2 SYNOPSIS

Sponsor: Kedrion S.p.A. 55051 Castelvecchio Pascoli (Lucca), Italy

Products used: Ig VENA 10g/200 ml AIC No. 025266178, SOLU-MEDROL 500 mg AIC No. 023202056, Placebo

Title of the study: Double-blind controlled Phase III study on the tolerability and efficacy of long-term treatment with high doses intravenous immunoglobulins (IVIG) versus high doses IV methylprednisolone (IVMP) in chronic inflammatory demyelinating poliradiculoneuropathy (CIDP).

Study Period: August 2007- April 2011	**Study Phase**: III

Objectives:
The primary objective of the study was to determine whether treatment with intravenous immunoglobulin (IVIG) was better tolerated and/or more effective than high-doses IV methylprednisolone (IVMP) in achieving clinical improvement of CIDP (at 15 days) and maintenance of long-term results (6 months). This has been assessed by comparing the proportion of patients who suspended IVIG with those who suspended IVMP as a result of side effects or treatment ineffectiveness (non-response or clinical deterioration) during the 6 months of treatment.

The secondary objective was to assess whether treatment with IVIG was more effective than high-dose IV methylprednisolone (IVMP) in preventing relapses in the 6 months following the suspension of therapy.

Methods:
Multicentre, randomized, controlled double-blind study.
Patient were randomly allocated to receive IVIG treatment and IVMP placebo or IVMP treatment and IVIG placebo with the use of computerized methods of randomization.

Number of patients:
46 patients were enrolled and 45 (21 in the IVMP and 24 in the IVIG arm respectively) evaluable for the assessment of the efficacy primary endpoint

Patients' characteristics and inclusion/exclusion criteria:

Inclusion criteria:

1. The patient must be suffering from a typical CIDP diagnosed according to the clinical, neurophysiologic and instrumental criteria set by: "European Federation of Neurological Societies/Peripheral Nerve Society guidelines on management of chronic inflammatory demyelinating poliradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS)" (Journal of Peripheral Nervous System, 2005; 10 (3): 220-228).
2. The patient must be in stationary condition or in an active phase of the disease without spontaneous improvement.
3. The patient must be over 18 years old and have signed the informed consent.
4. The patient must have a significant disability of the upper and lower extremities based on the INCAT ONLS scale (scoring 2 or more in the upper lower extremities), or based on the Rankin scale (scoring 2 or more).

Exclusion criteria:

1. Atypical CIDP defined according to EFNS/PNS.
2. Presence of associated diseases that can cause neuropathy such as diabetes, IgM monoclonal gammopathy with anti-MAG or anti-sulfatides antibodies (the presence of IgG or IgA monoclonal gammopathy is not an exclusion criteria), cancer, HCV or HIV infection, vasculitides, systemic lupus erythematous (SLE), hypothyroidism, and cryoglobulinemia.
3. Ongoing or planned pregnancy.
4. Serious systemic disease or concomitant condition which represents a contraindication to steroid use (heart failure, peptic ulcer, cataract, uncontrolled hypertension, history of psychosis or schizophrenia) or for IVIG use (renal insufficiency, allergic reactions to IVIG).
5. Treatment with steroid doses >25 mg/every-other-day or 12.5 mg/day p.o. or IV in the previous 3 months (the patient can be treated with maintenance oral doses of steroids equal to or less than 25 mg /every-other-day or 12.5 mg /day, provided that these have not been increased in the last 3 months).
6. Treatment with IVIG in the previous 8 weeks.
7. History of non-response or intolerance to adequate doses of steroids (methylprednisolone IV 0.5 g for at least 3 consecutive days or prednisone orally 1 mg/kg day for at least 1 month) or IVIG (2g/kg in 5 days or less).
8. Increase in the dose of any other immunosuppressive drug in the 12 months prior to admission.
9. Multineuropathic clinical and electrophysiological involvement, exclusively motor, compatible with a diagnosis of multifocal motor neuropathy.
10. Subjects will be excluded from the study in presence of any condition that in the Investigator`s opinion may interfere with the evaluation of study results.
11. Subjects who had participated in a clinical trial with another product within one month (30 days) from enrollment or subjects who do not wish to give their consent to participate will be excluded from the study.
12. Number of leukocytes >10/mm^3 at exam of the cerebrospinal fluid (CSF), if this was necessary to make the diagnosis of CIDP, defined according to EFNS/PNS.

Study product, dosage and administration route:

Ig VENA (Human normal immunoglobulins for intravenous use - 10 g/200 ml)
Dosage: 2 g/kg in 4 consecutive days, every 28 days (± 3 days) x 6 months;
Administration route: intravenous

SOLU-MEDROL (methylprednisolone sodium succinate for intravenous use - 500 mg)
Dosage: 0.5 g for 4 consecutive days, every 28 days (± 3 days) x 6 months
Administration route: intravenous

Ig VENA Placebo: 10% maltose solution in a 200 ml bottle for 4 consecutive days, every 28 days (± 3 days) x 6 months. Administration route: intravenous

Methylprednisolone Placebo: normal saline 250 ml for 4 consecutive days, every 28 days (± 3 days) x 6 months Administration route: intravenous

Study duration per patient:

12 months: 6 months (double blind treatment) + 6 months follow-up

Evaluation criteria:

Primary outcome:

1. Difference in the proportion of patients discontinuing treatment with IVIg or IVMP during the 6 months of therapy because of side effects, intolerance or inefficacy (absence of improvement after 2 months or worsening by at least 1 point in Overall Neuropathy Limitations Scale (ONLS) after 15 days).

Secondary outcomes:

1. Difference in the proportion of patients worsening during the 6 month of follow-up after therapy discontinuation.
2. Difference in the change of assessment scores after 15 days, 2 & 6 months of therapy compared to baseline between patients treated with IVIg or MP (a-i scales).

   a) MRC sumscore

   b) Sensory sum score INCAT

   c) Vibratory threshold "graded tuning fork"

   d) Strength of the fist

   e) Time on 10 meters

   f) Neuropathic limitation scale (modified INCAT)

   g) Modified Rankin Scale

   h) Rotterdam Scale

   i) SF-36 QoL Scale

3. Difference in the proportion of patients without functional limitation [ONLS lower body LB (0/1), upper body UB (0/1) and Rankin scale (0/1)] after 6 month therapy.
4. Difference in the mean time to worsening after therapy discontinuation.
5. Difference in the proportion of patients unresponsive to the first therapy who improved after the alternative therapy.
6. Difference in the number of treatment cycles in the two groups.
7. Difference in the change of conduction block (CB) and change in the negative area of the distal compound muscle action potential (CMAP) in 2 representative nerves after 15 days & 6 months.
8. Difference in the proportion of nerve with demyelinating features (CB, abnormal temporal dispersion (TD), reduced conduction velocity (MCV), increased distal latency (DL) or F-wave latency) in the 6 months evaluation compared to the one conducted within 1 month of therapy*
9. Difference in the number of nerves with reduced distal CMAP amplitude after 6 months of therapy compared to the one conducted within 1 month of therapy*

* Since nerve conduction studies on the eight motor and six sensory nerves after six month of therapy were often incomplete the data were not analysed.

Safety outcomes:

1. Difference in patients with Adverse Events (AEs) during the treatment and list of type of AEs.
2. Hematological and hematochemical assessment.
3. Blood pressure assessment after each infusion.
4. Intraocular pressure assessment.

Evaluation of efficacy and safety parameters:
Assessment by the primary care physician/supervisor of the therapy side effects, including evaluation of vital signs (systolic and diastolic blood pressure [BP], heart rate) and any disease or disorder occurred during treatment.

1. Electroneurographic evaluation of the 2 nerves most indicative for CIDP at T0 and 15 days after starting treatment. In all cases the CMAP extent and area at wrist/ankle and the elbow / knee, forearm/leg nerve conduction velocity (NCV), distal latency, and minimal latency of the F-wave have been recorded. At the end of the 6th month the patients have repeated a complete electroneurography (8 motor nerves, including the 2 most indicative nerves and 6 sensory nerves), similarly to the one performed before inclusion.
2. Haematology and blood tests (CBC, urea, creatinine, glucose, ESR, ALT, GGT, alkaline phosphatase, bilirubin, Na+, K+, calcium, serum electrophoresis, HCV, HIV, serum immunoglobulins levels) within two weeks before start of therapy (pre-inclusion evaluation, see above) and at 6 months (one month after the 6th monthly cycle). Two weeks after and 24 hours prior to the 2nd and 4th treatment cycle the following tests have been performed: CBC, urea, creatinine, glucose, VES, ALT, GGT, alkaline phosphatase, bilirubin, Na+, K+, and calcium. Serum samples have been taken at each exam and stored at -70° C for possible viral testing, if it became necessary. The exams have been carried out at the laboratories of each centre since this represents a routine clinical practice for patients undergoing such treatments.
3. A serum sample (3 ml) has been taken before the start of the study, 15 days, 24 hours before the 2nd and 4th therapy cycle and at 6 months, and has been stored at -70° C for possible viral testing for a period of 12 months and then destroyed (CPMP/BPWG/388/95 rev.1).
4. BP evaluation at the end of each infusion.
5. Evaluation of the intraocular pressure by an ophthalmologist at the 4th treatment cycle and at 6 months (in the 24 hours preceding the infusion).

Statistical Analysis:

Forty six patients were required under the hypothesis of a 40% absolute difference in the discontinuation rate between the two treatments with 80% power and alpha set at 0.005 and allowing for 15% dropout rate. All statistical analyses were performed with significance set at the 5% level and using 2-sided tests or 2-sided 95% confidence intervals (CIs). All the analyses were performed in two study populations:

- Intention to treat (ITT) population: all patients randomized with analyses assessed using the Last Observation Carried Forward (LOCF) method.
- Per protocol (PP) population: patients not switching or discontinuing the treatment till the six months visit.

The primary outcome was assessed both trasversally and longitudinally with univariate (Fisher exact test and actuarial methods) and multivariate (logistic regression and COX proportional hazard model) tests. Multivariate analyses were conducted in order to compare treatment failures, with the demographic and clinical features set as confounders. A (per-person) incidence rate of adverse events was performed for each group, its 95% confidence interval was computed using the Poisson distribution method. The two groups were compared on the secondary binary outcome with the Fisher exact test. All the other secondary outcomes were evaluated both transversally and longitudinally with the Wilcoxon Mann Whitney Test and the McNemar or Friedmann Test or the repeated measures analysis of variance (ANOVA), or Cochrane-Armitage test for trend, as appropriate. Despite the large number of tests on the secondary outcomes, the I type error rate was not adjusted as these analyses were mainly supportive and the 5% level was considered a sufficient cut-off value.

Efficacy results:

Primary efficacy variable:

Ten of the 21 patients treated with IVMP (47.6%) completed the 6 months of the study compared to 21/24 on IVIg (87.5%)(p = 0.0085). The cumulative probability of treatment discontinuation was significantly higher with IVMP than with IVIg at 15 days, 2 months and 6 months. When the model was adjusted by multivariate analyses for sex, age, disease duration, co-morbidity, modified Rankin Scale and ONLS scale at enrolment, and previous treatment with IVIg and steroids the difference between the two groups remained significant (Odds Ratio [OR] 7.7; 95% confidence interval [CI] 1.7-33.9; p = 0.0070). The difference was also significant when we used the Cox model to analyzed failure occurrence within 6 months (HR 3.7; 95% CI 1.0-13.9; p = 0.0414) and the actuarial method for survival analysis to failure occurrence (log-rank p-value=0.0043). Of the 11 patients who discontinued IVMP, eight did so because of progressive worsening after treatment start (5 patients) or failure to improve after two courses of therapy (3 patients), while one had adverse events (gastritis) (9.1%) and two voluntarily withdrew (18.2%). Three patients discontinued IVIg for progressive worsening after starting the therapy (two patients), or absence of improvement after two courses of therapy (one patient). All the patients worsening or not improving after IVMP or IVIg were shifted to the alternative therapy while the three patients who discontinued IVMP for adverse event or who voluntary withdrew after IVMP refused further therapy.

Secondary efficacy variables:

Both groups significantly improved at six months compared to the baseline in the Rankin, Rotterdam and the SF-36 Quality of life scores. IVIg treated patients also significantly improved in the ONLS, MRC sumscore, quantified fist strength, INCAT sensory sumscore, vibratory scores in the lower limbs and timed 10 meters walk. There were however no significant differences in the degree of improvement between the two groups with the only exception of the higher improvement in the vibration score in the right malleolus in the IVIg than IVMP group and the close to significant improvement in fist strength and timed10 meter walk in the IVIg group. When the data were analyzed in the per-protocol population, all the improvement were significant in the IVIg treated patients while IVMP treated patients significantly improved only in fist strength and ONLS score. No significant difference in the degree of improvement was observed between the two groups. Variations were analyzed in the two most relevant motor nerves for the diagnosis of CIDP in each patient at baseline, 15 days and six months after starting therapy. There was a non significant improvement in both groups in distal and proximal CMAP amplitude, in motor conduction velocities and in the number of nerves with definite conduction block as defined by the EFNS/PNS.

On the basis of results presented in the Statistical Report the only significant difference was the reduction in the distal latency in the IVIg group (p= 0.0007). This reduction was significant compared to the change observed in the IVMP group (p= 0.0131). When the data were analyzed in the per-protocol population there was a significant improvement in motor nerve conduction velocity and reduction in distal latency in the IVIg group but also an increase in the number of nerve with CB in the IVIg group but there was no difference compared to the IVMP group. Seven of the eight patients who did not respond to IVMP and who were shifted to IVIg improved after this later therapy (87.5%). The same occurred in the three patents who did not respond to IVIg and who were shifted to IVMP (100%). Only one patient did not respond to IVMP and to subsequent IVIg.

During the six month of follow-up after therapy discontinuation, none of the patients who had improved with IVMP presented worsening and required further therapy while 8/21 (38.1%) patients who had responded to IVIg had subsequent worsening and had to restore therapy (p= 0.0317). They all responded to the resumed therapy. At the end of the 12 months of the study, 10/21 (47.6%) patients treated with IVMP who improved remained stable without therapy. The same occurred in 13/24 (54.1%) patients treated with IVIg (p= 0.763).

Safety results:

A total of 33 adverse events were observed in patients treated with IVMP and 26 in patients treated with IVIg: 21 non serious AEs were reported in 11 of the 24 patients affected by CIDP who received infusions of Ig VENA; in addition 2 more patients experienced 5 non serious AEs following the shift to the alternative therapy. More patients with IVMP (14, 66.7%) than with IVIg (11, 45.8%) had at least one adverse event (p= 0.1606). Two fatal adverse events occurred during follow-up after IVIg therapy. One patient died because of cardiac arrest one month after the last IVIg course and two days after the 6 months visit. Despite a possible temporal correlation between the last IVIg infusion and the onset of the event, both the Sponsor and the Investigator considered the death as not IVIg related since it occurred in a hypertensive patient with cardiovascular risk factors and under treatment with oral anticoagulants. The other death occurred in a patient who received 6 courses of IVIg after one course of IVMP. Two months after the last IVIg course and one month after the 6 months visit he died of respiratory failure. Even in this patient, death was not thought to be related to IVIg.

Both groups had a similar number of abnormal laboratory tests.

Considering only events occurred before any possible switch, incidence rates (95% CI) of adverse events were 1.62 (1.12-2.26) and 0.75 (0.45-1.18) respectively for the IVMP and the IVIg group (p= 0.0724).

Conclusions:

Forty-five patients (24 on IVIg and 21 on IVMP) completed the study while one was excluded for inappropriate inclusion. More patients stopped IVMP (10/21, 52.4%) than IVIg (3/24, 12.5%) (p = 0,0085) for lack of efficacy or intolerance. At the end of the 6-month therapy, both groups had improved in the Rankin, Rotterdam and SF-36 quality of life scale while the IVIg group had also improved in the ONLS, motor and sensory scores and in the time to walk 10 meters. There was no difference in the degree of improvement between the two groups. More patients experienced adverse events during therapy with IVMP (66.7 %) than with IVIg (45.8%) (p= 0.1606). After therapy discontinuation more patients on IVIg (8/21, 38.1%) than IVMP (0/10) worsened and required further therapy.

IVIg were more frequently effective and better tolerated than IVMP during the six months of therapy but, when effective, IVMP was less frequently associated with relapse after therapy discontinuation than IVIg.