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Abstract: Background: Approximately two-thirds of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) need long-term intravenous immunoglobulins (IVIg). Subcutaneous immunoglobulin (SCIg) is an alternative option for Ig delivery but has not previously been investigated in a large-scale trial in CIDP. The PATH study compared relapse rates in CIDP patients treated with two doses of SCIg versus placebo.
Methods: In 69 neuromuscular centers worldwide between March 2012 and September 2016, a randomized, double-blind, placebo-controlled trial investigated 0·2 and 0·4 g/kg SCIg IgPro20 (Hizentra®, CSL Behring) weekly versus placebo in 172 patients for maintenance treatment. Adults with definite or probable CIDP according to EFNS/PNS criteria dependent on IVIg treatment were eligible. Randomization was done in a 1:1:1 ratio with an interactive web/voice response system. Patients, caregivers, and study personnel were unaware of treatment assignment. The primary outcome was the percentage of patients with a CIDP relapse or who were withdrawn for any other reason during 24-weeks of SCIg-treatment. Analyses were performed in intention-to-treat and per protocol sets. This trial is registered with Clinicaltrials.gov, number NCT01545076.
Findings: The primary outcome was met in 19 (33%) of 58 patients on high-dose SCIg, in 22 (39%) of 57 patients on low-dose SCIg, and in 36 (63%) of 57 patients on placebo. Absolute risk reduction were high-dose vs. placebo 30% (95%CI: 12, 46); low-dose vs. placebo 25% (6, 41); high vs. low-dose 6% (-11, 23). Both SCIg doses were statistically significantly superior to placebo (p-values of 0·0010 and 0·0073, respectively) with no difference between high and low-dose.
Causally related adverse events, mostly mild or moderate, occurred in 47 (27%) patients (10 (18%) placebo, 17 (30%) low-dose, and 20 (35%) high-

dose). Six patients encountered 11 serious adverse events; only one was assessed to be causally related: an acute allergic skin reaction in the low-dose group.
Interpretation: This first long-term SCIg trial showed that both doses of SCIg IgPro20 were efficacious and well tolerated as maintenance treatment of CIDP. SCIg can be used as alternative maintenance treatment in CIDP.
Funding: CSL Behring.

Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (CIDP), a multicenter randomized double-blind placebo-controlled trial: the PATH Study

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Summary

Background: Approximately two-thirds of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) need long-term intravenous immunoglobulins (IVIg). Subcutaneous immunoglobulin (SCIg) is an alternative option for Ig delivery but has not previously been investigated in a large-scale trial in CIDP. The PATH study compared relapse rates in CIDP patients treated with two doses of SCIg versus placebo.

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Findings: The primary outcome was met in 19 (33%) of 58 patients on high-dose SCIg, in 22 (39%) of 57 patients on low-dose SCIg, and in 36 (63%) of 57 patients on placebo. Absolute risk reduction were high-dose vs. placebo 30% (95%CI: 12, 46); low-dose vs. placebo 25% (6, 41); high vs. low-dose 6% (-11, 23). Both SCIg doses were statistically significantly superior to placebo (p-values of 0·0010 and 0·0073, respectively) with no difference between high and low-dose.

Causally related adverse events, mostly mild or moderate, occurred in 47 (27%) patients (10 (18%) placebo, 17 (30%) low-dose, and 20 (35%) high-dose). Six patients encountered 11 serious adverse events; only one was assessed to be causally related: an acute allergic skin reaction in the low-dose group.

Interpretation: This first long-term SCIg trial showed that both doses of SCIg IgPro20 were efficacious and well tolerated as maintenance treatment of CIDP. SCIg can be used as alternative maintenance treatment in CIDP.

Funding: CSL Behring.

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired neuropathy with an assumed autoimmune-mediated pathogenesis.[1] CIDP runs a progressive, relapsing–remitting or monophasic course and can lead to significant activity limitations and participation restrictions with decreased quality of life expectations.[2]

Intravenous immunoglobulin (IVIg) is a well-established therapy for patients with CIDP with an estimated two-thirds of patients needing these infusions over many years.[3] Subcutaneous Ig (SCIg), an alternative route of Ig administration , has been used successfully in patients with primary immunodeficiency syndromes (PID) for more than 25 years.[4] Systemic side effects are reduced using SCIg compared to IVIg. In an open-label prospective study, the severity and frequency of headache and nausea was significantly reduced after SCIg infusions compared to IVIg infusions.[5] Furthermore, hemolytic anemia, which may be seen in IVIg therapy may improve or disappear after switching to SCIg.[6] SCIg is absorbed into the bloodstream over 24-72 hours, leveling out the sharp peak in serum IgG which occurs immediately following an IV infusion.[7] Moreover, when the same total dose of IgG is given as 4 weekly SCIg infusions, rather than a single IV infusion, a near-steady state IgG level will be achieved which is 12-15% higher than the trough level after the IVIG infusion.[8] These differences in pharmacokinetics likely explain the favorable systemic side-effect profile of SCIg over IVIg.[7, 9]

SCIg infusions are well-tolerated, efficacious and preferred by many of the PID patients.[10-12] SCIg increases patient autonomy, quality of life, and leads to cost-savings.[13-16] Similar preference has been suggested in patients with CIDP treated with SCIg.[17]

However, the efficacy, safety and tolerability of weekly SCIg in CIDP have not been studied in an adequately powered, randomized clinical trial with appropriate disability outcome measures.[18] We hypothesized that the percentage of patients having a CIDP relapse or who are withdrawn from the study for any other reason would be reduced by SCIg as compared to placebo. Moreover, we wished to determine if there was a difference in dose as most studies in CIDP use a standard IVIg dose developed long ago for a different condition. We investigated this hypothesis in an international multicenter, double-blind, randomized placebo-controlled parallel-group phase III study which compared two doses of SCIg IgPro20 (Hizentra®, CSL Behring, Bern, Switzerland) with placebo for maintenance treatment of patients with CIDP.

Methods

Study design and participants

The trial protocol and statistical analysis plan were published in detail previously.[19]

Patients were eligible if they were at least 18 years of age and had been diagnosed with definite or probable CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society

(EFNS/PNS) criteria 2010[20] and if they responded to IVIg treatment as assessed by the treating physician within 8 weeks before enrollment. Exclusion criteria were any polyneuropathy of other causes; any other disease that may cause neurological symptoms and signs or that may interfere with treatment or outcome assessments; severe conditions that may interfere with a satisfactory conduct of the study; history of thrombotic episodes within two years before enrollment; known allergic or other severe 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; pregnancy or nursing mother; intention to become pregnant during the course of the study; female patients of childbearing potential either not using or not willing to use a medically reliable method of contraception for the entire duration of the study. Full inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix. All included patients gave written informed consent before study entry. The study protocol was approved by the ethics committees of all participating centers. The study was overseen by an independent data and safety monitoring board and is registered with Clinicaltrials.gov, number NCT01545076.

Randomization and masking

All patients, caregivers, and study personnel were blinded and unaware of treatment assignment. Standard measures were taken for the placebo (2% human albumin solution) and IgPro20 (e.g., same container / closure system, storage conditions, color, and foaming properties) to ensure adequate blinding. A "two-physician" approach was implemented to reduce the chance of potential study unblinding. The "treating" physician was the primary contact for the patient and was responsible for all patient-related questions, adverse event (AE) evaluation, and for all other study-related tasks. A second "evaluating" physician was responsible for assessment of efficacy variables. The evaluating physician did not have access to any data collected by the treating physician.

Based on data transmitted by the treating physician patients were randomized into three arms using an interactive voice/web-response system (IVRS/IWRS) maintained by Parexel. Treatment allocation was in a 1:1:1 ratio using block randomization with a block size of six, stratified for region (Japan/non-Japan). Access to the randomization list was restricted to designated people of the service provider not involved in the conduct or analysis of the trial.

Procedures

After screening all eligible patients progressed through three study periods: an IgG dependency test period (up to 12 weeks), an IVIg re-stabilization period (up to 13 weeks) and a randomized SC treatment period (25 weeks; Figure S1 and more details on all three study periods can be found in table S2). The IgG dependency test period was necessary to ensure that only patients were randomized who were still in need of IgG. Only

patients who were determined to be IgG dependent were enrolled into the IVIg re-stabilization period. This period was performed with IgPro10 (Privigen®, CSL Behring, Bern, Switzerland) using the EFNS/PNS guideline recommended dose of 2 g/kg induction followed by 1 g/kg every three weeks[20] and was deemed necessary to ensure standardized IVIg re-stabilization conditions before initiation of placebo-controlled, randomized SC treatment with IgPro20 or placebo.

Only patients whose Inflammatory Neuropathy Cause and Treatment (INCAT) total score improved during the IVIg re-stabilization period to at least the INCAT total score recorded at screening visit (ie, ≤INCAT score at screening) and who maintained a stable INCAT total score during the last three weeks the of re-stabilitzation period were eligible for randomization.

During the SC treatment period, the total dose/volume for all three treatment groups was calculated on the basis of body weight. One group received IgPro20 at 0·4 g/kg, one group received IgPro20 at 0·2 g/kg plus placebo to match volume in all three groups, and one group received only placebo. The weekly SC infusion of IgPro20 or placebo was performed during 1 or 2 consecutive days in 2 sessions using infusion pumps (for more details see the protocol[19]). SCIg infusions were self-administered or administered by a care-giver at home, after site training. Treatment compliance was monitored (table S2). To this end patients had to fill out a "drug accountability form" which was checked by investigator and sponsor. Patients had to return empty and not fully used vials. A completion visit was performed for all patients following SC completion or withdrawal for any reason during the SC treatment period.

Patients experiencing a CIDP relapse during the SC treatment period were rescued, within 1 week, with IgPro10 medication (2 g/kg bw induction and 1 g/kg bw maintenance) and were discontinued from the study following rescue.

Outcomes

The primary outcome was defined as the percentage of patients who experienced a CIDP relapse during SC treatment or who were withdrawn from the study during SC treatment for any reason.

CIDP relapse was defined as a deterioration (ie, increase) by at least 1 point in the total adjusted INCAT score (range 0 [healthy] to 10 [unable to make any purposeful movements with arms or legs])[21] at any SC treatment period visit compared with baseline. Baseline scores were defined as the scores assessed at the end of the IVIg re-stabilization period. Secondary outcomes for the SC treatment period were time to the primary endpoint, between-group differences of the median changes from baseline to completion visits in INCAT score, mean grip strength for both hands separately as assessed using the handheld Martin Vigorimeter,[22] Medical Research Council (MRC) sum score (range 0-80; including shoulder abduction, elbow flexion, wrist extension, index finger abduction, hip flexion, knee extension, foot dorsiflexion, great toe dorsiflexion)[23] and Inflammatory neuropathy-Rasch-built Overall Disability Scale (I-RODS) (range 0 [most severe activity and social participation limitations] to 100 [no activity and social participation

limitations]).[24] INCAT scores, grip strength, MRC sum score and I-RODS were assessed at screening; during the IgG dependency test period, before IVIg infusions during the IVIg re-stabilization period; at baseline; at all visits during the SC treatment period including the completion visit; and at any unscheduled visit. To assess safety and tolerability of IgPro20 versus placebo, adverse events (AEs) per infusion and the number and percentage of patients with AEs were determined. Various exploratory outcomes were also measured. Quality of life was assessed using the EuroQoL 5-Dimension Questionnaire (EQ-5D), and Treatment Satisfaction Questionnaire for Medication (TSQM).[25] The TSQM captures the ease of use on a 7 point scale, ranging from extremely difficult to extremely easy. Patient preference was assessed with a questionnaire at the end of the study. Furthermore, serum IgG trough levels were measured (prior to administration of study drug).
All outcomes for the two pre-randomization periods, rescue treatment and other exploratory outcomes will be reported separately.

Statistical analysis
Sample size calculation was based on the null hypothesis that the percentage of relapsed or withdrawn patients during SC treatment was non-increasing from placebo to low-dose to high dose arm, with at least one of the examined SCIg dose arms have a strictly lower percentage than the placebo arm. It was assumed that the percentages of patients who reached the primary endpoint was 35% for the IgPro20 high dose, 52% for the IgPro20 low-dose, and 65% for placebo.[19] These numbers were based on data of the ICE study extension period.[21] Using the exact Cochran-Armitage trend test with equally spaced scores and a one-sided significance level of 0·025, a sample size of 58 was needed in each treatment arm to achieve a power of 90% in an intention-to-treat analysis based on the above assumptions. Accounting for patients who would not pass the IgG dependency test and IVIg re-stabilization period, it was expected that up to 350 patients would need to be screened to ensure that 174 patients were randomized.

The exact Cochran-Armitage trend test was used for the primary outcome to test for a trend over the three trial arms at a one-sided type-I error of 0·025. If the hypothesized superiority could be demonstrated, one-sided Fisher's exact tests were to be used for the subsequent pairwise comparisons: placebo vs. low-dose IgPro20, placebo vs. high-dose IgPro20, and low-dose IgPro20 vs. high-dose IgPro20. The proportions and corresponding two-sided 95% Wilson-Score confidence intervals were calculated for each treatment group. Point estimates for the difference in proportions and the corresponding exact two-sided 95% confidence intervals were calculated for all pair-wise treatment comparisons. Three pre-specified sensitivity analyses with modified primary endpoint definitions investigated the potential bias for any reason other than CIDP relapse).[19] Complementary to the primary analysis and the sensitivity analyses, two time-to-event analyses were performed and Kaplan-Meier estimates were derived. In the first patients who withdrew for other

reasons were considered to have reached the endpoint, in the second withdrawals for other reasons contributed to a censored outcome. Between-treatment group comparisons were performed using the log-rank test for trend. When an overall trend was demonstrated, subsequent pairwise one-sided comparisons were performed using the log-rank test.

Secondary endpoints were presented as median changes from baseline and compared between the three groups using the asymptotic Jonckheere-Terpstra test.[26] Pairwise comparisons based on median changes from baseline were done using one-sided Wilcoxon rank sum tests. Multiple testing for the primary analysis was accounted for by using a closed testing procedure. All other comparisons are not adjusted and therefore considered exploratory.

The primary outcome, including all sensitivity analyses, was assessed in the intention-to-treat set (ITTS) and per protocol set (PPS).[19] Secondary endpoints were assessed in the ITTS. Safety was assessed in the safety data set including all randomized patients who received at least one dose of IgPro20/placebo. The rate per infusion was calculated as number of events divided by the overall number of infusions in the respective treatment groups.

During the conduct of this trial, the protocol was amended five times. Two relevant protocol changes were made to increase recruitment: amendment 3 introduced 2 other measures to define IgG dependency (Grip strength & I-RODS) and amendment 4 deleted one inclusion criterion reducing the length of time required for pre-study IVIg to 8 weeks. As a consequence to amendment 3 sample size was increased from 150 to 174. Approximately half of the study population was recruited after amendment 3. 40 patients were recruited that met the newly introduced criteria. Amendment 1 was introduced before the study started recruitment, amendment 2 never included patients and amendment 5 was an update to insert new safety language.[19] (for more details see table S3).

The independent data monitoring committee performed an unblinded formal interim analysis for futility based on the outcome data of 60 patients completing 3 months of treatment.

Role of the funding source

The funder of the study together with a steering committee was responsible for the design of the trial and the data analysis and contributed to the data interpretation and writing of the manuscript. A statistician was a member of the steering committee and critically reviewed all results. The funder had no role in the data collection. The authors had full access to all data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Patients were enrolled in 69 neuromuscular centers worldwide from March 2012 until November 2015, with last patient visit in September 2016. A total of 276 unique patients were screened (Figure 1). Of these 276 patients, 245 entered the Ig dependency test period. Twenty-eight patients (11%) were considered not IgG dependent and 9 withdrew for other reasons. One additional IgG dependent patient withdrew consent before IgPro10 dosing. Twenty-two patients of the 207 patients who were treated with IgPro10, were not restabilized after a maximum of 13 weeks and were withdrawn (Four-week post-study follow up information was obtained in 16 of these 22 patients, revealing that 9 (56%) eventually restabilized). Fourteen withdrew for other reasons. In total, 172 patients were randomized and received treatment: 58 were assigned to high-dose SCIg, 57 to low-dose SCIg, and 57 to placebo. All patients received their allocated treatment and 99·7% of planned volumes were actually administered. Patients tolerated volumes up to 50 ml per injection site with two to eight infusion sites running in parallel and up to 50 ml/h/site infusion rate (6 patients), maximum total infusion volume was 140 ml; this maximum volume was applied in two patients. Infusion time was approximately one hour. No patients were lost to follow-up. Table 1 shows the baseline characteristics of all randomized patients. Patients in the three groups were similar in demographic, clinical, disability, disease, and treatment related parameters at baseline, except for gender with slightly more males in the low-dose IgPro20 group.

During SC treatment, 77 patients had a CIDP relapse or were withdrawn from the study: 36 (63%) in the placebo group, 22 (39%) in the low-dose group and 19 (33%) in the high-dose group (Figure S2, Table 2). The absolute risk reduction (ARR) for reaching the primary endpoint was 25% (95%CI 6·2%, 40·8%) in the low-dose group and 30% (12·2%, 46·0%) in the high dose group as compared with placebo. Comparing low-dose with high-dose, the ARR was 6% (-11·4%, 22·6%). Superiority of at least 1 active dose over placebo was demonstrated with the Cochran–Armitage trend test (p=0·0007). Both SCIg doses were superior to placebo (p=0·0073 and p=0·0010, respectively). The sensitivity analyses showed that the patients, who withdrew for reasons other than relapse, did not influence the primary endpoint outcome (Table 2). Forty-seven (81%) of 58 patients in the high-dose group and 38 (67%) of 57 patients in the low-dose group (sensitivity analysis A) remained relapse-free. Sixteen patients withdrew for other reasons than CIDP relapse (figure 1) during SC treatment (nine in the high-dose, three in the low-dose and four in the placebo group): two patients withdrew for AE (one AE related to SC treatment); 13 withdrew consent; and one was withdrawn by physician decision. Subsequent investigation after database lock revealed that six patients withdrew because of issues with self-injecting, handling pumps and infusions, and/or preparation of the infusion and syringe.

The probability to reach the primary endpoint (to relapse or be withdrawn for other reasons) was significantly lower in both SCIg groups than in the placebo groups (Figure 2, Table 2).

A complementary time to relapse analysis was performed censoring all withdrawals at time of withdrawal. The Kaplan-Meier estimates for CIDP relapse alone was 59% (95%CI 46%, 72%) in placebo, 35% (24%, 49%) in low-dose SCIg, and 22% (13%, 37%) in high-dose SCIg patients. Both SCIg doses were superior to placebo (log-rank test p=0·0094 and p<0·0001, respectively). Both IgPro20 doses were associated with lower relapse rates as compared to placebo and the probability of a relapse was lower at all time points between SC week 3 and 25 in IgPro20-treated patients when compared with placebo-treated patients (figure 2).

The probability to remain relapse-free was 78% in the high-dose group, 65% in the low-dose group and 41% in the placebo group. The number needed to treat to prevent one CIDP relapse is 2·7 for high-dose IgPro20 and 4·4 for low-dose IgPro20. All per protocol analyses supported the results of the ITT analysis.

Sixty-two patients experienced a relapse after randomisation (32 on placebo, 19 on low-dose and 11 on high-dose) of which 55 were treated with IgPro10: 22 patients received one induction dose (standard rescue protocol before AM3) and 33 patients received one induction dose and up to four maintenance doses (standard rescue protocol after AM3). Patients were then discontinued to either continue with the extension study or with their standard of care treatment. The recovery rate (assessed at last study visit) was 70% (23/33) in patients who received more than one IgPro10 dose which was similar to the recovery rate based solely on adjusted INCAT score during the restabilization period (73%, 151 of 207 patients).

The median changes from baseline in secondary outcome variables showed similar patterns as the primary outcome across the different treatment groups (Table 3). All median changes with high- and low-dose were significantly better than with placebo except for the median change with low-dose in the I-RODS scores. No significant differences were observed between the two dose groups.

Health related quality of life measures (EQ-5D, TSQM-14) generally showed better outcomes for both SCIg groups over placebo (Table S4). Eighty-eight of patients reported that learning the technique of self-administration was easy (Table S4). Sixty-one of 115 (53%) SCIg-treated patient preferred current treatment versus 22 of 57 (39%) of placebo patients whereas 21 of 115 (18%) SCIg-treated patients and 14 of 57 (25%) placebo patients preferred their previous IVIg treatment (Table S4).

At the last post SC dose observation the serum trough IgG concentrations had decreased in the placebo group, remained stable in the low-dose group, and increased in the high-dose group (Table S6).

In the placebo group 21 (37%) patients had 52 adverse events over 1514 infusions. In the low-dose group 33 (58%) patients had 158 adverse events over 2007 infusions; in the high-dose group 30 (52%) patients had 114 adverse events over 2218 infusions (Table 4). Local reactions at the infusion site such as erythema, swelling, skin induration, pain, pruritus, warmth, and local skin haematoma occurred in 32 (19%) patients and more frequently in SCIg groups 11 (19%) low-dose patients and 17 (29%) high-dose patients compared

to 4 (7%) placebo patients [Table 4]). All 110 local reactions were either mild (95%) or moderate (6%), frequency decreased during the first eight infusions, and none led to discontinuation. Eleven serious AEs were encountered in one placebo patient, three low-dose and two high-dose patients. Only one of those 11 SAEs was assessed to be causally related: in the low-dose group one patient developed an acute allergic skin reaction. This SAE led to discontinuation of treatment. No hemolysis or thrombosis occurred during the SC treatment period. Patients using higher infusion rates reported the same number of adverse events (Table S5).

Discussion

This randomized trial is the largest performed to date in CIDP, the first investigating SCIg long-term in CIDP, and the first investigating multiple doses of Ig in CIDP. The study demonstrated that both doses of IgPro20 were effective in maintaining stable disease over 24 weeks in patients with CIDP who previously were shown to be dependent on IVIg treatment. The primary endpoint occured more often in the placebo group (63%) as compared to both SCIg groups (39% and 33% respectively). This result was achieved using a conservative endpoint including not only patients who relapsed but also patients who were withdrawn for any other reason. A total of 76%-81% of patients in the high-dose group and 65-67% in the low-dose group remained relapse-free in three sensitivity analyses accounting for premature withdrawal of subjects with no relapse in different ways. All differences were statistically significant compared to placebo.The analyses along with the secondary outcome measures and health related quality of life measures supported these results as did the per protocol analyses. We did not find large difference in secondary outcomes as our study was designed to show whether IgPro20 could maintain the improvement achieved during the IVIg restabilization period and patients were discontinued at the time of relapse preventing relapsing patients to further deteriorate.

Both doses of IgPro20 were well tolerated when given in high volumes using multiple injection sites. Important reasons for patients to prefer weekly SCIg over monthly IVIg were a gain in independence and less side effects. Local reaction were mostly mild, their frequency was low, and decreased considerably over time.

Our trial employed an unique design. We used an IgG dependency test period to ensure that only patients who were still in need of IgG were randomized. For a trial investigating maintenance treatment in CIDP, the necessity of including a run-in period in which the IVIg dose is reduced or withheld to prove IgG dependency became clear during the RMC-trial.[27] During the second phase, patients were all treated with standard doses of IgPro10 to ensure standardized IVIg restabilization conditions. Each phase had specific rules which had to be fulfilled by a patient to enter the next phase to ensure a comparable baseline before randomization and assignment to IgPro20 or placebo. The IVIg loading dose and maintenance doses for the restabilization period were based on the EFNS/PNS guidelines and evidence from a large international

study.[20, 21] The study was designed to show whether IgPro20 could maintain the improvement achieved during the IVIg restabilization period in patients with CIDP.

Our findings are in accordance with several SCIg studies; Two small placebo-controlled randomized trials have been published investigating SCIg in CIDP patients. The first trial included 30 CIDP patients who were successfully treated with IVIg and were switched for 12 weeks to SCIg.[28] A second trial included 19 treatment naïve CIDP patients.[29] Both trials showed promising results on impairment. A one-year open label follow-up study has suggested SCIg may be used as long-term maintenance treatment in CIDP.[30] Open-label case series and a relatively large prospective observational study have reported clinical efficacy and safety of weekly SCIg to treat CIDP.[16, 18, 31]

In patients treated with high-dose IgPro20 the ARR for reaching a relapse only was 37% with a corresponding NNT of 2·7. The Cochrane review on IVIg for CIDP[32] has summarized all trials comparing IVIg with placebo. The review reports that a significantly higher proportion of partients improved in disability within six weeks after the onset of treatment with IVIg compared with placebo, RR 2.40 (95% CI 1.72 to 3.36) and an NNT of 3.03 (95% CI 2.33 to 4.55). For the parallel design trials only, the RR was 2.14 (95% CI 1.48 to 3.09) and NNT was 3.33 (95% CI 2.38 to 5.88). The NNT for subcutaneous Ig to prevent relapse in the PATH study is therefore in the similar range to the NNT for intravenous Ig found in previous studies.

CIDP guidelines suggests a maintenance dose for IVIg ranging from 0·4–1·2 g/kg every 2–6 weeks.[20] This would translate into a maximum dose of 0·2 to 0·6 g/kg every week. In previous studies, weekly doses from 0·1g to 0·4 g /kg were administered SC by converting the IV dose 1:1 to an equivalent SC dose. In CIDP, after switching 1:1 from IVIg to SCIg, small dosage increases were observed ranging from 6% in almost half of patients[30] to 20% in a minority of the patients.[31] In one study in CIDP patients after a follow-up period of 33 months, dose had been increased on average with 8% to maintain clinical stability.[17] In the PATH trial an IVIg dose requirement of more than 1·6 g/kg every 4 weeks was an exclusion criterion. The two doses tested in our study (0·2g and 0·4g/kg bw weekly dose) were based on the IVIg maintenance dose recommended by the EFNS/PNS guidelines for CIDP (1g/kg every 3 weeks, equivalent to 0·33g/kg bw weekly dose). The high dose SCIg is thus 21% higher and the lower dose 39% lower than this recommended dose.

Our study has some limitations. Firstly, we did not compare IgPro20 directly with IVIg. A direct comparison needs an inferiority design. We considered this, but the results of the power calculations learned that we would need an infeasible amount of CIDP patients which makes such a study impossible to complete within an acceptable timeframe. Secondly, our IgG dependency test was not perfect in the sense that we were able to select only patients who remained IgG dependent throughout the study. CIDP is a disease with a highly variable disease course and patients have an intrinsic chance of relapsing over time. We know from previous studies that this is the case in treated and untreated patients, albeit that with treatment a significant reduction

in relapse chance could be reached. In our study 37% of IgG-dependent patients (excluding four patients who discontinued the study for other reasons than adjusted INCAT defined relapse) on placebo did not relapse. In the ICE trial 58% of patients who responded during the first phase and who were randomized to placebo in the second phase did not relapse. The lower non-relapse rate in our placebo patients compared to the ICE trial placebo patients suggests that the IgG-dependency test had the intended effect of selecting patients who were still dependent on IgG.

Thirdly, we missed a considerable number of data for the exploratory outcomes especially for the preference question.

Fourthly, we did not follow up on patients who were withdrawn for other reasons and on patients who were rescued during the SC phase of our trial apart from patients who entered the extension study. Therefore we do not know exactly what the fate of all those patients is.

What are the practical implications of our study? Patients on a standard regime of IVIg can be safely transitioned to subcutaneous treatment. Our findings indicate that both SCIg doses are efficacious in maintaining CIDP patients and preventing relapse. The potential of relapse risk reduction with SCIg is compatible to what has been observed in studies of IVIg. We have used SCIg doses that were 21% higher and 39% lower than what would have been a 1:1 conversion of 1g/kg IVIg given every 3 weeks. In accordance with current treatment guidelines that recommend to individualize IgG dose we suggest that SCIg to be given in doses of 0.2g/kg – 0.4g/kg with the final maintenance dose to be determined based on patient situation, clinical response, and previous IVIg dose and frequency.

This large long-term treatment trial with SCIg therefore supports a weekly SCIg dose-range of 0.2 – 0.4g/kg and shows that SCIg can be used as alternative maintenance treatment in CIDP patients.

Panel: Research in Context

Evidence before this study

We searched PubMed (September 2017) with the search terms “subcutaneous immunoglobulin”, “CIDP”, and “clinical trial” for reports published before March 2012. No clinical trials investigating the efficacy, safety and tolerability of SCIg in CIDP had been published. Two case reports described seven CIDP patients who were successfully switched from IVIg to SCIg.

Subcutaneous Ig (SCIg), as alternative route of Ig administration, has been used successfully in patients with immuno-deficiency syndromes (PID) for more than 25 years and more recently in patients with multifocal motor neuropathy (MMN). Since the start of our studies two small placebo-controlled randomized trials have been published investigating SCIg in CIDP patients. Both trials showed promising results on impairment. A one-year open label follow-up study has suggested SCIg may be used as long-term maintenance treatment in CIDP. Several open-label case series and one relatively large prospective observational study have reported clinical efficacy and safety of weekly SCIg to treat CIDP.

Added value of this study

This is the first randomized study that has studied subsequently both routes of administration and two Ig doses in CIDP. This study demonstrated that SCIg can be used as an alternative in the maintenance treatment of patients with CIDP. Our findings indicate that both doses are efficacious in maintaining CIDP patients and preventing relapse. . Both doses of IgPro20 were well tolerated with an excellent safety profile. The most frequently reported adverse events were local reaction at the infusion site; most of the local reactions were mild.

Implications of all the available evidence

The data from this study support a weekly SC dose of 0·2 – 0·4g/kg. Maintenance SCIg dose should be individualized based on patient situation and previous IVIg dose and frequency.

Contributors

INvS, VB, HPH, RAL, GS, OM, DRC, and ISJM contributed substantially to the conception and design of the study. JPL wrote the statistical analysis plan, which was critically reviewed by NvG, BLD and MP. INvS, VB, NvG, ISJM, BLD, OM, JPL and MP reviewed and analyzed all the data in the study. INvS, VB, NvG, and ISJM drafted the manuscript, which was revised critically by all other authors. All authors read and approved the final manuscript before submission.

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study and/or the sponsor.

Declarations of interest

I. N. van Schaik chairs a steering committee for CSL Behring and received departmental honoraria for serving on scientific advisory boards for CSL Behring and Baxter. He received departmental research support from The Netherlands Organization for Scientific Research and from the Dutch Prinses Beatrix Fonds. All lecturing and consulting fees for INS were donated to the Stichting Klinische Neurologie, a local foundation that supports research in the field of neurological disorders. He serves on the editorial board of the Cochrane Neuromuscular Disease Group, is a member of the organizing committee of the Inflammatory Neuropathy Consortium (INC), a standing committee of the Peripheral Nerve Society, and is a member of the Scientific Board of the Kreuth III meeting on the optimal use of plasma-derived medicinal products, especially coagulation factors and normal immunoglobulins organized under the auspices of the European Directorate for the Quality of Medicines & HealthCare (EDQM).

V. Bril is consultant to CSL Behring, Grifols, UCB, Bionevia, and ArgenX. She serves on international scientific advisory boards for MGFA and the CIDP/GBS International Foundation, and has received research support from CSL Behring, Grifols, Bionevia UCB and ArgenX.

N. van Geloven received departmental honoraria for serving at a scientific advisory board for CSL Behring.

H. P. Hartung received fees for consulting, serving on steering committees or ad boards from Baxter, Bayer Healthcare, Biogen, CSL Behring, Geneuro, Kedrion, LFB, Medimmune, Merck, Novartis, Octapharma, Receptos Celgene, Roche, Sanofi Genzyme, and Teva with approval by the Rector of Heinrich-Heine-University Düsseldorf.
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G. Sobue served on the scientific advisory boards for Kanae Science Foundation for the Promotion of Medical Science and the Takeda Foundation. He serves on a steering committee for CSL Behring. He received funding for travel and speaker honoraria from Mitsubishi Tanabe Pharma Co, Shionogi Co Ltd, Bristol Myers Squibb, Sumitomo Dainippon Pharma Co Ltd, Novartis Pharma KK, Bayer Yakuhin Ltd, Pfizer Japan Inc, Boehringer Ingelheim Japan, Inc, Kissei Pharmaceutical Co Ltd, Janssen Pharmaceutical KK, Teijin Pharma Ltd, FP Pharmaceutical Co, Nihon Pharmaceutical Co Ltd, Japan Blood Products Organization, Kowa Pharmaceutical Co Ltd, Ono Pharmaceutical Co Ltd, Eisai Co Ltd. He also received grants from the Ministry of Health, Labour and Welfare Japan, Japanese Ministry of Education, Culture, Sports, Science and Technology, and Japan Society for the Promotion of Science.
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Figure titles

Figure 1. Trial profile

*Note: One patient in the low dose IgPro20 group relapsed at the End-of-Study Visit but was not discontinued and one patient in the high dose IgPro20 group relapsed at the End-of-Study Visit, but was discontinued due to an AE (total relapse counts for study IgPro20 were 19 and 11 respectively). CIDP=chronic inflammatory demyelinating polyneuropathy. EFNS=European Federation of Neurological Societies. Ig=immunoglobulins. INCAT=Inflammatory Neuropathy Cause and Treatment. ITTS=intention-to-treat set. IVIg=intravenous immunoglobulins. PNS=Peripheral Nerve Society.

Figure 2. Time to reach primary endpoint (CIDP relapse or withdrawal for any reason)

CIDP=chronic inflammatory demyelinating polyneuropathy.

Table

Table 1. Baseline characteristics

	Placebo n=57	Low dose IgPro20 n=57	High dose IgPro20 n=58
Male	37 (65)	42 (74)	31 (53)
Age (years)	57·6 (Q1,Q3 46·7,65·9)	58·9 (Q1,Q3 50·5,66·5)	55·2 (Q1,Q3 49·2,66·4)
Body weight (kg)	86·5 (Q1,Q3 73·5, 98·0)	80·0 (Q1,Q3 72·0,93·0)	80·0 (Q1,Q3 60·3,96·0)
BMI (kg/m^2)	28·4 (Q1,Q3 24·5,30·9)	26·4 (Q1,Q3 24·4,29·3)	26·6 (Q1,Q3 22·6,29·2)
Duration of disease (years)	2·7 (Q1,Q3 1·1,4·7)	2·8 (Q1,Q3 1·4,5·0)	3·3 (Q1,Q3 1·3,8·6)
EFNS/PNS CIDP criteria			
Definite	53 (93)	51 (89)	53 (91)
Probable	4 (7)	6 (11)	5 (9
Patients with ≥ 4 IVIg treatments in 9 months before enrolment	51 (89·5)	52 (91·2)	54 (93·1)
IVIg dose during 3 months prior to screening (g/kg)	2·3 (Q1, Q3 1·3, 3·4)	2·3 (Q1, Q3 1·3, 3·0)	2·7 (Q1, Q3 1·3, 3·4)
INCAT disability scale (possible range 0-10)	2 (Q1,Q3 1,3)	2 (Q1,Q3 1,3)	2 (Q1,Q3 1,3)
I-RODS (possible range 0-100)[#]	68 (Q1,Q3 51-83)	63 (Q1,Q3 51,73)	69 (Q1,Q3 54,80)
Grip strength Dominant hand (kPa; possible range 0-160)	68·0 (Q1,Q3 49·3,83·7)	67·0 (Q1,Q3 56·7,86·2)	68·4 (Q1,Q3 46·0,93·3)
MRC sum score (possible range 0-80)	76 (Q1,Q3 72,78)	75 (Q1,Q3 70,78)	76 (Q1,Q3 70,79)

Data are number (%), median (1st quartile, 3rd quartile). Larger INCAT disability scale values indicate greater limitation. Larger MRC sum score indicates greater strength. The I-RODS scores range from 0 indicating most severe activity and social participation limitations to 100 if a patient is fully able. Q1 = 1st quartile, Q3 = 3rd quartile. [#]total n=152: missing data in 11 placebo, 6 low dose and 3 high dose patients.

Table 2. Primary outcome

	%, 95% CI (number of patients)			Exact Cochran-Armitage test (p)	Fisher's exact test (p)		
	Placebo n=57	**Low-dose SCIg n=57**	**High-dose SCIg n=58**	**Overall test**	**Low-dose vs placebo**	**High-dose vs placebo**	**High-dose vs low-dose**
Primary outcome ITT	63, 50·2-74·5 (36)	39, 27·1-51·6 (22)	33, 22·1-45·6 (19)	0·0007	0·0073	0·0010	0·3233
Difference in % (95% Wilson score CI					-25 (-40·7,-6·2)	−30 (−46·0, −12·2)	-6 (-22·6, 11·4)
	n=52	n=54	n=47				
PP	64, 50·0-75·2 (33)	39, 27·0-52·2 (21)	26, 15·3-39·5 (12)	<0·0001	0·0095	0·0001	0·1119
Difference in % (95% Wilson score CI)					-25 (-41·2, -5·5)	-38 (-53·5, -18·4)	-13 (-30·2, 5·0)
	N=57	*N=57*	*N=58*				
Sensitivity analysis A "CIDP relapse analysis"	*56, 43·3-68·2 (32)*	*33, 22·5-46·3 (19)*	*19, 10·9-30·9 (11)*	<0·0001	*0·0117*	*0·0001*	*0·0612*
Difference in % (95% Wilson score CI)					-23 (-39·0, -4·6)	-37 (-51·7, -19·7)	-14 (-29·6, 1·7)
Sensitivity analysis B "mixed-case analysis"	*60, 46·7-71·4 (34)*	*33, 22·5-46·3 (19)*	*24, 15·0-36·5 (14)*	<0·0001	*0·0041*	*0·0001*	*0·1885*
Difference in % (95% Wilson score CI)					-26 (-42·3, -8·0)	-36 (-50·4, -17·6)	-9 (-25·1, 7·3)
	n=53	*n=54*	*n=50*				
Sensitivity analysis C "complete-case analysis"	*60, 46·9-72·4 (32)*	*35, 23·8-48·5 (19)*	*22, 12·8-35·2 (11)*	<0·0001	*0·0077*	*<0·0001*	*0·1024*
Difference in % (95% Wilson score CI)					-25 (-41·7,-6·3)	-38 (-53·6, -19·5)	-13 (-29·4, 4·3)
				log-rank test for trend	regular log-rank test		
Probability of primary outcome at 24 weeks[#]	63·2 (50·9, 75·4)	39·0 (27·7, 53·1)	33·7 (22·8, 47·8)	0·0002	0·0071	<0·0005	0·4833
Hazard ratio (95%CI)					0·49 (0·29, 0·84)	0·38 (0·22, 0·67)	0·8 (0·43,1·49)
Probability of a relapse at 24 weeks[#]	58·8 (46·1, 72·0)	35·0 (23·9, 49·3)	22·4 (12·9, 37·2)	<0·0001	0·0094	<0·0001	0·0895
Hazard ratio (95%CI)					0·48 (0·27, 0·85)	0·25 (0·12, 0·49)	0·53 (0·25,1·12)

Three pre-specified sensitivity analyses with modified primary endpoint definitions investigated the potential bias for any reason other than CIDP relapse): (A) "CIDP relapse analysis", all patients who did not experienced a CIDP relapse were considered as non-relapsers; (B) "mixed-case analysis", patients who had a relapse including patients who were withdrawn because the investigator advised that the patient's safety or well-being could be compromised by further participation in the study or who received prohibited medication were compared to patients without a relapse including all patients who were withdrawn for any other reasons; (C) "complete-case analysis", patients with a relapse were compared with those without a relapse, excluding from analysis all patients who were withdrawn from the study. Exact Cochran-Armitage tested for a trend with superiority of at least one IgPro20 dose over placebo. #Kaplan-Meier estimates (%,(95%CI)). All tests are one-sided with statistical significance defined at a p-value of < 0·025. Baseline scores were the last scores before randomization. ITT = intention treat analysis; PP = per protocol analysis; SCIg = subcutaneous immunoglobulins.

Table 3. Secondary outcomes

				Asymptotic Jonckheere-Terpstra test (p)	Wilcoxon rank sum test (p)		
	Placebo n=57	**Low-dose SCIg n=57**	**High-dose SCIg n=58**	**Overall test**	**Low-dose vs placebo**	**High-dose vs placebo**	**High-dose vs low-dose**
	INCAT [total score]						
Value at endpoint	3·0 (3·0, 4·0)	3·0 (2·0, 4·0)	2·0 (1·0, 3·0)				
Change from baseline, median (Q1, Q3)*	1·0 (0·0, 2·0)	0·0 (0·0, 1·0)	0·0 (0·0, 0·0)	<0·0001	0·0046	<0·0001	0·1015
Median difference (95% Moses CI)					0·0 (-1·0, 0·0)	-1·0 (-1·0, 0·0)	0·0 (0·0, 0·0)
	I-RODS [centile score]						
Value at endpoint	60·0 (45·0, 69·0)	61·0 (55·0, 69·0)	65·0 (52·0, 80·0)				
Change from baseline, median (Q1, Q3)*	-3·0 (-16·0, 0·0)	-2·0 (-7·0, 2·0)	0·0 (-2·0, 3·5)	0·0002	0·0302	<0·0002	0·0414
Median difference (95% Moses CI)					3·0 (0·0, 9·0)	5·0 (2·0, 9·0)	2·0 (0·0, 4·0)
	Grip strength [kPa, dominant hand]						
Value at endpoint	62·0 (36·0, 75·3)	64·0 (55·5, 87·0)	66·7 (43·3, 90·7)				
Change from baseline, median (Q1, Q3)*	-6·6 (-21·6, 0·3)	-0·6 (-8·9, 7·0)	-2·7 (-6·6, 2·0)	0·0223	0·0041	0·0135	0·1985
Median difference (95% Moses CI)					7·6 (2·0, 14·0)	5·7 (0·7, 11·7)	-1·7 (-5·4, 2·3)
	Grip strength [kPa, non dominant hand]						
Value at endpoint	60·0 (37·7, 73·3)	66·7 (52·7, 85·0)	65·2 (42·0, 89·0)				
Change from baseline, median (Q1, Q3)*	-8·3 (-24·7, 1·7)	-0·4 (-10·3, 7·0)	-1·7 (-6·0, 4·6)	0·0026	0·0051	0·0019	0·4627
Median difference (95% Moses CI)					8·3 (1·7, 15·0)	8·3 (2·4, 15·6)	0·3 (-4·1, 4·9)
	MRC [sum score]						
Value at endpoint	73·0 (66·0, 77·0)	74·0 (67·5, 78·0)	76·0 (68·0, 80·0)				
Change from baseline, median (Q1, Q3)*	-2·0 (-6·0, 0·0)	0·0 (-2·0, 2·0)	0·0 (-2·0, 1·0)	0·0026	0·0025	0·0022	0·4653
Median difference (95% Moses CI)					2·0 (1·0, 4·0)	2·0 (1·0, 4·0)	0·0 (-1·0, 1·0)

INCAT = Inflammatory Neuropathy Cause and Treatment; MRC = Medical Research Council; R-ODS = Rasch-built Overall Disability Scale; SC = subcutaneous; SCIg = subcutaneous immunoglobulins. Baseline scores were the last scores before randomization. All tests are one-sided with statistical significance defined at an unadjusted p-value of < 0·025 (statistical testing was not adjusted for multiple testing for the secondary endpoint. These comparisons are therefore considered exploratory). * at last SC post-dose observation

Table 4. All adverse events reported in ≥5% of patients in a treatment group

	Placebo		Low-dose SCIg		High-dose SCIg	
	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)[@]**
System Organ Class Preferred Term	n=57	n=1514[#]	n=57	n=2007[#]	n=58	n=2218[#]
Any adverse event (treatment-emergent)	21 (36·8)	52 (0·034)	33 (57·9)	158 (0·08)	30 (51·7)	114 (0·05)
General disorders and administration site conditions[&]	6 (10·5)	10 (0·007)	16 (28·1)	60 (0·03)	18 (31·0)	52 (0·02)
Fatigue	*1 (1·8)*	*1 (<0·001)*	*5 (8·8)*	*5 (0·002)*	*0*	*0*
Local reactions[$]	4 (7·0)	7 (0·005)	11 (19·3)	54 (0·03)	17 (29·3)	49 (0·02)
Infusion site erythema	*0*	*0*	*5 (8·8)*	*11 (0·005)*	*10 (17·2)*	*28 (0·013)*
Infusion site swelling	*2 (3·5)*	*2 (0·001)*	*5 (8·8)*	*8 (0·004)*	*6 (10·3)*	*8 (0·004)*
Infusion site induration	*1 (1·8)*	*1 (< 0·001)*	*2 (3·5)*	*10 (0·005)*	*3 (5·2)*	*3 (0·001)*
Infusion site warmth	*0*	*0*	*0*	*0*	*3 (5·2)*	*3 (0·001)*
Infusion site pain	*2 (3·5)*	*2 (0·001)*	*3 (5·3)*	*15 (0·007)*	*2 (3·4)*	*2 (< 0·001)*
Infusion site pruritus	*0*	*0*	*0*	*0*	*2 (3·4)*	*3 (0·001)*
Infusion site extravasation	*0*	*0*	*0*	*0*	*1 (1·7)*	*1 (< 0·001)*
Infusion site mass	*1 (1·8)*	*1 (< 0·001)*	*0*	*0*	*1 (1·7)*	*1 (< 0·001)*
Infusion Site haematoma	*1 (1·8)*	*1 (< 0·001)*	*2 (3·5)*	*2 (< 0·001)*	*0*	*0*
Infusion site haemorrhage	*0*	*0*	*1 (1·8)*	*1 (< 0·001)*	*0*	*0*
Infusion site oedema	*0*	*0*	*1 (1·8)*	*6 (0·003)*	*0*	*0*
Infusion site rash	*0*	*0*	*1 (1·8)*	*1 (< 0·001)*	*0*	*0*
Infections and infestations	8 (14·0)	11 (0·007)	13 (22·8)	18 (0·009)	6 (10·3)	9 (0·004)
Nasopharyngitis	*1 (1·8)*	*1 (< 0·001)*	*4 (7·0)*	*6 (0·003)*	*2 (3·4)*	*2 (< 0·001)*
Upper respiratory tract infection	*2 (3·5)*	*2 (0·001)*	*3 (5·3)*	*3 (0·001)*	*2 (3·4)*	*2 (< 0·001)*
Urinary tract infection	*3 (5·3)*	*3 (0·002)*	*1 (1·8)*	*1 (< 0·001)*	*0*	*0*
Musculoskeletal and connective tissue disorders	*4 (7·0)*	*4 (0·003)*	*10 (17·5)*	*14 (0·007)*	*6 (10·3)*	*7 (0·003)*
Arthralgia	*1 (1·8)*	*1 (< 0·001)*	*3 (5·3)*	*4 (0·002)*	*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)*
Pain in extremity	*0*	*0*	*1 (1·8)*	*1 (< 0·001)*	*3 (5·2)*	*3 (< 0·001*
Nervous system disorder	4 (7·0)	6 (0·004)	6 (10·5)	9 (0·004)	6 (10·3)	7 (0·003)
Headache	*2 (3·5)*	*2 (0·001)*	*4 (7·0)*	*5 (0·002)*	*4 (6·9)*	*4 (0·002)*
Injury, poisoning and procedural complications	2 (3·5)	2 (0·001)	7 (12·3)	16 (0·008)	3 (5·2)	4 (0·002)
Fall	*0*	*0*	*3 (5·3)*	*8 (0·004)*	*1 (1·7)*	*1 (< 0·001)*

[#]number of infusions; [&]preferred terms in the virtual system organ class (SOC) of Local reactions were not repeated in the SOC of General disorders and administration site conditions. [$]The virtual System Organ Class of Local Reactions included all AEs reported within the MedDRA high level terms "Administration Site Reactions NEC", "Infusion Site Reactions", and "Injection Site Reactions"; [@]the rate per infusion is calculated as number of events divided by the overall number of infusions in the respective treatment groups.

Figure
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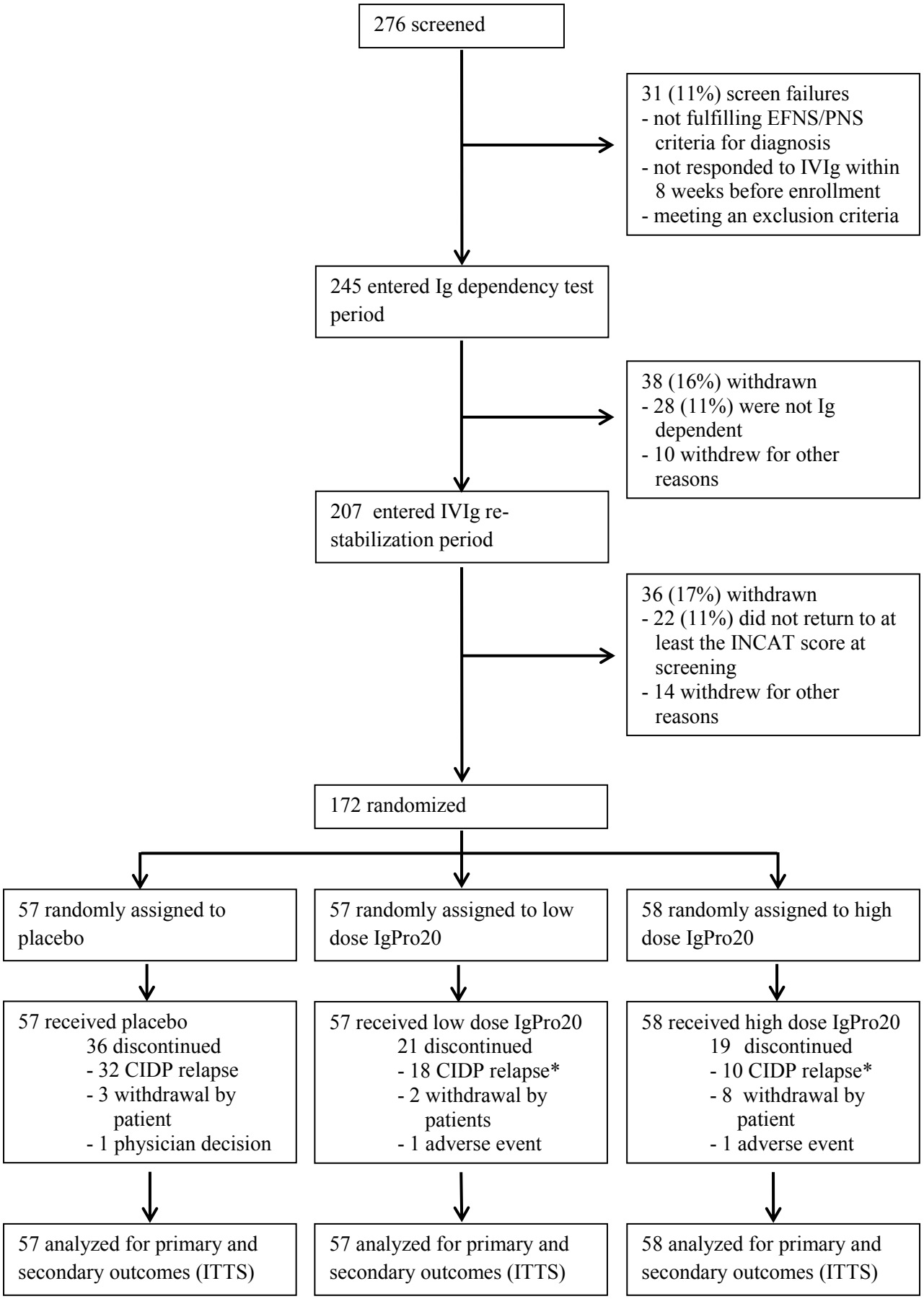
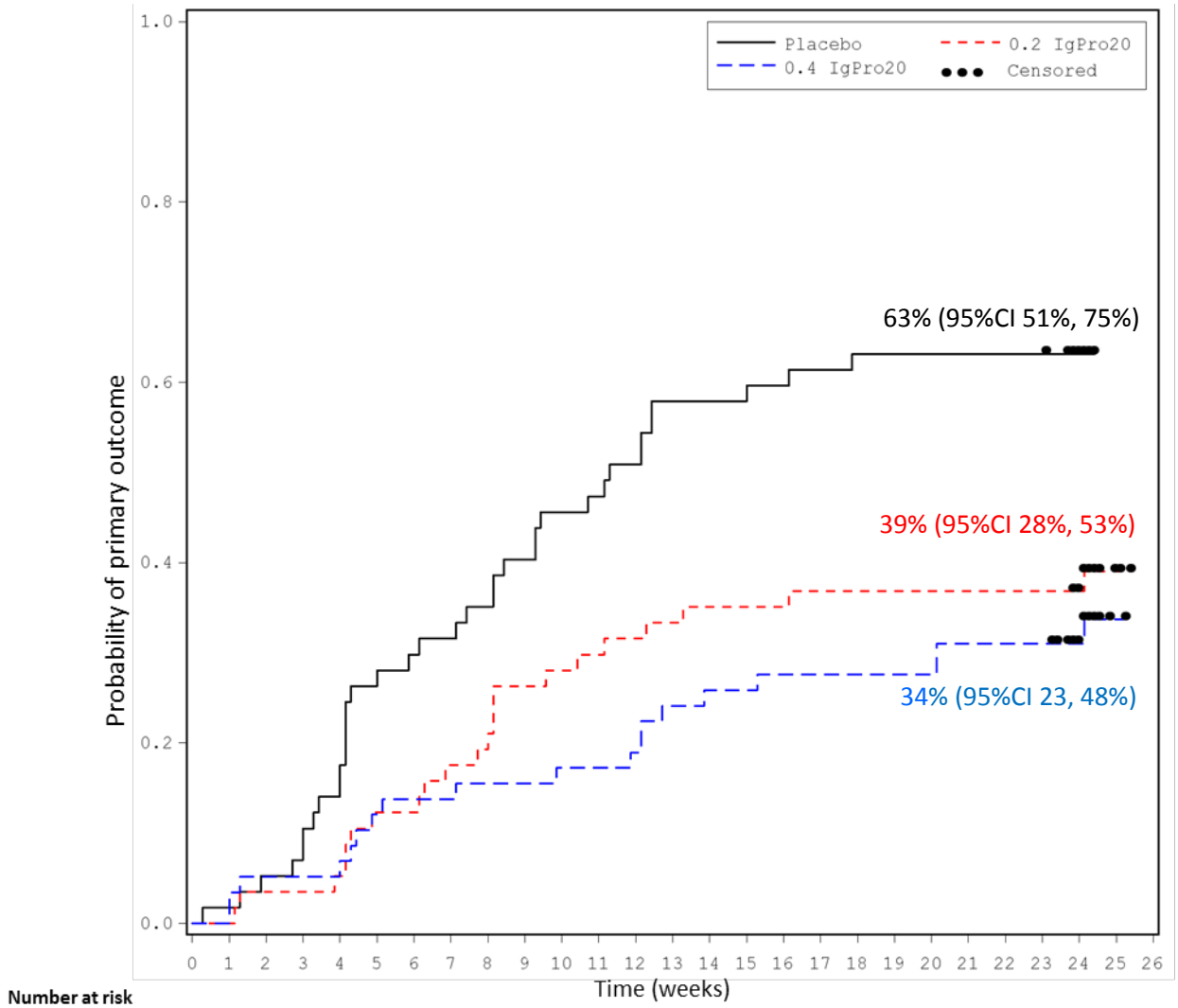


Figure 1.



Number at risk

High dose	58	56	55	51	49	44	42	40	39#
Low dose	57	57	55	50	42	38	36	36	35#
Placebo	57	56	54	41	34	24	22	21	21#

#number of patients censored at completion visit

Figure 2.

figure2

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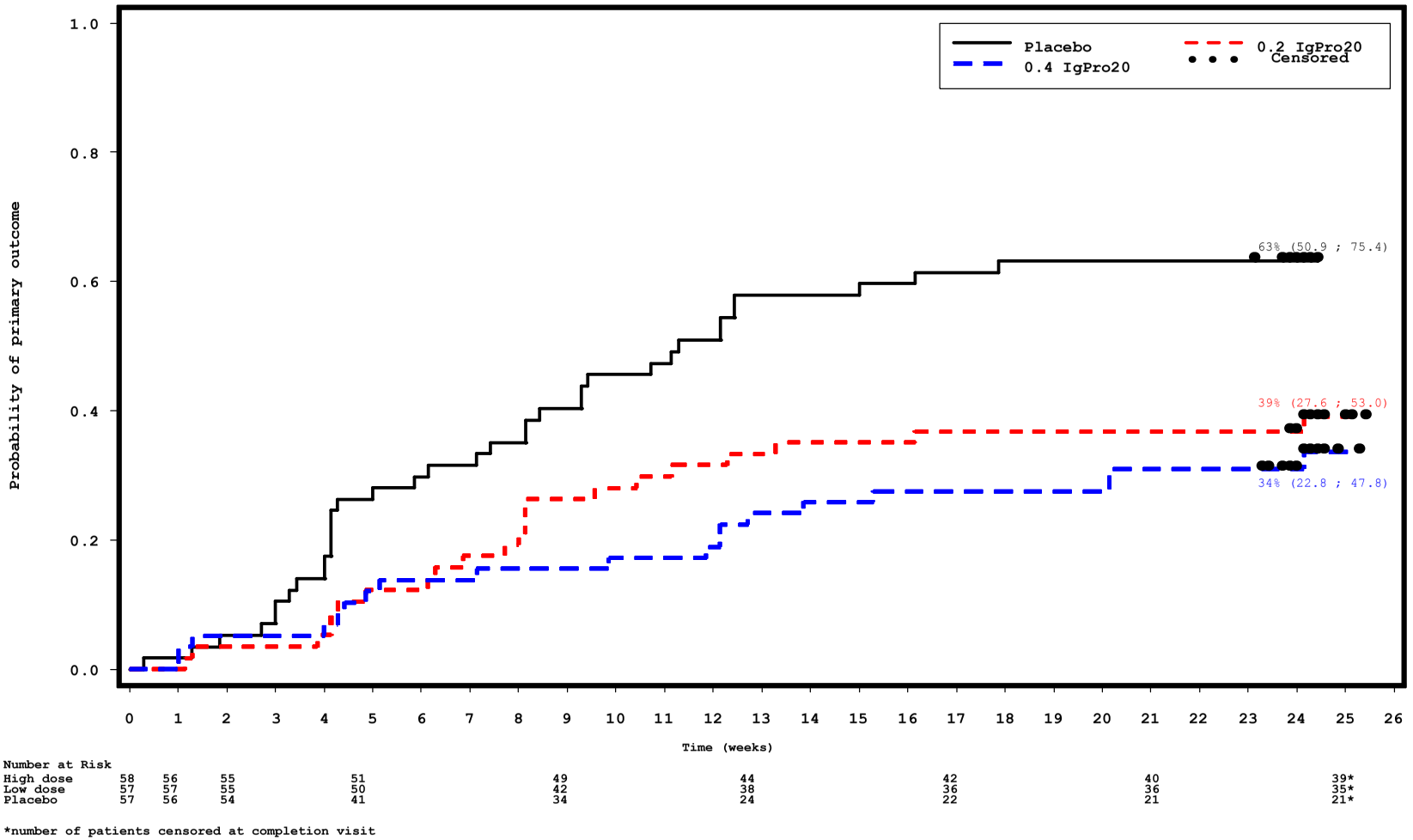

Number at Risk

High dose	58	56	55				51				49				44				42				40				39*
Low dose	57	57	55				50				42				38				36				36				35*
Placebo	57	56	54				41				34				24				22				21				21*

*number of patients censored at completion visit

Supplementary Appendix to
Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (CIDP), a multicenter randomized double-blind placebo-controlled trial: the PATH Study

Table of content page

Table S1. Inclusion and exclusion criteria

Inclusion criteria
Adults (age ≥18 years)
Definite or probable CIDP according to the EFNS/PNS criteria (these criteria were checked by a central medical monitor)
response to IVIg treatment as assessed by the treating physician within 8 weeks before enrollment
Written informed consent
Exclusion criteria
Any polyneuropathy of other causes, including multifocal motor neuropathy; monoclonal gammopathy of uncertain significance with anti–myelin-associated glycoprotein IgM antibodies; hereditary demyelinating neuropathy; polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes syndrome; lumbosacral radiculoplexus neuropathy; polyneuropathy associated with diabetes mellitus; polyneuropathy associated with systemic illnesses ; or drug or toxin induced polyneuropathy.
Any other disease that may cause neurological symptoms and signs, or may interfere with treatment or outcome assessments.
Severe conditions that may interfere with evaluation of the study product or satisfactory conduct of the study, such as current malignancy or history of allogeneic bone marrow/stem cell transplant, cardiac insufficiency (New York Heart Association Classes III/IV), cardiomyopathy, significant cardiac arrhythmia requiring treatment, unstable or advanced ischemic heart disease, congestive heart failure or severe hypertension, chronic kidney disease stage IV and V, known hyperprolinemia, known bleeding disorders, severe skin disease at the planned injection sites, alcohol, drug or medication abuse.
History of thrombotic episodes within the 2 years before enrollment, such as pulmonary embolism, deep vein thrombosis, myocardial infarction, thromboembolic stroke or known hypercoagulable state.
Known allergic or other severe 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.
Treatment with the following medications:
Within 3 months before enrollment: plasma exchange.
Within 6 months before enrollment: cyclophosphamide, interferon, tumor necrosis factor–alpha inhibitors, fingolimod or any other immunosuppressive medications.
Within 12 months before enrollment: rituximab or alemtuzumab.
With a change in treatment within 3 months before enrollment: methotrexate, azathioprine or mycophenolate; patients on corticosteroids not on a maintenance dose (usually below 20 mg/day prednisone equivalent) and where the dosage is likely to be tapered during the duration of the trial; or patients requiring more than 1·6 g/kg IgG every 4 weeks.
Patients with the following laboratory results:
Serum IgA level less than 5% of the lower limit of normal.
Positive result at screening on any of the following viral markers: human immunodeficiency virus-1 or 2, or hepatitis B or C virus.
Abnormal laboratory parameters: creatinine greater than 1·5 times the upper limit of normal (ULN), blood urea nitrogen greater than three times the ULN if the increase is related to potential kidney disease, or haemoglobin less than 10 g/dL.
Fulfilling the following general criteria: inability to comply with study procedures and treatment regimen; mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study; pregnancy or nursing mother; intention to become pregnant during the course of the study; female patients of childbearing potential either not using, or not willing to use, a medically reliable method of contraception for the entire duration of the study or not sexually abstinent for the entire duration of the study or not surgically sterile; participation in another clinical study or use of another investigational medicinal product within 3 months before enrollment; employee at the study site; or spouse/partner or relative of any study staff.

Table S2. PATH Study procedures

IgG dependency test period	
	In this period, no IgG treatment was given. Patients were monitored by collecting grip strength, Inflammatory-Rasch-built Overall Disability Scale (I-RODS), and INCAT total score data every 2 weeks, alternating by a site visit or by phone. Any patient showing a clinically meaningful deterioration that was confirmed by the investigator at the site entered the IVIg restabilization period immediately. A clinically meaningful deterioration was defined as a total INCAT disability score increase by ≥ 1 point, I-RODS deterioration by ≥ 4 points (using the centile metric), or a mean grip strength deterioration by ≥ 8 kiloPascal (kPa) in one hand using the handheld vigorimeter. Patients were instructed on how to self-assess grip strength and I-RODS at home as part of a weekly diary. Patients performed three assessments for each hand in arbitrary order (with approximately 30 seconds rest between each assessment) on a daily basis and at a fixed time during the day. The mean grip strength for each hand was used to determine IgG dependency. Patients who had stable disease or who showed improvement were asked at week 4 to delay the next IVIg administration and to continue with self-assessment of grip strength and I-RODS at home. Patients who did not showed signs of IgG dependency after a maximum of 12 weeks were withdrawn from the study.
IVIg restabilization period	
	In this period, patients received IVIg IgPro10 (Privigen®, CSL Behring, Bern, Switzerland) for up to 13 weeks at the study site. The total dose/volume of IgPro10 was calculated based on the patient's body weight (bw) with a maximum of 200 g. The loading dose was 2 g/kg (week 1) and 1 g/kg at week 4, 7, and 10 and, if necessary, week 13. The infusion rates were in conformity with the recommended rates for IgPro10 and with the market authorization for IgPro10 (Privigen®) with a maximum of 100 g per infusion day. Only patients whose INCAT total score improved to at least the INCAT total score recorded at the screening visit (i.e., ≥ INCAT score at screening) and who maintained a stable INCAT total score at weeks 7 and 10 (or at weeks 10 and 13) were eligible for randomization. All other patients were not randomized and were withdrawn from the study.
SC treatment period	
	Three-arm randomization was performed: one group received IgPro20 at 0·2 g/kg bw plus placebo to match the volume in all three groups, one group received IgPro20 at 0·4 g/kg bw, and one group received only placebo. The total dose/volume of IgPro20 was calculated on the basis of bodyweight. The weekly SC infusion of IgPro20 or placebo were performed on 1 or 2 consecutive days in two sessions using special infusion pumps and started within one week of the last IVIg administration. Multiple injection sites and two pumps could be used depending on the total volume to be administered. The maximum allowed rate was 20 mL/h in week 1, and 35 mL/h for subsequent infusions. The maximum allowed volume per injection site was 20 mL/site in week 1 and 50 mL/site for the subsequent infusions. Patients were advised to change the injection site(s) with each administration. Patients (or their caregiver) were trained to apply SC home therapy during the first four SC treatment sessions at the site. If needed, up to four additional trainings were offered. Patients also received detailed written instructions. A completion visit was performed at SC week 25 for patients who completed the SC treatment period. Patients experiencing a CIDP relapse during the SC treatment period received, within 1 week, IgPro10 as IVIg rescue medication (2 g/kg bw) and underwent a completion visit before the start of the rescue medication. Patients who withdraw for any other reason underwent the completion visit within a week of discontinuation.
Monitoring of treatment compliance	
	To ensure compliance, patients were instructed to follow the treatment instructions carefully and to contact the treating physician/study nurse to discuss any problems with SC infusion. Patients brought their used, partially used, and unused vials of IgPro20/placebo every visit to the site. Treatment compliance was monitored through a drug accountability form checking the unique vial numbers used by a patient and the recorded infusion scheme. Use of patient Drug Application Form (DAF): • In addition to the IgPro20 Accountability Log which had to be completed by the site, there were Subject Drug Application Forms (DAFs) to be completed for each visit after randomization when IgPro20 was dispensed. • The site staff completed the top part of the form with the infusion session instructions. • When subjects were able to do the infusions at home, they had to complete the patient section for each infusion and also per session. • Vial labels had to be stuck on page 2 by patients. • When DAFs were returned by patients, site staff confirmed if required that columns were completed. If not, they asked patients to complete while patients were still onsite. • PI or designee reviews, signed and dated the form and confirmed that patients performed the infusions correctly. Monitoring of compliance • CRAs verified all entries on all subject specific accountability logs, referring to the IXRS Drug Assignment Printout and also compared to vial labels on the Subject DAFs to ensure they matched. • CRAs initialed and dated Subject DAFs once their review was complete, discrepancies were addressed and comments entered by site staff or CRA if applicable. • CRAs also verified infusion start/stop date and time, number of infusion sites and volume against EDC. • CRAs inspected all vials for accountability (returned, expired, and unused) against IXRS inventory. • Once accountability has been completed and no issues remained regarding used vials. The vials were destroyed per the site's drug destruction policy or were returned to depot

Table S3 Protocol amendments

Protocol Amendment	Date of Implementation	Changes Relevant for	
		Pre-randomization Phase	**Post-randomization Phase**
Amendment 1	17 November 2011	Updated with regard to measurements and information on the occurrence of hemolysis	Changes in timing of SC treatment: allowed to be performed on 1 or 2 consecutive days each study week
		Revised inclusion criteria to a less strict definition of pre-study IVIG treatment	A change in dosing for loading and rescue with IVIG: a total dose of ≤ 200 g was to be administered for subjects with a body weight greater than 100 kg
			Improved wording for primary endpoint, without a change to the primary efficacy analysis
Amendment 3 [a]	12 April 2013	'IVIG Withdrawal Period' was changed to the 'IgG Dependency Test Period'. Daily self-assessments (R-ODS score and grip strength) were added to prove subjects´ ongoing need for IVIG	
			The schedule and loading / maintenance dosing for the IgPro10 Rescue Period was revised to match the IgPro10 Restabilization Period. The dosing was continued until the INCAT score was back to the result at the Rescue Reference Visit.
		Addition of laboratory parameters (blood urea nitrogen, gamma-glutamyltransferase)	
		Additional efficacy assessments during the IgPro10 Restabilization Period	
		Collection of additional data on subjects' pre-study IVIG treatment	
		Applicable to Japan only:	
		Assessment of IgPro10 as investigational medicinal product instead of as non-investigational medicinal product	Additional safety assessment at 4 weeks after final administration of IgPro20
		Additional safety assessments: gamma-glutamyltransferase and electrocardiogram	
		Additional efficacy assessments during the IgPro10 Restabilization Period	
		Change in administration of the 2 g/kg bw loading dose of IgPro10: now over 5 days instead of 2 to 5 days	
		Collection of additional data on subjects' pre-study IVIG treatment	
		The addition of Fingolimod in 6b. of the exclusion criteria	
		The addition of Blood Urine Nitrogen in 7c. of the exclusion criteria	
Amendment 4[b]	11 September 2014	Addition of new post-marketing adverse reactions (Thrombotic Events and Aseptic Meningitis Syndrome)	Number of SC infusion sites in parallel no longer specified, focus on maximum rate and volume per site allowed per protocol; volume per infusion site increased to 50 mL
		Addition of interim safety analysis (March 2014) summary, which revealed no additional safety issue	
		Deletion of inclusion criterion #2, reducing the length of time required for pre-study IVIG to 8 weeks	

		Specification of rescreening criteria (1 of 2 criteria must be met) Clarification of IVIG withdrawal criteria Addition of Screening Period details: assessments could now be performed over > 1 visit; eligibility had to be determined before Screening efficacy measurements were performed and Screening IVIG was administered Alignment with current SAP
Amendment 5[b]	08 December 2015	Precautions for IgPro10 were updated to include Transfusion-related Acute Lung Injury Adverse reactions were updated per current safety information (Transfusion-related Acute Lung Injury) Definition of "CIDP relapse" was clarified to be applicable to IgPro10 Restabilization as well as when it occurs during the SC Treatment Period. **Applicable to Japan only:** Safety follow-up telephone call 4 weeks after last SC treatment was only required if the subject didn't roll over into the safety extension study, IgPro20_3004.

bw = body weight; CIDP = chronic inflammatory demyelinating polyneuropathy; IVIG = intravenous immunoglobulin; R-ODS = Rasch-built Overall Disability Scale; SAP = statistical analyses plan; SC = subcutaneous.

a. Amendment 2 was restricted to the Japanese sites and was never submitted to the FDA. The changes were incorporated into Amendment 3. SC extension period relevant for Japan under amendment 2 was covered in a new, separate protocol (IgPro20_3004). b. This amendment included minor text changes to correct errors and / or inconsistencies and / or to provide additional clarifications that are not described above.

Table S4. Quality of life measures and patient preferences, n (%)

	Placebo n=57	Low-dose SCIg n=57	High-dose SCIg n=58
EQ-5D	n=44	n=54	n=53
Mobility			
Maintained	30 (53)	44 (77)	41 (71)
Improved	2 (4)	3 (5)	4 (7)
Worsened	12 (21)	7 (12)	8 (14)
Self-Care			
Maintained	34 (60)	39 (68)	44 (76)
Improved	1 (2)	8 (14)	3 (5)
Worsened	9 (16)	7 (12)	6 (10)
Usual activities			
Maintained	29 (51)	41 (72)	44 (76)
Improved	1 (2)	5 (9)	4 (7)
Worsened	14 (25)	8 (14)	5 (9)
Pain/discomfort			
Maintained	30 (53)	48 (84)	39 (67)
Improved	7 (12)	2 (4)	9 (16)
Worsened	7 (12)	4 (7)	5 (9)
Anxiety/depression			
Maintained	32 (56)	40 (70)	43 (74)
Improved	4 (7)	7 (12)	4 (7)
Worsened	8 (14)	7 (12)	6 (10)
TSQM	n=45	n=54	n=55
Ease of use			
Easy	42 (93)	49 (91)	44 (80)
Difficult	3 (7)	5 (9)	11 (20)
Patient Preference	n=57	n=57	n=58
Prefer current SC treatment	22 (39)	30 (53)	31 (53)
• Prefer the frequency of administration of my current therapy	9 (16)	16 (28)	14 (24)
• Believe that my current therapy offers me more independence for doing the things I want to do	15 (26)	25 (44)	27 (47)
• Seem to feel fewer side effects from my current therapy	7 (12)	14 (25)	15 (26)
• Believe that overall I will spend less time dealing with my current therapy	14 (25)	19 (33)	18 (31)
• My current therapy works better	5 (9)	8 (14)	12 (21)
• Prefer my current therapy for another reason	0	2 (4)	5 (9)
Prefer previous IV treatment	14 (25)	10 (18)	11 (19)
• Prefer the frequency of administration of my previous therapy	5 (9)	2 (4)	5 (9)
• Believe that my previous therapy offers me more independence for doing the things I	3 (5)	3 (5)	4 (7)

want to do			
• Seem to feel fewer side effects from my previous therapy	1 (2)	2 (4)	5 (9)
• Believe that overall I will spend less time dealing with my previous therapy	3 (5)	3 (5)	4 (7)
• My previous therapy works better	8 (14)	7 (12)	4 (7)
• Prefer my previous therapy for another reason	1 (2)	2 (4)	0
No preference	1 (2)	3 (5)	0
Missing	20 (35)	14 (25)	16 (28)

Baseline scores, i.e. the last scores before randomization were compared to the last SC post-dose observation. EuroQoL 5-Dimension Questionnaire (EQ-5D) is a generic measure of health status, consisting of two components: a 0 to 100 mm visual analog scale (VAS) assessing overall health on the day of assessment and five questions covering five health dimensions. More patients in both IgPro20 dose groups maintained and improved their health status on the EQ-5D compared to placebo. This was statistically significant for each health dimension (unadjusted one-sided p-value of < 0·025; statistical testing was not adjusted for multiple testing; these comparisons are therefore considered exploratory). The Treatment Satisfaction Questionnaire for Medication (TSQM, version 1.4) is a 14-item general instrument that measures the major dimensions of satisfaction with a medication. The ease of use is captured with the TSQM on a 7 point scale, ranging from extremely difficult to extremely easy. This set was dichotomized into difficult for the categories: extremely difficult, very difficult, and difficult; and into easy for the categories: somewhat easy, easy, very easy, and extremely easy.
Patient preference for IV or SC treatment was assessed via a questionnaire consisting of three options: prefer current treatment [SCIg], prefer previous treatment [IVIg] and no preference. The patient preference for treatment questionnaire was completed at SC week 9 and at the completion visit.
SCIg = subcutaneous immunoglobulins.

Table S5 Adverse events in relation to infusion volume and infusion rate

	Maximum Volume Infused per Site		
	≤25 mL	**>25 – <50 mL**	**≥50 mL**
Number of Infusions, I	4865	826	46
Any AEs, n (n/l)	271 (0·056)	49 (0·059)	4 (0·087)
Any Causally Related AEs, n (n/l)	127 (0·026)	19 (0·023)	3 (0·065)
Local	83 (0·017)	11 (0·013)	3 (0·065)
Non-Local	44 (0·009)	8 (0·010)	0
	Maximum Infusion Rate per Site		
	<35 mL/h	**35 mL/h**	**>35 mL/h**
Number of Infusions, I	4617	890	229
Any AEs, n (n/l)	258 (0·056)	54 (0·061)	12 (0·052)
Any Causally Related AEs, n (n/l)	132 (0·029)	14 (0·016)	3 (0·013)
Local	89 (0·019)	6 (0·007)	2 (0·009)
Non-Local	43 (0·009)	8 (0·009)	1 (0·004)

Table S6 Serum trough IgG concentrations

	Serum IgG Concentration, g/L											
	Placebo N = 57				Low-dose SCIg N = 57				High-dose SCIg N = 58			
	Result		Change from Baseline		Result		Change from Baseline		Result		Change from Baseline	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	56	16·1 (3·91)	–	–	55	16·3 (2·34)	–	–	58	16·4 (3·20)	–	–
Last SC Post-dose Observation	49	12·3 (4·19)	48	−4·4 (3·40)	53	15·4 (3·06)	51	−0·9 (2·84)	55	20·4 (3·24)	55	4·1 (2·70)

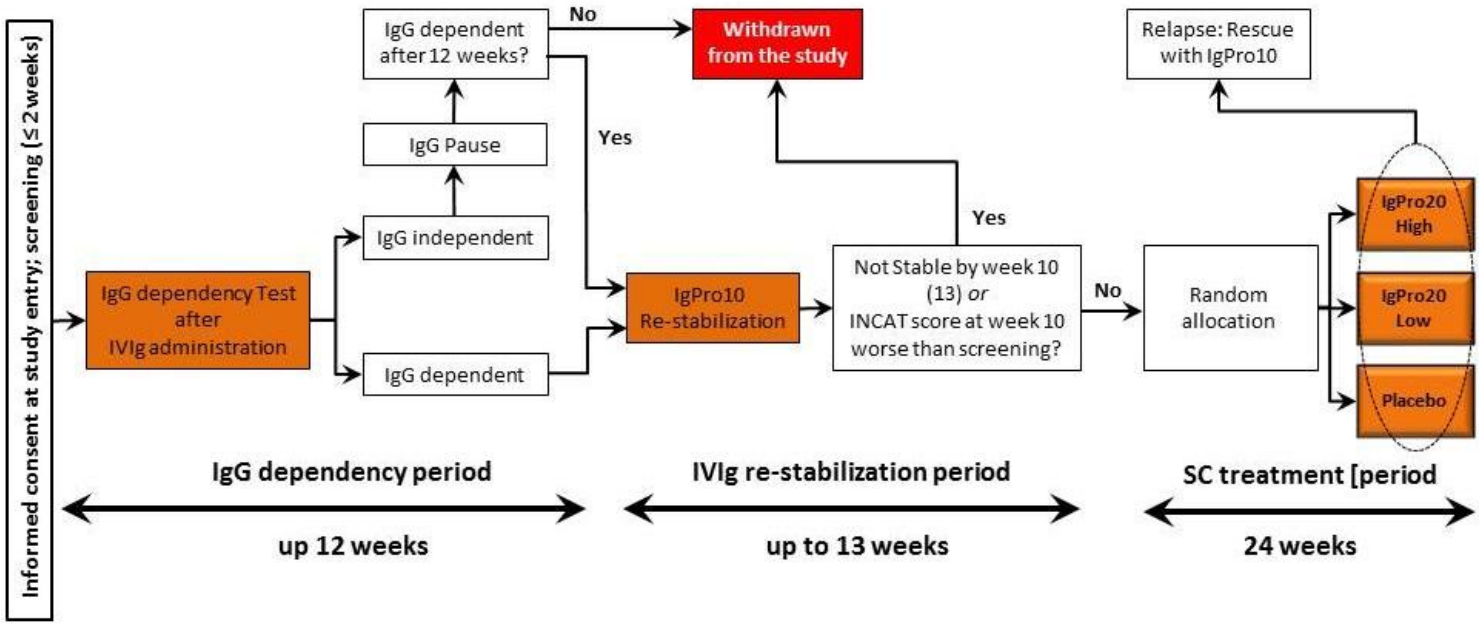

Figure S1. PATH study design
IgG=immunoglobulin G. INCAT=Inflammatory Neuropathy Cause and Treatment. IVIg=intravenous immunoglobulins. SC=subcutaneous.

Primary outcome measure in the ITTS
CIDP=chronic inflammatory demyelinating polyneuropathy. ITTS=intention-to-treat set.
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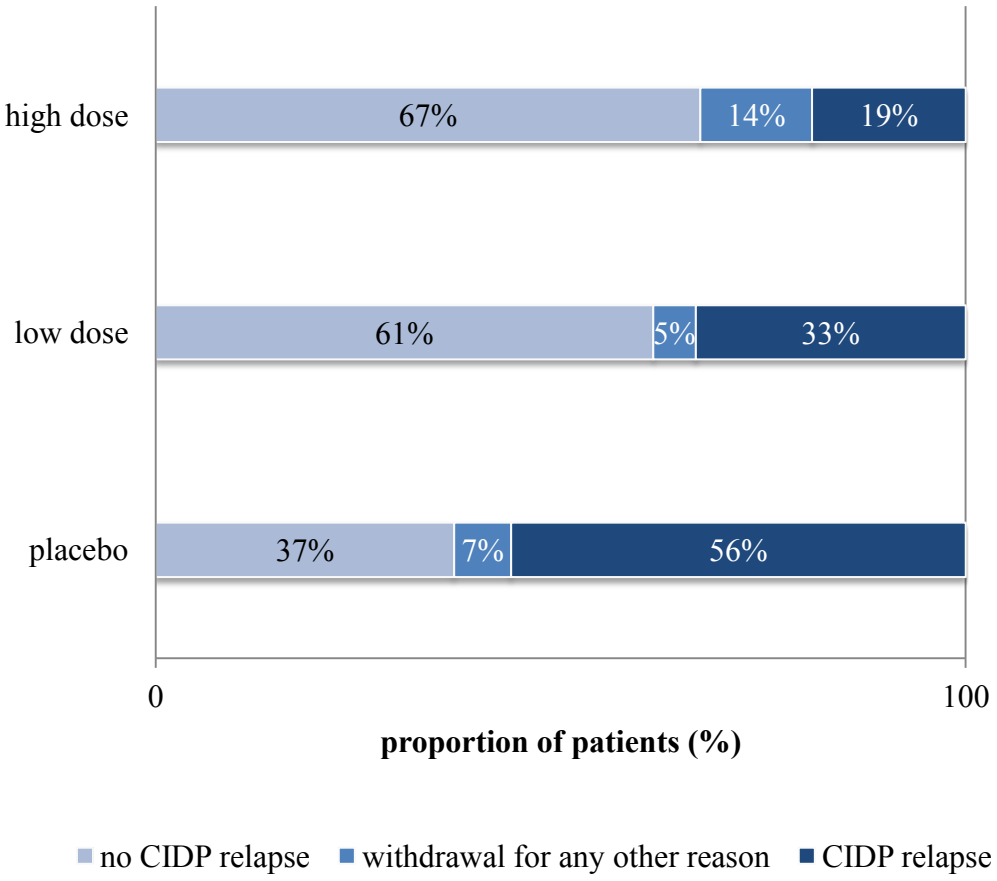

Figure S2. Primary outcome measure in the ITTS
CIDP=chronic inflammatory demyelinating polyneuropathy. ITTS=intention-to-treat set.