

**Immune Globulin Intravenous (IGIV) For Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (ICE Study)**

<b>Title of the study:</b>	Multicenter, randomized, double-blind, placebo-controlled, study to evaluate the efficacy and safety of IGIV-Chromatography 10% (IGIV-C) treatment in subjects with chronic inflammatory demyelinating polyneuropathy.																										
<b>Publications (references):</b>	Hughes RAC, Donofrio P, Bril V, et al. Randomized placebo-controlled trial of immune globulin intravenous, 10% caprylate/chromatography purified for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy. Lancet Neurology 2008 Feb; 7(2):136-144.																										
<b>Clinical phase:</b>	3																										
<b>Methodology (design of study):</b>	Multi-center, double-blind, parallel group, placebo-controlled, prospective study with two randomized study periods that included a requirement of Rescue treatment with the alternate study drug in case of worsening in adjusted INCAT score during the Efficacy Period. Responders in adjusted INCAT score after a full 24 week treatment period during the Efficacy Period or Rescue Treatment entered into the re-randomized, double-blind 24 week Randomized Withdrawal Period.																										
<b>Number of subjects:</b>	<p>The study population consisted of 117 subjects randomized to either Gamunex® or Placebo in the Efficacy Period.</p> <p>An overview of the number of subjects in the different study periods and their distribution between the two treatment groups are shown below:</p> <table border="1"> <thead> <tr> <th colspan="4"><b>Number of subjects</b></th> </tr> <tr> <th></th> <th>IGIV-C N</th> <th>Placebo N</th> <th>Total N</th> </tr> </thead> <tbody> <tr> <td>Randomized</td> <td>59</td> <td>58</td> <td>117</td> </tr> <tr> <td>Efficacy Period</td> <td>59</td> <td>58</td> <td>117</td> </tr> <tr> <td>Rescue Treatment</td> <td>45</td> <td>23</td> <td>68</td> </tr> <tr> <td>Randomized Withdrawal Period</td> <td>43</td> <td>31</td> <td>73</td> </tr> </tbody> </table>			<b>Number of subjects</b>					IGIV-C N	Placebo N	Total N	Randomized	59	58	117	Efficacy Period	59	58	117	Rescue Treatment	45	23	68	Randomized Withdrawal Period	43	31	73
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<b>Test product:</b>	Immune Globulin Intravenous (Human), 10%, Caprylate / Chromatography Purified (IGIV-C; Gamunex®)																										
<b>Duration of treatment:</b>	The maximum duration of the Efficacy Period, Randomized Withdrawal Period and Rescue treatment Phase was 24 weeks each. Only a subset of subjects would have required Rescue treatment with alternative study drug. The maximum duration of either IGIV-C or Placebo given to an individual subject was 48 weeks.																										

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**Statistical methods:** The primary efficacy endpoint was the comparison of the Responder rates in the Intent to Treat (ITT) population. Treatment group differences were tested by a Chi-square test. Subjects who did not complete the 24 week Efficacy Period and entered Rescue treatment with the alternative treatment were counted as Non-responders. As a supportive analysis a Cochran-Mantel-Haenszel test, adjusted for regions, was performed.

For secondary efficacy endpoints, analysis of covariance was used to compare the treatment differences for change from baseline in proximal amplitude of the most severely affected motor nerve, and change from baseline in grip strength. Kaplan-Meier estimates and log-rank test were used to compare the treatment difference for time to relapse in the Randomized Withdrawal Period.

**Summary of efficacy:** Primary endpoint

The primary efficacy objective was the comparison of IGIV-C and Placebo group Responder rates, using the adjusted Inflammatory Neuropathy Cause And Treatment (INCAT) score in the Efficacy Period as the primary outcome measure. An Efficacy Period Responder was defined as a subject with  $\geq 1$  point improvement in the adjusted INCAT score, with the improvement maintained through the end of Week 24 in the Efficacy Period. The primary analysis of the Responder rate was statistically significant - 54.2% for IGIV-C and 20.7% for Placebo during the Efficacy Period ( $P < 0.001$ .)

Secondary endpoints

Two of the three secondary endpoints reached statistical significance.

- a. The mean change in proximal amplitude in the most severely affected motor nerve during the Efficacy Period was  $69 \pm 1.86$  millivolt (mV) for IGIV-C group and  $0.47 \pm 2.28$  for the Placebo group. The point estimate of the treatment difference between IGIV-C and Placebo was 24 mV and its 95% confidence interval (CI) was -0.53 mV to 1.00 mV. This did not reach statistical significance ( $P = 0.542$ ).

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- b. The mean change in dominant hand grip strength during the Efficacy Period was  $13.2 \pm 19.3$  kPa for the IGIV-C group and  $1.5 \pm 15.6$  kPa for the Placebo group. The point estimate of the treatment difference between IGIV-C and Placebo for the dominant hand was 10.94 kPa and its 95% CI was 4.65 kPa to 17.22 kPa. The mean change in the non-dominant hand was  $13.3 \pm 17.4$  kPa for the IGIV-C group and  $4.3 \pm 14.9$  kPa for the Placebo group. The point estimate of the treatment difference between IVIG-C and Placebo for the non-dominant hand was 8.63 kPa and its 95% CI was 2.62 kPa to 14.64 kPa. The greater increases in grip strength with IVIG-C treatment than with Placebo treatment were statistically significant for the dominant hand ( $P < 0.001$ ) and for the non-dominant hand ( $P = 0.005$ ).
- c. The time to relapse, for subjects who were IVIG-C Responders or IVIG-C Rescue Successes, during the Randomized Withdrawal Period, was longer for the 31 subjects re-randomized to treatment with IGIV-C than for the 26 subjects re-randomized to treatment with Placebo. This treatment difference was statistically significant ( $P = 0.011$ ).

**Summary of safety:** A total of 113 subjects were exposed to IGIV-C and 95 subjects to Placebo. Subjects receiving Placebo had higher rates of entry into Rescue treatment and higher rates of study discontinuation, primarily due to deterioration of adjusted INCAT scores. Subjects remained on Placebo treatment for a mean duration of  $14.1 \pm 12.0$  weeks, which was about 50% of the mean duration of  $23.8 \pm 16.4$  weeks that subjects remained on IGIV-C. The total number of single infusions of IGIV-C in the study was 1096, and the total number of Placebo infusions was 575.

The overall incidence rate of Treatment Emergent Adverse Events (TEAEs) was 75% for IGIV-C treatment and 47% for Placebo treatment. The incidence density of TEAEs, i.e., the number of TEAEs per infusion, was calculated. The overall incidence density of TEAEs was 0.344 for IGIV-C treatment and 0.209 for Placebo treatment. Total serious adverse events (SAEs) were 0.008 and 0.019, respectively.

'Headache' was the most frequently reported TEAE. Besides 'headache', the most common TEAEs were 'pyrexia', 'dizziness', 'asthenia', 'chills', 'back pain', 'arthralgia', 'nausea' or 'abdominal pain'. The incidence densities for 'headache' were 0.052 for IGIV-C and 0.026 for Placebo, 'pyrexia' (0.025 and 0, respectively), 'rash' (0.012 and 0.002, respectively), and 'influenza-like illness' (0.012 and 0.002, respectively).

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There was one death in this study. One subject, who had received IGIV-C during the Efficacy Period and Placebo during the Rescue treatment, developed fatal sepsis three months after she had withdrawn from the study due to insufficient therapeutic effect. Neither the preceding CIDP relapse, which occurred when the subject was receiving Placebo, nor the sepsis was considered by the investigator to be drug-related.

During this study, no new safety issues occurred for the various hematological, chemistry, or urine microscopic examination tests.