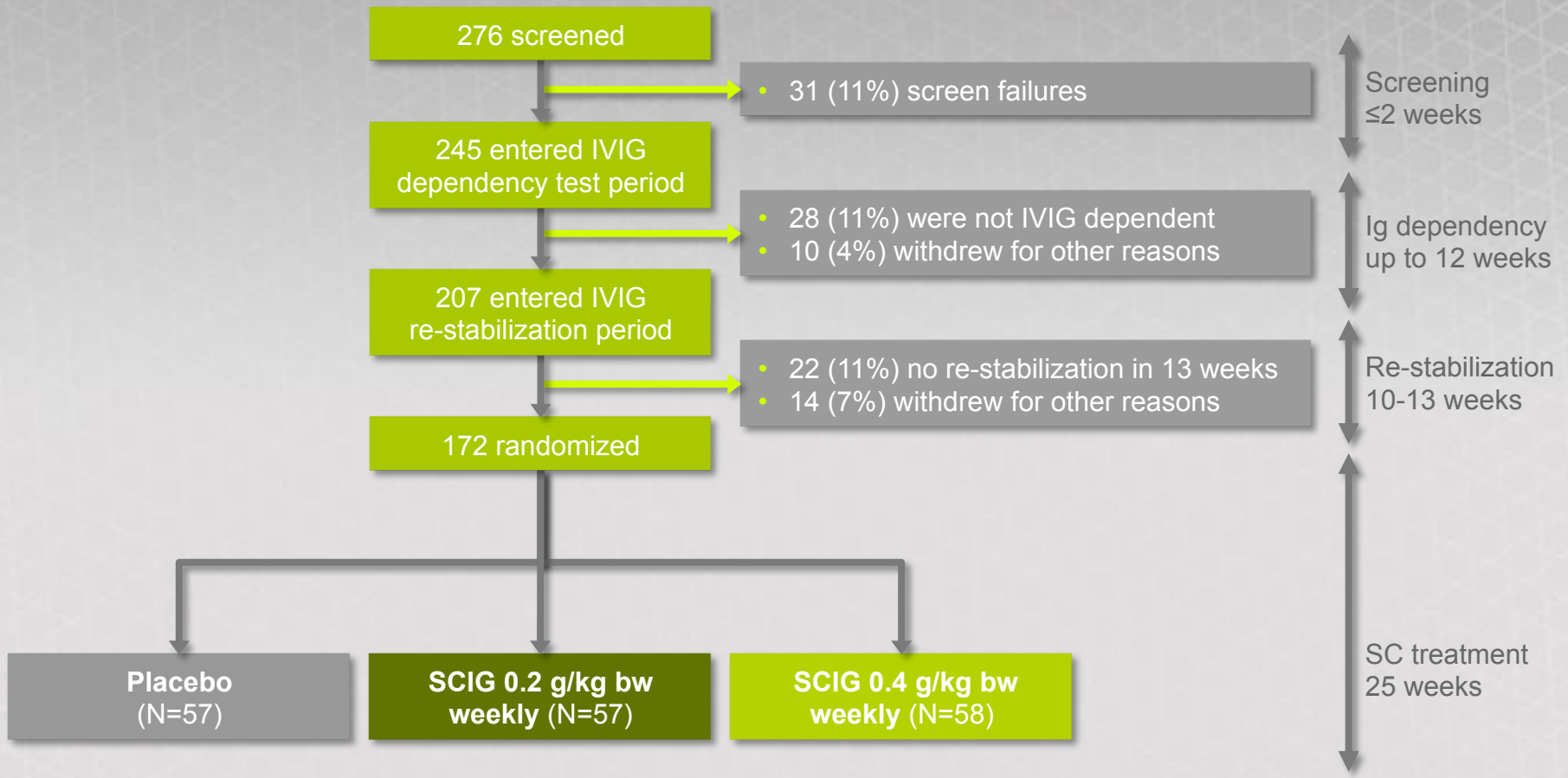
A randomized, multicenter, double-blind, placebo-controlled, parallel-group phase 3 study of subcutaneous immunoglobulin following re-stabilization on intravenous immunoglobulin



bw: body weight; CIDP: chronic inflammatory demyelinating polyneuropathy; IVIG: intravenous immunoglobulin; SCIG: subcutaneous immunoglobulin

1. van Schaik IN *et al*. Trials. 2016;17:345.

PATH: Study Design & Patient Disposition[1]



bw: body weight; Ig: immunoglobulin; IVIG: intravenous immunoglobulin; SC: subcutaneous

1. van Schaik IN *et al*. Poster and abstract presented at Annual Meeting of the American Academy of Neurology (AAN); April 22-28, 2017; Boston, MA.

PATH: Patient Demographics

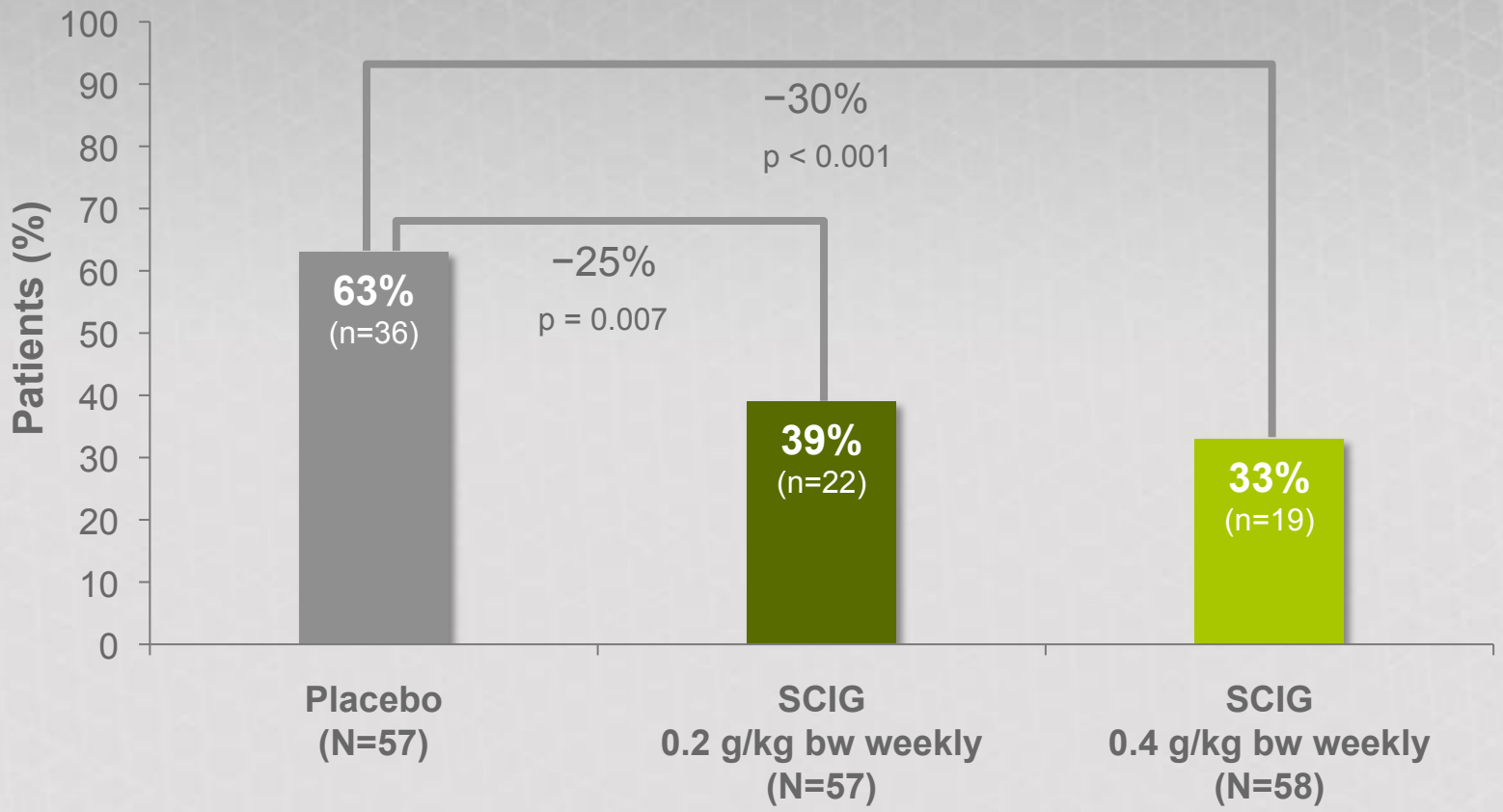
	Placebo (N=57)	SCIG 0.2 g/kg bw weekly (N=57)	SCIG 0.4 g/kg bw weekly (N=58)
Age, years			
Median	57.6	58.9	55.2
Min, Max	28.6, 77.0	25.8, 77.6	24.7, 82.7
Weight, kg			
Mean	85.8	83.3	79.4
Min, Max	41.7, 130.2	55.0, 125.0	42.0, 133.0
Sex, n (%)			
Male	37 (64.9)	42 (73.7)	31 (53.4)
Female	20 (35.1)	15 (26.3)	27 (46.6)
Time since initial diagnosis, (years)			
Median	2.7	2.8	3.3
Previous IVIG treatments prior to enrollment, n (%)			
<4	6 (10.5)	5 (8.8)	4 (6.9)
≥4	51 (89.5)	52 (91.2)	54 (93.1)

bw: body weight; IVIG: intravenous immunoglobulin; SCIG: subcutaneous immunoglobulin

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

Efficacy

PATH Randomization Results: CIDP Relapse Or Withdrawal (Primary Endpoint)[1]

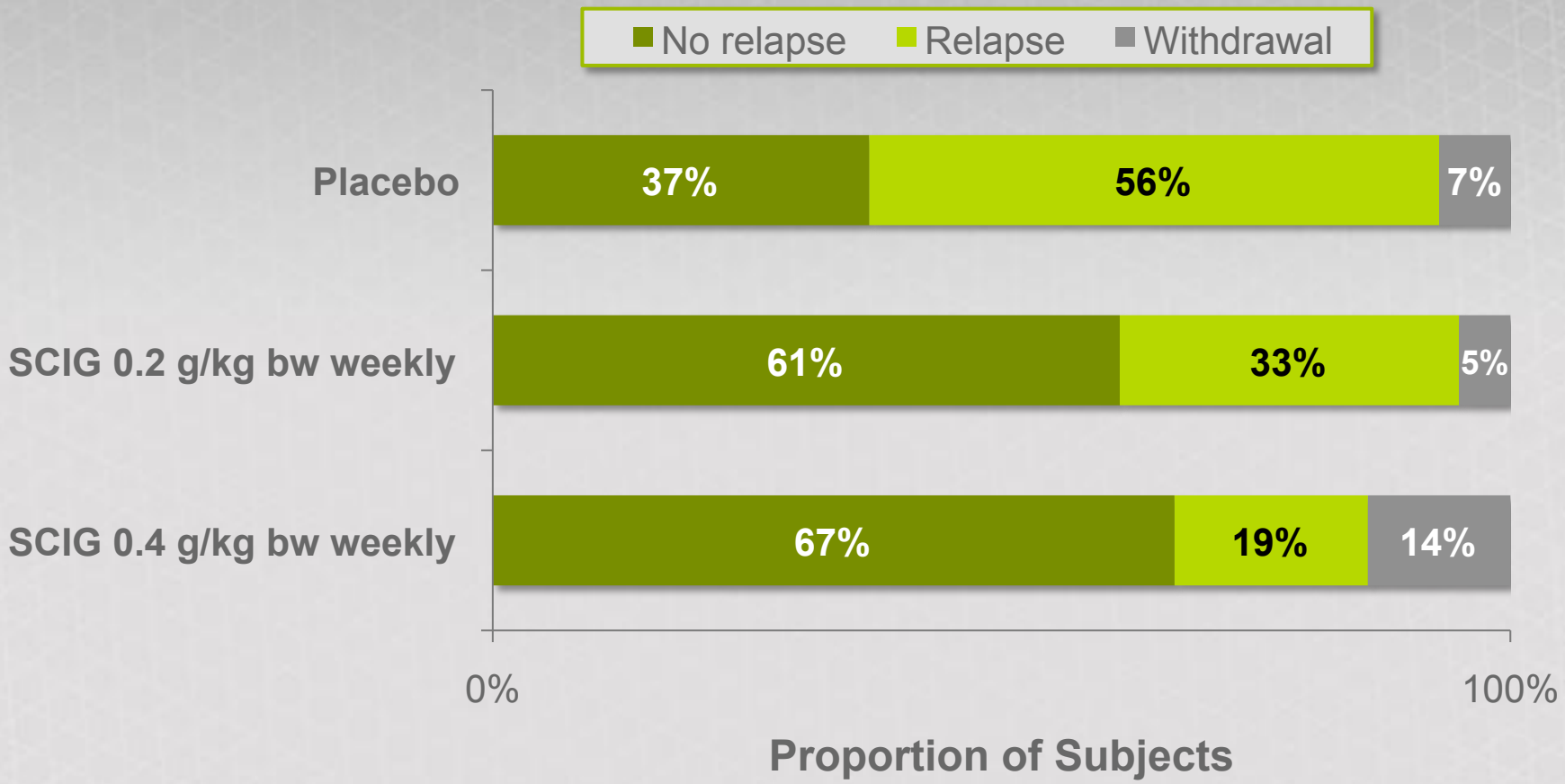


- When assessing CIDP relapse only, relapse rates were 56% for placebo, 33% for SCIG 0.2 g/kg bw weekly, and 19% for SCIG 0.4 g/kg bw weekly

bw: body weight; CIDP: chronic inflammatory demyelinating polyneuropathy; SCIG: subcutaneous immunoglobulin

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

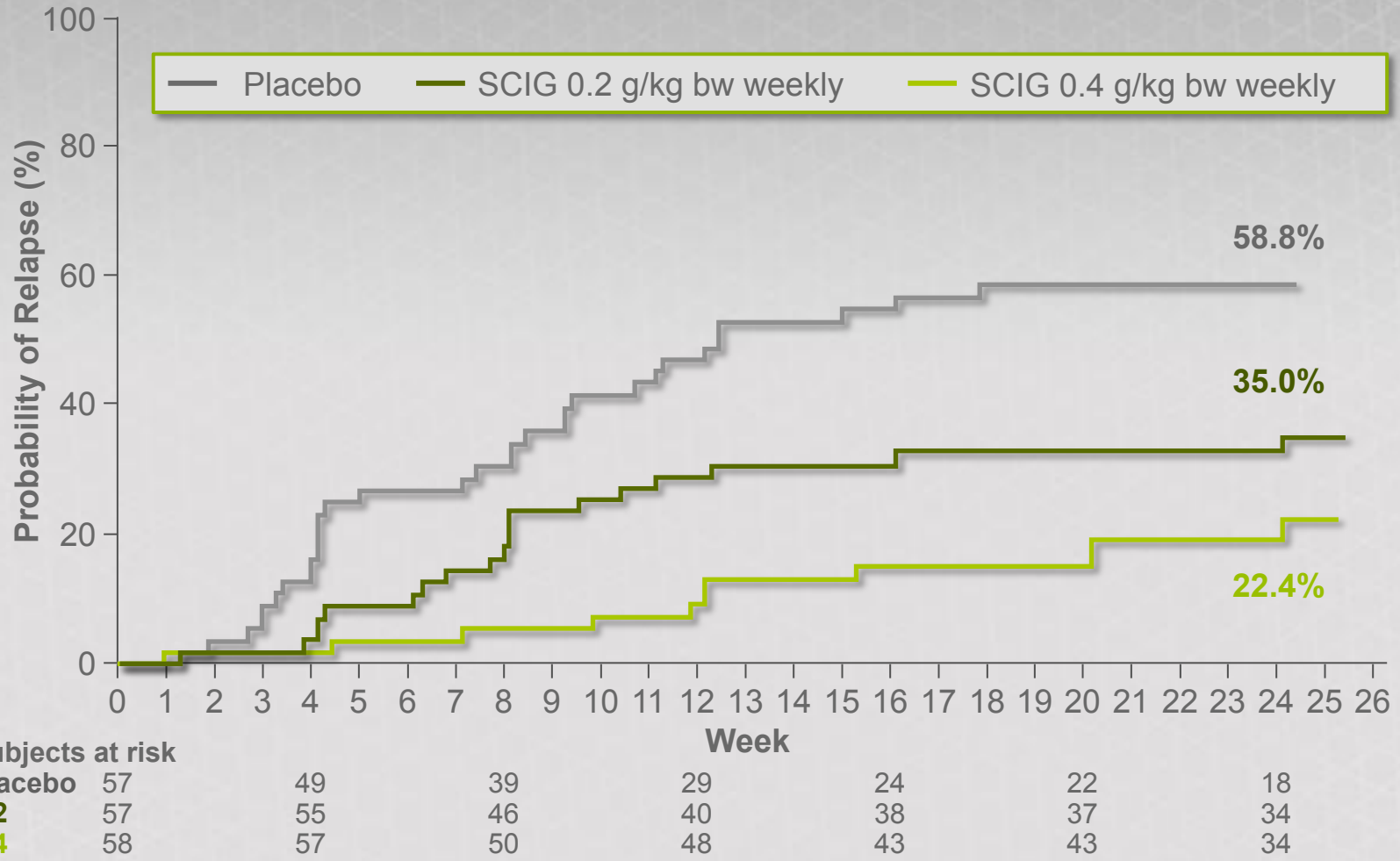
PATH: Primary Endpoint Analysis[1]



bw: body weight; SCIG: subcutaneous immunoglobulin

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

PATH Secondary Endpoints: Time To CIDP Relapse (Kaplan-Meier)[1]



bw: body weight; CIDP: chronic inflammatory demyelinating polyneuropathy; SCIG: subcutaneous immunoglobulin

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

PATH Secondary Endpoints: Changes From Baseline In Efficacy Outcomes[1]

Median change from baseline at 24 weeks					
	Placebo	SCIG 0.2 g/kg bw weekly	p vs Placebo	SCIG 0.4 g/kg bw weekly	p vs Placebo
INCAT total score	1.0	0.0*	0.005	0.0*	<0.001
R-ODS score	−3.0	−2.0	0.030	0.0*	<0.001
Grip strength (kPa)	−6.6	−0.6*	0.004	−2.7*	0.014
MRC sum score	−2.0	0.0*	0.003	0.0*	0.002

Baseline scores were the last scores before randomization. All tests were one-sided p values. Statistical significance was defined at a p value of <0.025 (explorative). For INCAT, an increase in score is a deterioration; for R-ODS, grip strength, and MRC, a decrease in score (negative number) is a deterioration.
*Changes were statistically significant vs placebo. No significant differences were observed between the two dose groups
†kPa dominant hand

bw: body weight; INCAT: Inflammatory Neuropathy Cause and Treatment; I-RODS: Inflammatory Rasch-built Overall Disability Scale; MRC: Medical Research Council; SCIG: subcutaneous immunoglobulin

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

Safety

PATH: Safety – General[1]

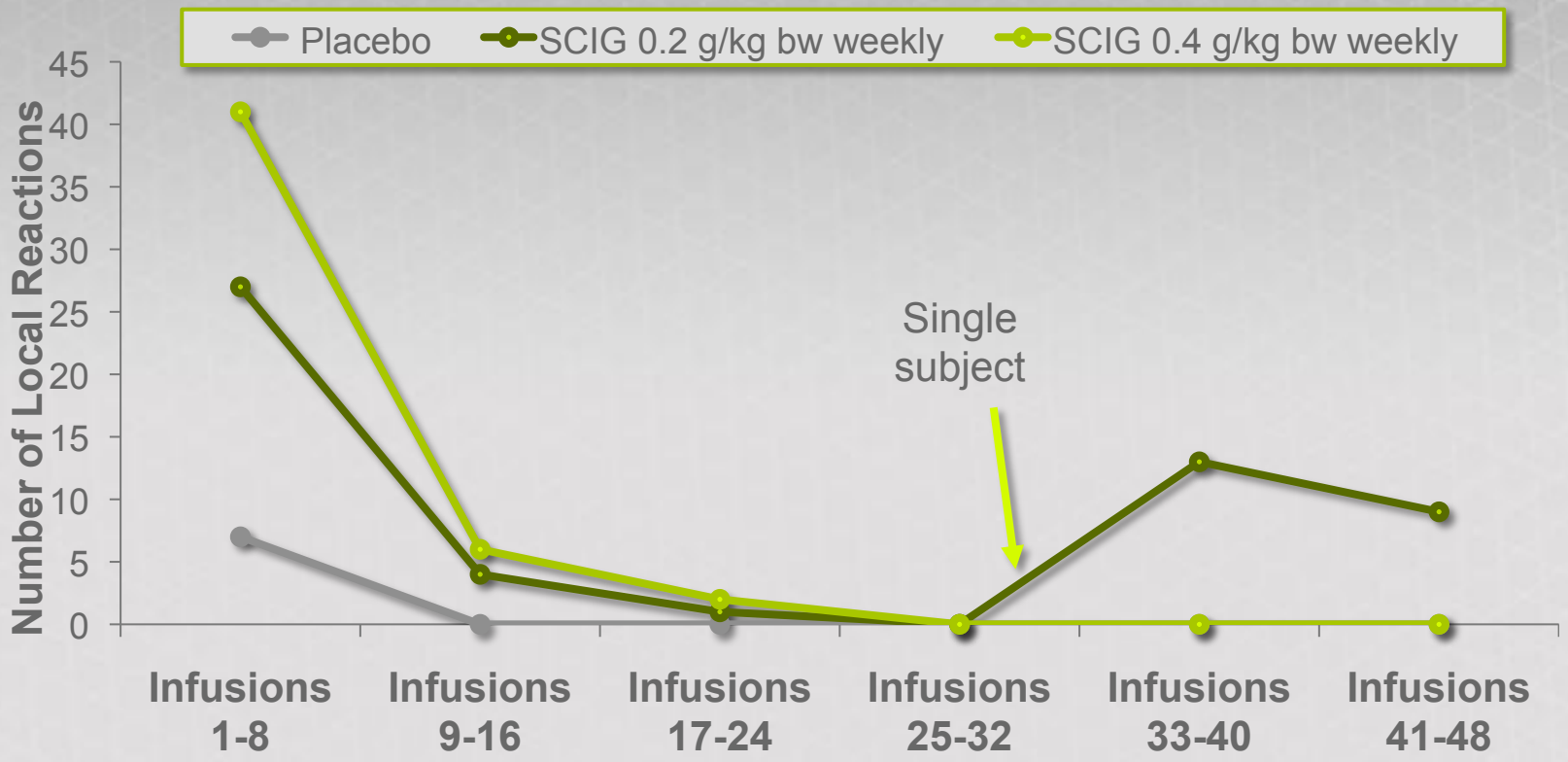
	Placebo (N=57), n (%)	SCIG 0.2 g/kg bw weekly (N=57), n (%)	SCIG 0.4 g/kg bw weekly (N=58), n (%)
Any subjects with AEs	21 (36.8)	33 (57.9)	30 (51.7)
AE severity			
Mild	18 (31.6)	31 (54.4)	25 (43.1)
Moderate	11 (19.3)	13 (22.8)	9 (15.5)
Severe	1 (1.8)	4 (7.0)	3 (5.2)
Any serious AEs	1 (1.8)	3 (5.3)	2 (3.4)
Local reactions	4 (7.0)	11 (19.3)	17 (29.3)

- No thromboembolic events, renal failure, or aseptic meningitis were seen with SCIG

AE: adverse event; bw: body weight; SCIG: subcutaneous immunoglobulin

1. van Schaik IN *et al*. Poster and abstract presented at Annual Meeting of the American Academy of Neurology (AAN); April 22-28, 2017; Boston, MA.

PATH: Local Reactions Over Time (AE/Infusion)[1]



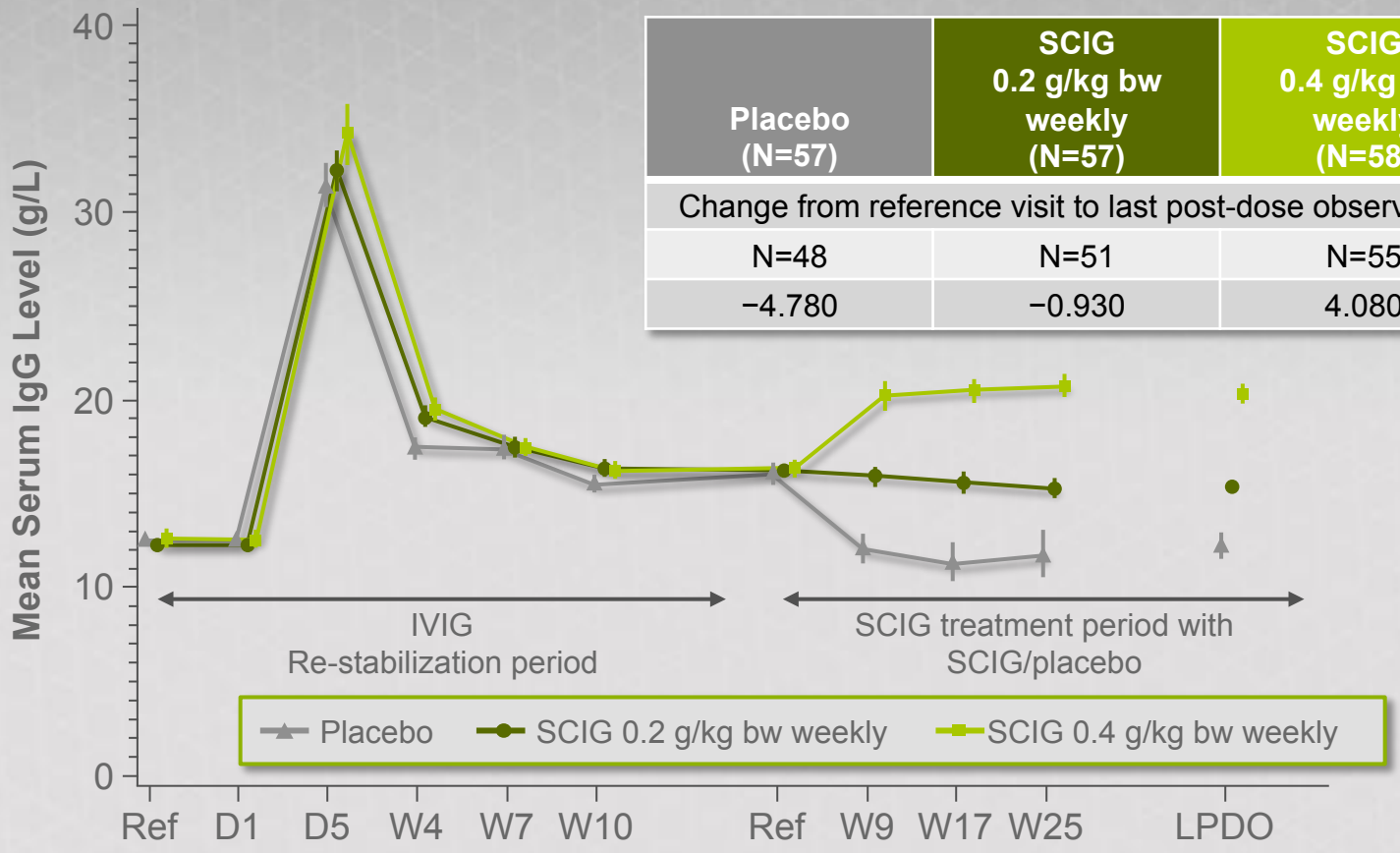
- Local reactions decreased over time
- Most local reactions were mild

AE: adverse event; bw: body weight; SCIG: subcutaneous immunoglobulin

1. van Schaik IN *et al*. Poster and abstract presented at Annual Meeting of the American Academy of Neurology (AAN); April 22-28, 2017; Boston, MA.

Exploratory Endpoints

PATH: Serum IgG Levels



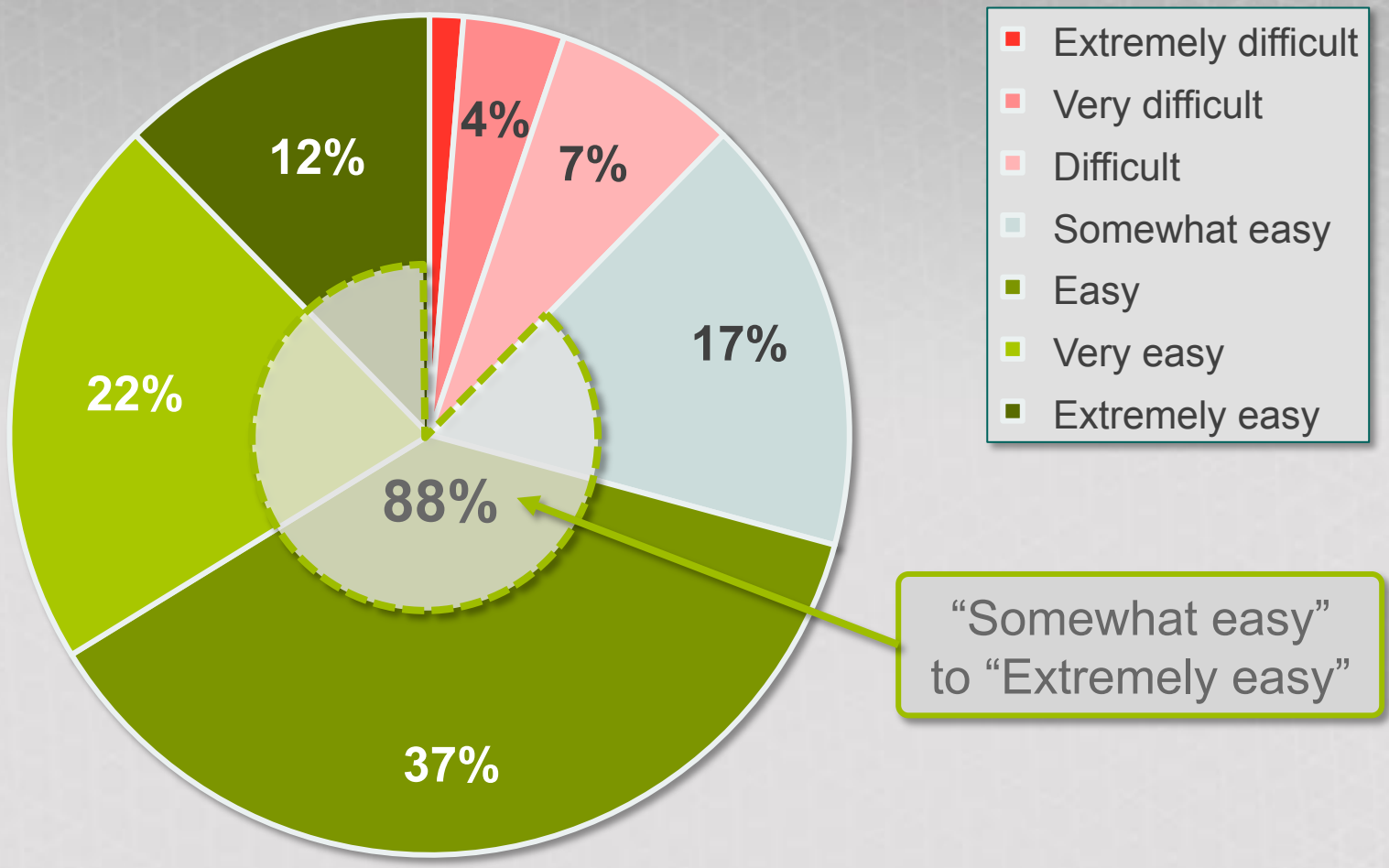
Placebo (N=57)	SCIG 0.2 g/kg bw weekly (N=57)	SCIG 0.4 g/kg bw weekly (N=58)
Change from reference visit to last post-dose observation		
N=48	N=51	N=55
−4.780	−0.930	4.080

Compared with the baseline measurement, serum IgG levels increased in the high-dose group, remained stable in the low-dose group, and decreased in the placebo group

bw: body weight; D: day; IgG: immunoglobulin G; IVIG: intravenous immunoglobulin; LPDO: last post-dose observation; Ref: reference visit; SCIG: subcutaneous immunoglobulin; W: week

1. van Schaik IN *et al.* Oral presentation at the European Academy of Neurology (EAN); June 24-27, 2017; Amsterdam, NL.

PATH: Ease Of Use[1]*



- Most patients found SCIG easy to use

*Last post-dose observation

1. van Schaik IN *et al*. Poster and abstract presented at Annual Meeting of the American Academy of Neurology (AAN); April 22–28, 2017; Boston, MA.

PATH: Summary

Primary Endpoint

- A statistically significant lower percentage of subjects treated with SCIG had CIDP relapse and/or were withdrawn for other reasons (0.2 g/kg bw weekly: 39%, p=0.007; 0.4 g/kg bw weekly: 33%, p<0.001) compared with placebo (63%)

Secondary Endpoints

- Median INCAT, grip strength, and MRC scores remained stable in both SCIG groups and deteriorated in the placebo group
- R-ODS was maintained for the SCIG 0.4 g/kg bw weekly group and deteriorated in the SCIG 0.2 g/kg bw weekly and placebo groups
- Adverse event rate was similar in both SCIG groups (57.9% of 0.2 g/kg bw weekly; 51.7% of 0.4 g/kg bw weekly)

Exploratory Endpoints

- 88% of patients found SCIG somewhat or extremely easy to use
- Serum IgG levels increased in the SCIG 0.4 g/kg bw weekly group (+4.1 g/L change), remained stable in the 0.2 g/kg bw group weekly (−0.9 g/L change), and decreased in the placebo group (−4.8 g/L change)

bw: body weight; CIDP: chronic inflammatory demyelinating polyneuropathy; IgG: immunoglobulin G; INCAT: Inflammatory Neuropathy Cause and Treatment; MRC: Medical Research Council; R-ODS: Rasch-built Overall Disability Scale; SCIG: subcutaneous immunoglobulin