

Immune Globulin Intravenous (IGIV) To Treat Relapsing, Remitting Multiple Sclerosis (PRIVIG)

Title of the study:	Randomized, Double-Blind, Placebo-Controlled Study to Compare the Effects of Different Dose Regimens of IGIV- Chromatography (IGIV-C), 10% Treatment on Relapses in Patients with Relapsing Remitting Multiple Sclerosis (PRIVIG)
Principal Investigator:	Fred D Lublin, MD, Mount Sinai School of Medicine, New York, NY 10029 USA
Study center(s):	The study was conducted at 31 study centers: 1 in Austria, 3 in Canada, 4 in the Czech Republic, 8 in Germany, 1 in the United Kingdom, 1 in Greece, 4 in Hungary, 1 in Israel, 4 in Poland, and 4 in the United States of America.
Publications (references):	Fazekas F, Lublin FD, Li D, Freedman MS, Hartung HP, Rieckmann P, Sørensen PS, Maas-Enriquez M, Sommerauer B, Hanna K; PRIVIG Study Group; UBC MS/MRI Research Group. Intravenous immunoglobulin in relapsing-remitting multiple sclerosis: a dose-finding trial. <i>Neurology</i> . 2008 Jul 22;71(4):265-71
Period of study:	02 Dec 2002 (first subject's first visit) to 08 Feb 2005 (last subject's last visit)
Clinical phase:	2
Methodology (design of study):	Multi-national, randomized, double-blind, placebo-controlled prospective trial with 3 parallel groups. The treatment groups were stratified to the presence or absence of Gadolinium-enhancing (Gd-enhancing) lesions on T1 at baseline.
Number of patients:	128 subjects were randomized, 45 to the Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified (IGIV-C) 0.2 g/kg group, 42 to the IGIV-C 0.4 g/kg group, and 41 to the placebo group. 113 subjects completed the study, 38 in the IGIV 0.2 g/kg group, 38 in the IGIV 0.4 g/kg, and 37 in the placebo group. 127 of the 128 randomized subjects were included into the Intent to Treat (ITT) population. The ITT population consisted of 74.8% women and 25.2% men with a median age of 33.1 ± 8.0 years. With the exception of 3 Blacks and 1 Hispanic, all other subjects (96.9%) were Caucasians.
Diagnosis and main criteria for inclusion:	<ul style="list-style-type: none"> - Diagnosis of multiple sclerosis (MS) (McDonald Criteria) - Additional diagnosis of relapsing-remitting course of MS defined as periods of worsening of neurological function with full recovery or with sequelae and residual deficit upon recovery (periods between disease relapses characterized by a lack of disease progression) - Active disease with at least 1 defined documented relapse in the past year

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<p>Test product, dose and mode of administration:</p>	<p>Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified (IGIV-C; Gamunex®).</p> <p>The 2 IGIV-C dose groups were:</p> <ul style="list-style-type: none"> - 0.2 g/kg body weight/infusion (2 mL/kg bw) - 0.4 g/kg bw/infusion (4 mL/kg bw) <p>For blinding purposes, all subjects were to receive the same total volume as the 4 mL/kg bw dose group. For subjects receiving 0.2 g/kg bw of IGIV-C, the final volume of 4 mL/kg bw was to be adjusted with dextrose 5%.</p> <p>The maximum amount available per infusion was 400 mL (8 vials) calculated for a patient with a body weight of 100 kg. The suggested initial infusion rate was 0.02 mL/kg/min for the first 15 minutes. If there was no evidence of a hypersensitivity reaction, the infusion could be given at a slowly increasing rate over the next 30 minutes up to a maximum rate of 0.08 mL/kg/min.</p>
<p>Duration of treatment:</p>	<p>48 weeks (infusion every 4 weeks); 12 infusions in total.</p>
<p>Reference therapy, dose and mode of administration:</p>	<p>Placebo was supplied as Albumin (Human), USP, ie, albumin 5% or albumin 25% and diluted with either dextrose 5% or saline to a final concentration of 0.1% albumin. The infused volume was identical to that of the IGIV-C 0.4 g/kg dose group.</p>
<p>Criteria of evaluation:</p>	<p>Primary efficacy variable:</p> <ul style="list-style-type: none"> - Proportion of relapse free subjects during the study period, based on all reported relapses. <p>Secondary efficacy variable:</p> <ul style="list-style-type: none"> - Cumulative number on combined unique active lesions (new Gd-enhancing lesions on T1, non-enhancing new lesions on T2, enlarging lesions on T2) <p>Safety variables:</p> <ul style="list-style-type: none"> - Adverse events, laboratory data, vital signs, electrocardiogram

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Statistical methods:	<p>Statistical tests were performed for the primary endpoint using the Cochran-Mantel-Haenszel (CMH) test, with adjustment to the stratification factor at baseline, as two-sided tests in a hierarchical way. First, the 2 IGIV-C treatment groups combined were to be tested for treatment differences versus the placebo treatment group ('proof of principle'). If this comparison resulted in a <i>P</i> value of 0.05 or less, then the pair wise comparisons among two IGIV-C treatment group and placebo group were performed ('dose finding').</p> <p>For the secondary endpoint variables, treatment group comparisons were performed with corresponding contrast statements in analysis of variance (ANOVA) models based on all 3 treatment groups. In case that baseline values were available (eg, magnetic resonance imaging data; MRI) the ANOVA was replaced by an analysis of covariance (ANCOVA) using baseline values as covariate.</p>																					
Summary of efficacy:	<p>The proportion of relapse free subjects was 68.3% in the placebo group and 58.1% in the combined IGIV-C group, irrespective of the stratum (presence/absence of Gd-enhancing lesions). At least 1 relapse was reported for 31.7% of the subjects treated with placebo and for 41.9% of the subjects treated with IGIV-C. Comparing these proportions of relapse-free subjects by a CMH test resulted in <i>P</i> = 0.285. The difference in relapse rate between the placebo and IGIV-C groups was not statistically significant. A summary of the results for the primary efficacy parameter is shown for the ITT population in the following table.</p> <p style="text-align: center;">Proportion of relapse free subjects based on all reported relapses (ITT population)</p>																					
	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">Stratum</th> <th style="text-align: center;">Both IGIV-C Groups N = 86 n (%)</th> <th style="text-align: center;">Placebo Group N = 41 n (%)</th> </tr> </thead> <tbody> <tr> <td>Total</td> <td style="text-align: center;">50/86 (58.1)</td> <td style="text-align: center;">28/41 (68.3)</td> </tr> <tr> <td><i>P</i> value (CMH; primary analysis)^a</td> <td colspan="2" style="text-align: center;">0.285</td> </tr> <tr> <td>T1-positive (initial stratification)</td> <td style="text-align: center;">22/40 (55.0)</td> <td style="text-align: center;">11/15 (73.3)</td> </tr> <tr> <td>T1-negative (initial stratification)</td> <td style="text-align: center;">28/46 (60.9)</td> <td style="text-align: center;">17/26 (65.4)</td> </tr> <tr> <td>T1-positive (re-stratification)</td> <td style="text-align: center;">22/40 (55.0)</td> <td style="text-align: center;">13/18 (72.2)</td> </tr> <tr> <td>T1-negative (re-stratification)</td> <td style="text-align: center;">28/46 (60.9)</td> <td style="text-align: center;">15/23 (65.2)</td> </tr> </tbody> </table> <p>^aCMH adjusted to stratification factor (presence/absence of Gd-enhancing lesions) at baseline T1-positive: Gd-enhancing lesions on T1 present at baseline T1-negative: Gd-enhancing lesions on T1 absent at baseline</p>	Stratum	Both IGIV-C Groups N = 86 n (%)	Placebo Group N = 41 n (%)	Total	50/86 (58.1)	28/41 (68.3)	<i>P</i> value (CMH; primary analysis) ^a	0.285		T1-positive (initial stratification)	22/40 (55.0)	11/15 (73.3)	T1-negative (initial stratification)	28/46 (60.9)	17/26 (65.4)	T1-positive (re-stratification)	22/40 (55.0)	13/18 (72.2)	T1-negative (re-stratification)	28/46 (60.9)	15/23 (65.2)
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Immune Globulin Intravenous (IGIV) To Treat Relapsing, Remitting Multiple Sclerosis (PRIVIG)**Summary of efficacy
(continued):**

For the calculation of the secondary efficacy parameter, the cumulative number of unique newly active lesions, different statistical methods were applied for the replacement of missing data (ie, replacement by averaged number, by last value observation carried forward, by best value, and by worst value). With regard to the data obtained with the method of replacement by the averaged number, the cumulative number of unique newly active lesions was 5.0 (median; range: 0.0-538.0) in the IGIV-C group and 7.2 (median; range: 0.0-218.0) in the placebo group. Using the least square means from ANCOVA (main effect model with burden of disease volume as covariate; missing values replaced by averaged number), the treatment difference was 8.24 lesions (combined IGIV-C group minus placebo group) with a 95% confidence interval ranging between -13.65 and 30.13 lesions ($P=0.46$), ie, no difference was seen between the combined IGIV-C and placebo groups.

A summary of the results for the secondary efficacy parameter is shown for the ITT population in the following table.

Unique newly active lesions (ITT population)

	Both IGIV-C Groups		Placebo Group	
	N	Mean \pm SD median [range] or n/N (%)	N	Mean \pm SD median [range] or n/N (%)
Cumulative number of unique newly active lesions at Week 48 ^a	84	29.72 \pm 71.11 5.0 [0.0; 538.0]	40	18.02 \pm 37.12 7.2 [0.0; 218.0]
<i>P</i> value (ANCOVA)		0.46		
Averaged number of unique newly active lesions ^b	84	3.71 \pm 8.89 0.63 [0.00; 67.25]	40	2.25 \pm 4.64 0.90 [0.00; 27.25]
Number of subjects with \geq 1 unique newly active lesions		67/86 (77.9)		32/41 (78.0)
^a Missing values were replaced by the averaged number unique newly active lesions				
^b Averaged numbers of all documented MRI data per subject (no replacement of missing data)				

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Summary of safety: Treatment emergent adverse events were reported for 70.1 % of the IGIV-C treated and 78.0% of the placebo treated subjects. Three subjects in the combined IGIV-C group and 2 in the placebo group had adverse events were of severe intensity. No subject died during the study.

39.1% of subjects in the combined IGIV-C group and 46.3% in the placebo group experienced adverse events that were infusion-related. 'Headache', 'nausea' and 'arthralgia' were the most frequent infusion-related adverse events. Headache occurred in 4 subjects in the IGIV-C 0.4 g/kg group, 4 subjects in the IGIV-C 0.2 g/kg group, and 2 subjects in the placebo group. Nausea occurred in 3 subjects in the IGIV-C 0.4 g/kg group, 1 subject in the IGIV-C 0.2 g/kg group, and no subjects in the placebo group. Arthralgia occurred in 1 subject in the IGIV-C 0.4 g/kg group, 1 subject in the IGIV-C 0.2 g/kg group, and 2 subjects in the placebo group.

The incidence rate of adverse events considered drug-related was 31.0% in the IGIV-C 0.4 g/kg group, 17.8% in the IGIV-C 0.2 g/kg group, (24.1% of subjects in the combined IGIV-C group), and 19.5% in the placebo group. The event most frequently classified as drug-related in all treatment groups was 'headache' (2 subjects of the IGIV-C 0.2 g/kg group, 3 subjects of the IGIV-C 0.4 g/kg group, and 2 subjects of the placebo group). Fatigue occurred in 1 subject in the IGIV-C 0.4 g/kg group, 2 subjects in the IGIV-C 0.2 g/kg group, and 1 subject in the placebo group.

Three subjects (3.4%) of the combined IGIV-C group and 3 subjects (7.3%) of the placebo group experienced serious adverse events. None of these serious adverse events was considered drug-related by the investigators, but 1 subject (IGIV-C, 0.2 g/kg group) discontinued the study upon the diagnosis of vasculitis.