Health-related quality-of-life improvements in CIDP with immune globulin IV 10%

The ICE Study

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ABSTRACT

Background: Chronic inflammatory demyelinating polyradiculoneuropathy trials have demonstrated the efficacy of IV immunoglobulin vs placebo. However, these trails have not addressed the long-term impact on health-related quality of life (HRQoL).

Methods: One hundred seventeen patients in a randomized, double-blind, response-conditional crossover trial received immune globulin IV, 10% caprylate/chromatography purified (IGIV-C [Gamunex®]), or placebo every 3 weeks for up to 24 weeks in the first period (FP). Participants whose inflammatory neuropathy cause and treatment disability score did not improve by ≥1 point received alternate treatment in a 24-week crossover period (CP). In either period, participants who improved and completed treatment were eligible to be randomly reassigned to a blinded 24-week extension phase (EP). HRQoL analyses were conducted using the Short Form-36® (SF-36) and the Rotterdam Handicap Scale (RHS).

Results: In the FP, greater improvements in both SF-36 physical and mental component scores were observed with IGIV-C vs placebo, with a significant improvement in the physical component score (difference 4.4 points; 95% confidence interval [CI] 0.7–8.0). Improvements in all SF-36 domains favored IGIV-C vs placebo, with physical functioning, role–physical, social functioning, and mental health reaching significance. Participants receiving IGIV-C experienced a larger improvement in RHS vs those receiving placebo (difference 3.4 points; 95% CI 1.4–5.5; $p = 0.001$). In the CP, similar general trends were observed. In the EP, mean SF-36 improvements were generally improved or maintained in participants who continued IGIV-C therapy; however, worsening was observed in participants re-randomized to placebo.

Conclusions: Long-term therapy with immune globulin IV, 10% caprylate/chromatography purified, improves and maintains health-related quality of life in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology*® 2009;72:1337–1344

GLOSSARY

CI = confidence interval; **CIDP** = chronic inflammatory demyelinating polyradiculoneuropathy; **CP** = crossover period; **EP** = extension phase; **FP** = first period; **HRQoL** = health-related quality of life; **ICE** = IGIV-C CIDP Efficacy; **IGIV-C** = immune globulin IV, 10% caprylate/chromatography purified; **INCAT** = inflammatory neuropathy cause and treatment; **IVIg** = IV immunoglobulin; **LSM** = least squares mean; **RHS** = Rotterdam Handicap Scale; **SF-36** = Short Form-36®.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired peripheral nerve disorder[1,2] characterized by a predominantly symmetric distal and proximal weakness and distal sensory deficits. The disease may lead to considerable long-term activity limitations with possible decrement in health-related quality of life (HRQoL).[1-4] The worldwide prevalence of CIDP is 2 to 7 individuals per 100,000.[5-7] Small randomized trials have demonstrated

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the short-term efficacy of IV immunoglobulin (IVIg) treatment vs placebo, with improvement in strength and daily functionality.[8-12] However, the long-term benefits of IVIg treatment were unclear until the placebo-controlled immune globulin IV, 10% caprylate/chromatography purified (IGIV-C) CIDP Efficacy (ICE) Study reported on the long-term efficacy benefits of IGIV-C treatment.[13]

Despite CIDP being a chronic condition, only one randomized study has reported on the impact of CIDP on HRQoL.[14] This crossover study (n = 25) compared quality-adjusted life years gained with a single IVIg course (6-week assessment) vs 6 weeks of daily prednisolone. A 1-year longitudinal open-label study measured HRQoL in patients with CIDP treated with IVIg (0.4 g/kg/day for 1–2 days; interval, 3–21 weeks) and demonstrated HRQoL improvement in 12 of 13 patients, with a gradual shift of scores toward normative Short Form-36® (SF-36) values.[15] Similar findings were reported in a series of eight patients with CIDP.[16] A larger sample size and a long-term randomized trial were therefore essential for an adequate analysis of the efficacy of IVIg vs placebo on HRQoL because HRQoL does not always parallel disease activity.

METHODS Complete details of the patient population, study design, and methodology are described in the publication of the primary efficacy analysis.[13] Briefly, patients 18 years or older were recruited between April 2004 and June 2005 from 33 centers in Europe, North America, South America, and Israel. Eligible participants had a diagnosis of CIDP, progressive or relapsing motor and sensory dysfunction of at least one limb resulting from neuropathy over the 2 months before study entry, and clinical disability as defined by an overall inflammatory neuropathy cause and treatment (INCAT) disability score of 2 to 9.[17] Exclusion criteria included treatment with steroids (>10 mg/day prednisolone or equivalent), IVIg, or plasma exchange in the 3 months before study entry. The study was approved by the institutional review boards or ethics committees of all participating centers, and all participants provided written informed consent.

This study was a randomized, double-blind, placebo-controlled, response-conditional (rescue) trial and included a first period, a crossover (rescue) period, and an extension phase (figure 1).[13] Eligible participants were randomized to receive either IGIV-C (Gamunex®, Talecris Biotherapeutics, Inc., Research Triangle Park, NC) or placebo (0.1% albumin). Participants received a baseline loading dose of 2 g/kg (commencement of first or crossover periods) and then a maintenance infusion of 1 g/kg every 3 weeks for up to 24 weeks. An adjusted

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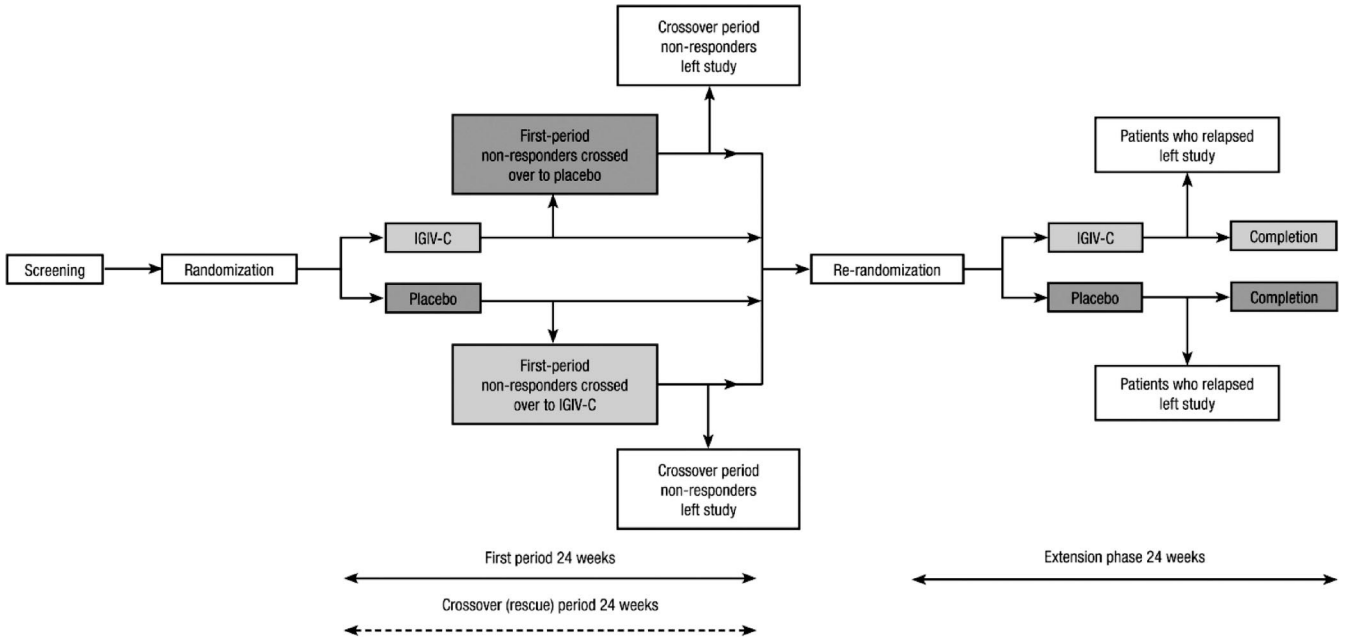
Figure 1 Study design



Eligible patients were randomized to receive either immune globulin IV, 10% caprylate/chromatography purified (IGIV-C), or placebo for up to 24 weeks. If the adjusted inflammatory neuropathy cause and treatment (INCAT) disability score worsened by ≥1 point relative to baseline at any time between day 16 and week 24 or if the adjusted INCAT disability score was stable starting at week 6, the patient crossed over to receive the alternate (rescue) treatment for up to 24 weeks. Patients who responded (≥1-point improvement from baseline) during the first period at week 24 or responded to treatment during the crossover (rescue) period at week 24 were eligible to be re-randomized in a double-blind extension phase for an additional 24 weeks of treatment with IGIV-C or placebo. Reprinted from Hughes RAC et al. IV immune globulin (10% caprylate/chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE Study): a randomized placebo-controlled trial. Lancet Neurol 2008;7:136–144, with permission from Elsevier.[13]

INCAT disability score was applied to assess functional disability at prespecified intervals. Any participant with an adjusted INCAT disability score that worsened from baseline by ≥1 point at any time from day 16 until week 24 during the first period was required to switch to rescue therapy during a crossover period of 24 weeks. Participants who were stable during the first period (no change from baseline in adjusted INCAT disability score) at week 6 or afterward were also required to switch to rescue therapy during a crossover period. This included participants who may have improved from baseline at week 6 but whose adjusted INCAT disability scores returned to baseline levels or lower after week 6. Participants who entered the crossover (rescue) period received the alternate treatment according to the same treatment schedule as the first period. During the crossover period, any participant who did not improve by ≥1 point from baseline on the adjusted INCAT disability score after the first rescue treatment infusion was withdrawn from the study. Participants who improved but subsequently deteriorated to the point where a ≥1-point improvement in adjusted INCAT disability score was no longer maintained also were withdrawn from the study.

Participants who completed either the first period or crossover (rescue) period and responded to therapy (≥1-point improvement from baseline in INCAT disability score that was maintained through week 24) were eligible for inclusion in a 24-week, double-blind extension phase (figure 1). Eligible participants were re-randomized to receive IGIV-C 1 g/kg or placebo every 3 weeks for up to 24 weeks. An adjusted INCAT disability score was assessed every 3 weeks for up to 24 weeks. If the adjusted INCAT disability score worsened from the extension baseline value by ≥1 point at any assessment (i.e., relapsed), the individual was withdrawn from the study.

HRQoL assessments. The SF-36 health survey measured changes in HRQoL, and the Rotterdam Handicap Scale (RHS) assessed participation restrictions. The SF-36 health survey is designed to be completed by participants and is composed of 36 items grouped into eight domains (range for each, 0–100).[15,18] A higher score indicates better health. The RHS is composed of nine items ranked from 0 to 4 by the investigator.[19] The RHS total score ranges from 9 (unable to fulfill any task/activity) to 36 (able to fulfill all applicable tasks or activities) if all questionnaire items are applicable. The SF-36 and RHS scores were recorded at screening/baseline and at the study endpoint of each period/phase. During the first period, the endpoint was defined as week 24 for participants who completed the first period (e.g., without crossing over to rescue therapy) or time of rescue or discontinuation for those participants who did not complete the first period. For the crossover period and extension phase, the endpoint was defined as week 24 or time of study discontinuation.

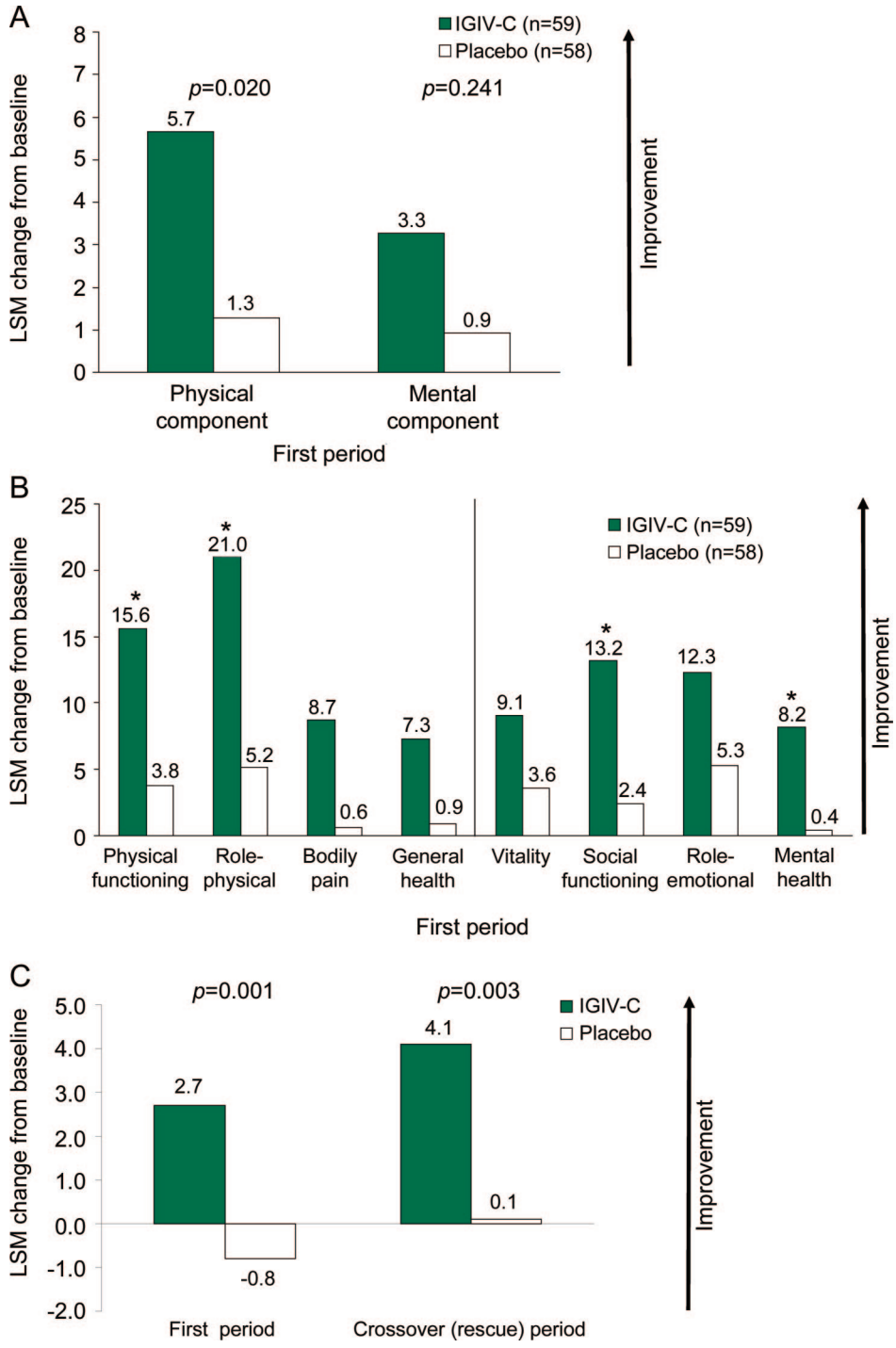
Statistics. Data were evaluated for the intention-to-treat population, defined as all randomized participants. For demographics and baseline characteristic comparisons between the two treatment groups, analysis of variance was used for continuous data, adjusted for geographic region, and a Cochran–Mantel–Haenszel test adjusted for geographic region was used for categorical data. For each period, a last-observation-carried-forward approach was applied for the change from baseline to endpoint, and analysis of covariance was performed to compare treatment differences. The corresponding physical component summary and mental component summary values for the randomized participants were calculated using the reported means, SDs, and factor score coefficients that came from the healthy general US population in 1990. A linear T-score transformation method was used so that both the physical component summary and the mental component summary scores were standardized with a range of 0 (lowest) to 100 (highest).[18] Data are reported as mean ± SD, unless indicated otherwise. All statistical analyses were conducted using SAS, version 8.2 (SAS Institute, Cary, NC).

Table 1 Baseline health-related quality of life and activity and participation limitation scores for first and crossover (rescue) periods

	First period		Crossover (rescue) period	
Characteristic	IGIV-C (n = 59)	Placebo (n = 58)	IGIV-C (n = 45)	Placebo (n = 23)
Short Form-36®				
Physical functioning	30.4 ± 23.1*	30.9 ± 22.8†	28.1 ± 23.4‡	32.1 ± 23.2§
Role-physical	20.7 ± 28.9*	21.0 ± 32.3†	19.2 ± 34.0‡	20.2 ± 35.0‖
Bodily pain	56.5 ± 28.9*	50.2 ± 27.6¶	44.1 ± 28.3‡	56.7 ± 29.8§
General health	47.5 ± 19.0*#	39.6 ± 16.3¶	37.1 ± 17.1‡	43.1 ± 17.5‖
Vitality	44.6 ± 22.7*	37.4 ± 17.6¶	37.3 ± 20.9‡	42.3 ± 17.4§
Social functioning	54.3 ± 29.3*	48.5 ± 23.3¶	42.7 ± 27.3‡	47.2 ± 28.9§
Role-emotional	53.5 ± 40.4*	42.1 ± 41.1¶	42.1 ± 43.6**	50.0 ± 45.2††
Mental health	62.6 ± 22.6*#	52.8 ± 20.0¶	50.0 ± 20.9‡	61.5 ± 18.3‖
Physical component summary	31.1 ± 8.3*	31.2 ± 8.4†	29.7 ± 8.5**	30.1 ± 7.6‡‡
Mental component summary	46.3 ± 12.3*#	41.0 ± 10.8†	40.1 ± 11.4**	43.3 ± 10.4‡‡
Rotterdam Handicap Scale	24.6 ± 6.9	25.5 ± 6.8	23.5 ± 7.5	24.1 ± 7.8§

Data are mean ± SD.
*n = 58; †n = 56; ‡n = 43; §n = 22; ‖n = 21; ¶n = 57; **n = 42; ††n = 20; ‡‡n = 18.
#Baseline scores were significantly higher for mental health, general health perception, and mental component summary in the group treated with immune globulin intravenous, 10% caprylate/chromatography purified (IGIV-C), compared with the placebo group.

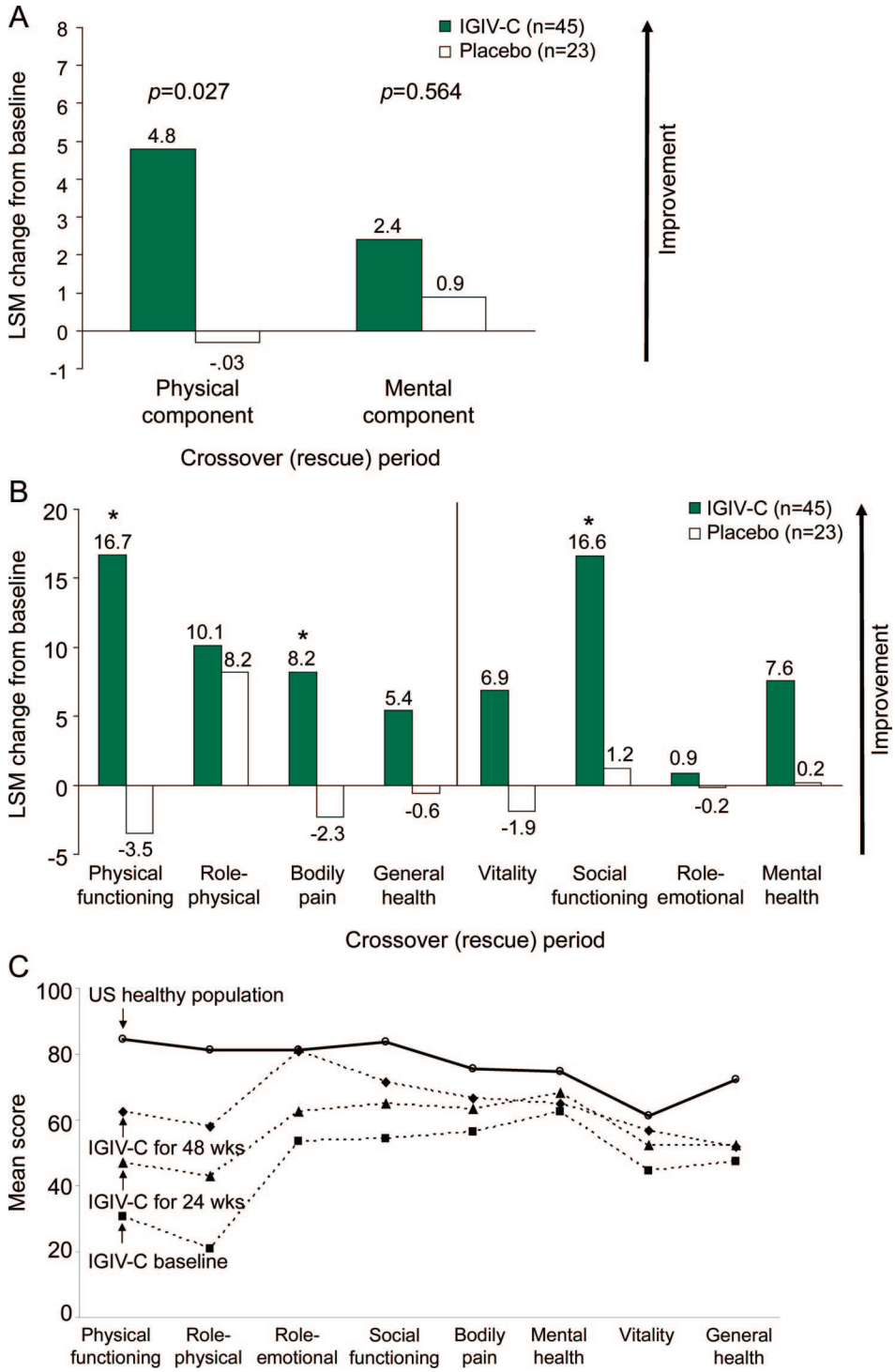
Figure 2 Changes in quality of life: First period and crossover period



During the first period, larger improvements in physical and mental component summary scores of the Short Form-36® (SF-36) were observed with immune globulin IV, 10% caprylate/chromatography purified (IGIV-C), vs placebo (A), with a great difference observed in the physical component summary score ($p = 0.020$). Larger improvements from baseline in all SF-36 domain scores were observed with IGIV-C vs placebo (B), particularly for physical functioning ($p = 0.013$), role-physical ($p = 0.033$), social functioning ($p = 0.044$), and mental health ($p = 0.020$). During the first period, patients treated with IGIV-C experienced an improvement from baseline in the Rotterdam Handicap Scale score compared with patients treated with placebo (C) ($p = 0.001$). Furthermore, during the crossover period, patients treated with IGIV-C experienced an improvement from crossover baseline in the Rotterdam Handicap Scale score compared with patients treated with placebo (C) ($p = 0.003$). *$p < 0.05$. LSM = least squares mean.

RESULTS First period. During the first period, 117 individuals were randomized; 59 participants received IGIV-C, and 58 participants received placebo. In general, baseline values in SF-36 and RHS scores were similar between the two treatment groups, although a few significant differences in some SF-36

Figure 3 Changes in quality of life: Crossover period and extension phase



During the crossover (rescue) period, larger improvements in physical and mental component summary scores of Short Form-36® (SF-36) were observed with immune globulin IV, 10% caprylate/chromatography purified (IGIV-C), vs placebo (A), with a difference observed in the physical component summary score ($p = 0.027$). Larger improvements from baseline in all SF-36 domain scores were observed with IGIV-C vs placebo (B), particularly for physical functioning ($p = 0.002$), bodily pain ($p = 0.026$), and social functioning ($p = 0.021$). An evaluation of changes in SF-36 scores for a subset of patients who received IGIV-C therapy for 48 weeks was compared with a US healthy population sample (C). Of 57 patients who received IGIV-C and completed the first period or crossover period, 31 patients were re-randomized to continue to receive IGIV-C for up to an additional 24 weeks during the extension phase. Twenty-seven of these 31 patients received 48 weeks of IGIV-C treatment (completed study through extension phase), and their mean scores were compared with US healthy population values. A gradual improvement from baseline (■) with IGIV-C maintenance therapy every 3 weeks was observed after 24 weeks (▲) and 48 weeks (◆) in all mean SF-36 domain scores, with a trend toward US normative scores (○) observed. Data from 2,474 healthy volunteers were used to calculate mean normal values.[18] *$p \leq 0.03$. LSM = least squares mean.

Table 2 Improvements in health-related quality of life and activity and participation limitation scores in patients who previously responded to IGIV-C during the first or crossover (rescue) periods and were re-randomized to IGIV-C maintenance or placebo during the 24-week extension phase

Measurement	LSM change from baseline* IGIV-C (n = 31)	Placebo (n = 26)	LSM difference (95% CI)	p Value*
Short Form-36®				
Physical functioning	2.75†	−9.94‡	12.7 (−0.8–26.1)	0.064
Role–physical	1.94†	−8.55‡	10.5 (−9.7–30.7)	0.300
Bodily pain	−0.81§	−11.91‖	11.1 (−0.4–22.6)	0.057
General health	−2.30†	−9.11‖	6.8 (−2.7–16.3)	0.156
Vitality	0.90§	−5.62‖	6.5 (−2.5–15.5)	0.152
Social functioning	−3.50§	−11.18‖	7.7 (−5.5–20.9)	0.248
Role–emotional	12.67†	−10.43‡	23.1 (3.1–43.1)	0.025
Mental health	−2.32§	−4.84‖	2.5 (−5.8–10.8)	0.543
Physical component summary	−0.25¶	−4.55‡	4.3 (−0.8–9.4)	0.098
Mental component summary	−0.21¶	−3.12‡	2.9 (−2.4–8.2)	0.272
Rotterdam Handicap Scale	−1.0§	−2.8	1.8 (−1.1–4.8)	0.210

*Least squares mean (LSM) and *p* values were obtained from the analysis of covariance model with change from baseline as the dependent variable, treatment and region as factors, and the baseline value as the covariate. Response was defined as maintenance of ≥1-point improvement from baseline in adjusted inflammatory neuropathy cause and treatment score through week 24 during the first period or through week 24 after crossover to rescue treatment.
†n = 29; ‡n = 24; §n = 30; ¶n = 27; ‖n = 25.
IGIV-C = immune globulin IV, 10% caprylate/chromatography purified.

domains were observed (table 1). The lowest scores for SF-36 domains at baseline were in role–physical and physical functioning in both the IGIV-C and placebo groups. Treatment with IGIV-C significantly improved the physical component summary score of the SF-36 survey from baseline compared with placebo (treatment difference 4.4 points; 95% confidence interval [CI] 0.7–8.0; figure 2A). Larger improvements from baseline in all domains were observed with IGIV-C than with placebo, with physical functioning, role–physical, social functioning, and mental health achieving significance (figure 2B). Participants treated with IGIV-C also experienced an improvement from baseline in the RHS score compared with participants treated with placebo, with an improvement in the ability to perform daily activities in the IGIV-C group but worsening observed in the placebo group (treatment difference 3.4 points; 95% CI 1.4–5.5; $p = 0.001$; figure 2C).

Crossover (rescue) period. Twenty-three participants treated with IGIV-C and 45 participants treated with placebo during the first period crossed over to receive alternate (rescue) treatment. Therefore, in the crossover (rescue) period, 23 participants were treated with placebo and 45 participants were treated with IGIV-C. Similar to the first period, the largest impairments in SF-36 domains at crossover period baseline were role–physical and physical functioning. Treatment with IGIV-C significantly improved the physical component summary score of the SF-36 survey from baseline compared with placebo to a similar degree as seen during the first period (treatment difference 5.2 points; 95% CI 0.6–9.8; figure 3A). Larger improvements from baseline in all domains were observed with IGIV-C vs placebo, with physical functioning, bodily pain, and social functioning reaching significance (figure 3B). Participants treated with IGIV-C also experienced greater improvement from baseline in the RHS score compared with participants treated with placebo, with an improvement in the ability to perform daily activities in the IGIV-C group but generally no change in the placebo group (treatment difference 4.0 points; 95% CI 1.4–6.5; $p = 0.003$; figure 2C).

Extension phase. All participants who completed the first period or crossover (rescue) period and had responded to treatment (IGIV-C or placebo) were eligible for continuation into a 24-week extension phase. For HRQoL, we analyzed data from the subset of 57 participants who responded to IGIV-C during the first or crossover period (including one individual, identified as a nonresponder, who was re-randomized in error into the extension phase). Of these 57 participants, 31 were re-randomized and continued to receive IGIV-C, and 26 were re-randomized to receive placebo. Extension phase baseline characteristics were similar between the IGIV-C (n = 31) and placebo (n = 26) groups, with a similar mean SF-36 physical component summary score (38.4 ± 10.8 vs 38.4 ± 9.5), mean SF-36 mental component summary score (48.2 ± 11.5 vs 48.3 ± 8.6), and mean RHS score (29.8 ± 5.6 vs 28.3 ± 7.6).

In participants who continued treatment with IGIV-C, mean improvements in SF-36 scores observed during the first period or the crossover period were further improved or at least maintained. However, in participants re-randomized to placebo, general deterioration in SF-36 scores was observed. Greater deterioration in the mean RHS score was also observed with placebo treatment compared with IGIV-C maintenance treatment during the extension phase (table 2).

Comparison with 1990 US normative data. Mean scores for 58 participants randomized to IGIV-C at baseline, 57 participants treated with IGIV-C for 24 weeks, and 27 participants treated with IGIV-C for 48 weeks were compared with US normative values. Twenty-seven participants received IGIV-C for 48

weeks, and mean scores were compared with US normative values (figure 3C). At entry into the first period, mean SF-36 domain scores were substantially lower compared with normative data. With IGIV-C treatment, mean SF-36 scores for each dimension reported by these participants either improved or were maintained. Although all mean SF-36 domain scores, except role–emotional, for this group of individuals remained lower after 48 weeks of IGIV-C therapy vs corresponding normal values, there was a gradual shift toward normal values for all SF-36 domains.

DISCUSSION The ICE Study has demonstrated the efficacy and safety of IGIV-C vs placebo in individuals with CIDP.[13] Improvements from baseline in disability measures assessed by the INCAT disability score, grip strength, Medical Research Council sum score, and INCAT sensory sum score were observed after up to 24 weeks of treatment with IGIV-C vs placebo. Furthermore, the extension phase of the study demonstrated, for the first time, the prolonged benefits of IGIV-C maintenance therapy for individuals who responded to initial IGIV-C therapy.

Given the substantial impact chronic diseases can have on HRQoL and the limited availability of HRQoL data in individuals with CIDP, the ICE Study also evaluated changes in HRQoL, in an exploratory manner, by using two validated measures, SF-36 and RHS. The SF-36 health survey has been previously evaluated as an HRQoL assessment tool in individuals with CIDP.[15] The RHS was also chosen as an assessment tool based on its brevity and ability to capture extended disability measures, including activity limitations and participation restrictions (e.g., social activities), and has also been previously evaluated in individuals with CIDP.[20]

Overall, individuals treated with IGIV-C in the ICE Study experienced larger improvements in HRQoL, activity limitations, and participation restrictions compared with individuals receiving placebo. Although both physically oriented and mentally oriented SF-36 dimensions were positively affected by IGIV-C treatment, a greater impact was observed for the physically oriented dimensions (i.e., physical component summary score, physical functioning, role–physical) vs mentally oriented SF-36 dimensions (i.e., mental component summary score, role–emotional, social functioning, and mental health). Although not all changes from baseline in dimension scores reached significance, overall, IGIV-C treatment resulted in larger improvements compared with placebo treatment. Furthermore, participants treated with IGIV-C experienced a gradual shift over time (48 weeks) in all SF-36 domain and component summary scores toward reported US normative values. These results are supported by earlier findings in a small open-label clinical study that evaluated the efficacy of maintenance treatment with IVIg over 1 year in 13 patients with CIDP.[15] In that study, general increases in SF-36 scores from baseline were observed and exhibited a shift toward normative values. Improvements in SF-36 scores with IGIV-C treatment vs placebo were also supported by significant improvements in RHS scores, a useful tool to assess patient disability.

The SF-36 and RHS both measure aspects of health that are more directly meaningful to individuals than impairment and activity limitation (i.e., disability), which also improved significantly more with IGIV-C treatment vs placebo treatment during the first period, crossover period, and extension phase.[13] Therefore, the results of the analyses in the current article support a clinically significant effect with IGIV-C treatment in individuals with CIDP. Furthermore, to enhance comparability of outcomes in clinical studies through standardization of clinical measures, we propose that SF-36 and RHS be incorporated as exploratory outcomes in future randomized trials in patients with CIDP. These scales have demonstrated clear validity, reliability, and responsiveness in this condition.[15,19,21]

The ICE Study supports the administration of IGIV-C therapy in individuals with CIDP and demonstrates a substantial long-term improvement in functionality, both physical and psychosocial, in this patient population. Assessing HRQoL in chronic conditions such as CIDP is important because HRQoL measures tend to be complementary to traditional assessments of symptoms, signs, clinical laboratory values, and measures of effectiveness in chronic conditions; therefore, HRQoL should be incorporated into clinical trials to capture results from the patient's perspective.[15] Evaluation of HRQoL allows for a more comprehensive assessment of the impact of CIDP on an individual patient and for better management of both the physical and mental components of the disease. The improvement in HRQoL and social participation, as well as activity limitations, further supports maintenance IGIV-C as a first-line therapy in the management of CIDP.

AUTHOR CONTRIBUTIONS

Statistical analyses were conducted by C. Deng.

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