Low-Dose Intravenous Immunoglobulin Treatment for Long-Standing Complex Regional Pain Syndrome (LIPS):

Objective: To confirm the efficacy of low-dose IVIg compared with placebo in reducing pain during a 6-week period in adult patients who had CRPS from 1 to 5 years.

Design: 1:1 parallel, randomized, placebo-controlled, Multicenter trial for 6 weeks, with an optional 6-week open extension. Patients were randomly assigned to 1 of 2 study groups between 27 August 2013 and 28 October 2015; the last patient completed follow-up on 21 March 2016. Patients, providers, researchers, and outcome assessors were blinded to treatment assignment. (ISRCTN42179756)

Setting: 7 secondary and tertiary care pain management centers in the United Kingdom.

Participants: 111 patients with moderate or severe CRPS of 1 to 5 years' duration.

Intervention: IVIg, 0.5 g/kg of body weight, or visually indistinguishable placebo of 0.1% albumin in saline on days 1 and 22 after randomization.

Measurements: The primary outcome was 24-hour average pain intensity, measured daily between days 6 and 42, on an 11-point (0- to 10-point) rating scale. Secondary outcomes were pain interference and quality of life.

Patients Between 27 August 2013 and 28 October 2015, 121 patients from 7 sites were screened for eligibility. Of these patients, 111 were randomly assigned to 1 of the 2 trial groups: 56 to the placebo group and 55 to the IVIg group. Three patients were randomly assigned in error: 2 had an average baseline pain score (during the first 7 days of screening) below 5 points, and 1 had CRPS for less than 12 months. These 3 patients (all randomly assigned to receive IVIg) were excluded from the primary analysis. Twelve patients withdrew from study medication before the end of the blinded phase (day 42). Of these patients, 2 (1 from the placebo group and 1 from the IVIg group) did not receive their first infusion and supplied no outcome pain data, and 3 (2 from the placebo group and 1 from the IVIg group) received their first infusion but also supplied no outcome pain data. The remaining 7 patients received their first infusion, and all completed their pain diaries for at least 2 weeks. Six of the 12 patients who withdrew indicated an adverse event as the reason for their withdrawal (3 from the placebo group and 3 from the IVIg group), 1 patient wished to pursue an alternative therapy, 2 patients stated problems with travel arrangements, and 3 patients gave no reason. The primary analysis sample included 108 patients, 56 in the placebo group and 52 in the IVIg group

Results: The primary analysis sample consisted of 108 eligible patients, 103 of whom had outcome data. Mean (average) pain scores were 6.9 points (SD, 1.5) for placebo and 7.2 points (SD, 1.3) for IVIg. The adjusted difference in means was 0.27 (95% CI, −0.25 to 0.80; P = 0.30), which excluded the pre-specified, clinically important difference of −1.2. No statistically significant differences in secondary outcomes were found between the groups. In the open extension, 12 of the 67 patients (18%) who received 2 IVIg infusions had pain reduction of at least 2 points compared with their baseline score. Two patients in the blinded phase (1 in the placebo and 1 in the IVIg group) and 4 in the open IVIg phase had serious events.

Limitations: Results do not apply to patients who have had CRPS for less than 1 year or more than 5 years and do not extend to full-dose treatment (for example, 2 g/kg). The study was inadequately powered to detect subgroup effects.

Conclusion: Low-dose immunoglobulin treatment for 6 weeks was not effective in relieving pain in patients with moderate to severe CRPS of 1 to 5 years' duration