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# A MULTI-CENTRE OPEN STUDY TO ASSESS THE SAFETY AND EFFICACY OF SUBGAM® GIVEN VIA THE SUBCUTANEOUS ROUTE IN PRIMARY ANTIBODY DEFICIENT PATIENTS (STUDY CODE SCIG01)

## LONG-TERM FOLLOW-UP

## SUMMARY of the CLINICAL STUDY REPORT

**27 APRIL 2007**

**Bio Products Laboratory**
**Dagger Lane**
**Elstree**
**Herts WD6 3BX**

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***Name of Sponsor/Company:***

Bio Products Laboratory (BPL)

Dagger Lane, Elstree

Herts, WD6 3BX,

United Kingdom

***Name of Finished Product:***

Subgam®

***Name of Active Ingredient:***

Human Normal Immunoglobulin (for subcutaneous infusion)

***Title of Study:***

A multi-centre open study to assess the safety and efficacy of Subgam® given via the subcutaneous route in primary antibody deficient patients.

***Investigators:***

All investigative sites were in the United Kingdom.

***Study period (for this report):*** Pre-study phase: 3 infusions on current therapy; then Subgam®, starting 1 week after last dose of previous therapy. Patients received Subgam® for a mean of 147.7 infusions over a mean of 147.5 weeks.

The overall study duration was 4.58 years (calculated from the date of first enrolment to the date the last subject completed, i.e. 53 months).

***Date of first enrolment:*** 14 June 2000

***Date of last completed patient:*** 12 January 2005

***Phase of development:*** Phase III (Continuing as Phase IV)

***Objectives:***

The primary objective was to determine the efficacy of Human Normal Immunoglobulin (Subgam®) given subcutaneously by weekly infusion to patients with primary antibody deficiency.

The secondary objective was to determine the safety of Subgam® given subcutaneously by weekly infusion to patients with primary antibody deficiency.

***Methodology:***

The study design was multi-centre, open and non-comparative. The study was performed in two parts: Stage 1 (safety and efficacy) and Stage 2 (long-term follow-up until product launch in the UK).

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Safety was assessed by the number and types of adverse events, monitoring of vital signs, haematology, clinical chemistry, virology and local tolerability assessment.

Efficacy was measured by serum immunoglobulin G (IgG) levels, the number and magnitude of changes in Subgam® dose required, the number and type of infections incurred, antibiotics usage, specific antibody (*Streptococcus pneumoniae* [anti-pneumococcus] and *Haemophilus influenzae* type B [anti-HIB]) levels, the length of time off work or education, time spent on home therapy and patients' satisfaction with Subgam®.

Diary cards were used by patients to record doses of Subgam® administered at home, adverse events, infections and other relevant information.
Trough serum immunoglobulin G (IgG) levels were measured from samples taken weekly during hospital infusions and 4-weekly during home infusions for the first six months of the study. Thereafter, IgG levels were measured from samples taken during the patients' approximately 3-monthly routine hospital visits.

An optional pharmacokinetic assessment was performed in a group of patients who chose to take part. Blood samples were taken for serial measurement of serum IgG on two separate occasions (once during the week of the first infusion of Subgam® and once after approximately 3-4 months' treatment). On each occasion, a pre-dose blood sample was taken and then a sample on each of the following seven days (except weekends).

The data have been analysed in different ways: the whole population; adults, teenagers and children separately; those receiving previous IVIG or SCIG separately; patients with conditions associated with relatively low endogenous production of IgG (e.g. XLA, CVID) and others (e.g. specific antibody deficiency).

***Number of patients:***

A total of 50 patients: 15 paediatric patients <12 years (12 males and 3 females), 7 teenagers 12-<20 years (3 male, 4 female) and 28 adults (10 male, 18 female) were recruited. The mean age of the paediatric patients was 6.2 years (range 0.8-10.6), the mean age of teenagers was 15.2 years (range 12.1-18.0) and the mean age of adults was 45.5 years (range 21.3-75.2). All patients whose data were used in the efficacy analysis had a diagnosis of primary antibody deficiency and had received at least 6 months immunoglobulin (IVIG or SCIG) therapy prior to starting the study.

***Diagnosis and main criteria for inclusion:***

The main criteria for inclusion in the study were as follows:

- A diagnosis of primary antibody deficiency;
- No lower or upper limit (any age was eligible);
- With stable disease and receiving immunoglobulin (IVIG or SCIG) therapy for at least six months prior to starting the study.

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***Test product, dose and mode of administration, batch numbers:***

Subgam® was given subcutaneously at an initial weekly dose of 100 mg/kg bodyweight. Doses were then adjusted for each patient in order to maintain adequate serum IgG levels.

A total of 12 separate batches of Subgam® were used during the 4.58 years of the study as follows:

SCBN276, SCBN276A SCBN5303, SCBN5565, SCBN5679, SCBN5786, SCBN5922, SCBN6004, SCBN6077, SCBN6079, SCBN6205, and SCBN6243. SCBN276 and SCBN276A were manufactured as part of the same batch but were given different batch numbers as they were packaged and labelled in two separate lots.

***Duration of treatment:***

Long-term patient follow-up was for approximately 4 years.

Patients received a mean of 147.7 infusions of Subgam®(range 22 to 317) over a mean of 147.5 weeks (range 24 to 208 weeks).

***Reference therapy, dose and mode of administration, batch numbers:***

There was no specific reference therapy.

***Criteria for evaluation:***

*Efficacy*:

*Trough IgG levels*:

The primary endpoint was the proportion of trough levels at each time point where serum IgG was ≥ 4 g/L for children and ≥ 6 g/L for adults.

Secondary efficacy measurements included: the change in Subgam® dose required to maintain trough levels at a minimum of ≥ 4 g/L for children and ≥ 6 g/L for adults; the proportion of trough levels at each time point where the IgG was ≥ 4 g/L for children and ≥ 6 g/L for adults; the time taken for each patient to reach a steady state IgG trough level, defined as the occurrence of three consecutive occasions when the IgG trough levels were within 1 g/L of each other; and the mean change in IgG trough level as compared to the baseline level at each time point.

*Infections*: the incidence of infections, days on antibiotics, and days off work/school.

*Antibiotic usage*: antibiotics included systemic antibiotics, but excluded topical fungicides.

*Specific antibodies*: during Stage 1 only, blood samples were taken for assay of antibodies to anti-pneumococcus and anti-HIB.

*Immunology parameters*: during Stage 1, and if clinically indicated in Stage 2, blood samples were taken for serum IgA and IgM measurements.

*Length of time off work or education*: the number of days each patient was absent from work or school (where applicable, some patients attended neither work nor school and the status of some patients changed during the 4.58 years of the study).

*Home therapy*: the length of home therapy training period and duration of home therapy.

*Patient Satisfaction Questionnaires*: patients' perception of using Subgam® compared to their previous IgG therapy.

*Pharmacokinetics*:

Inter-infusion serum IgG levels (optional) measured in a subgroup of patients who attended the hospital daily for blood sampling up to a week after the first Subgam® infusion and after an infusion approximately 3 months later.

*Safety*:

Monitoring of adverse events, infusion site reactions, laboratory assessments of haematology, clinical chemistry, and immunological and viral markers, and vital signs.

*Statistical methods:*

As this was a non-comparative study, data are presented with descriptive statistics only. The Pearson Chi-square test was used to test patients' perceptions of the comfort and convenience of infusions, their symptoms and how they liked Subgam® at the Month 6 visit. As expected, cell frequencies were anticipated to be low for some categories, so the exact version of this test was used.

***Summary - Results***:

In total 50 patients entered the study from 14 study centres, and of these 35 (70%) completed the study (up to 4.58 years). Fifteen patients withdrew prematurely; one patient withdrew from Stage 1 (patient 9 after infusion 25) because he emigrated, and the remaining 14 patients withdrew during Stage 2. Of the 14 patients that withdrew in Stage 2, 10 were at the patient's request, 2 for protocol deviations, 1 at the request of the investigator, and 2 for other reasons (one patient returned to IVIG therapy and the other patient did not wish to continue completing diary data after 995 days in the study).

*Efficacy Results*:

During Stage 1 of treatment, 85% of adults/teenagers and 93% of children achieved target trough serum IgG levels at all observations. The mean time to achieve a steady state serum IgG level was 6.14 infusions for patients who had previously received IVIG treatment and 6.50 infusions for patients who had

previously received SCIG treatment. (Refer to Table 12 for mean baseline serum IgG levels for prior SCIG and IVIG therapy).

Mean IgG level increased from 9.2 g/L to 9.75 g/L with Subgam® treatment and was maintained above the pre-Subgam® level for 30 months of treatment. For patients completing at least 36 months on Subgam®, the mean IgG levels for the periods 30-36 months and 0-6 months were compared by calculating the mean level for each patient in the 6 month period and then the overall mean for all patients who completed 36 months. The value for the 30-36 month period was similar (95.9%) to that in the first 6 months.

Overall, 93.6% of infusions were given at home. The dose of Subgam® required to maintain IgG levels increased with time from 104.6 mg/kg during the first 6 months, with the required dose reaching a plateau of 115 mg/kg at around 18-24 months of treatment. The trend in increased dose was seen in adults and children; however there was no noticeable increase with time observed in teenagers.

There was no notable change in serum IgA or IgM levels during Subgam® treatment.

There was no marked increase in the frequency, severity or seriousness of bacterial infections prior to and during Subgam® treatment. Among the 50 patients there were 3.40 infections per patient per year in the pre-Subgam® treatment phase and 3.62 infections per patient per year during Subgam® treatment; similarly patients experienced 0.19 serious infections per patient per year pre Subgam® treatment, and 0.16 serious infections per patient per year during Subgam® treatment. There were 18 potential serious acute bacterial infections in 11 patients during Subgam® treatment, equivalent to 0.13 serious acute bacterial infections per patient per year.

The majority of patients preferred Subgam® treatment to their previous therapy. After 3 months of treatment, 34 of 38 patients (who answered the questionnaire) preferred Subgam® “more” or “much more” than their previous treatment and after 6 months of treatment patients continued to prefer Subgam®. There was no noteworthy difference between patients previously treated with SCIG or IVIG.

*Safety Results*:

Overall, Subgam® was safe and well tolerated, with no increase in adverse events experienced during the treatment phase. Patients receiving Subgam® therapy experienced a similar number of adverse events and SAEs per study day compared with patients pre-Subgam® therapy. The most common adverse events were headache, cough and pharyngitis and the majority of these were considered unrelated to Subgam®. There were 82 reports of infusion site reactions in 25 of the 50 patients receiving Subgam® therapy. Apart from infusion site reactions, the most common product-related adverse events were headache (8 reports in 7 patients), pruritus (7 reports in 2 patients) and vomiting (5 reports in 3 patients). There were no withdrawals due to adverse events or safety considerations and no product-related SAEs.

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There was no notable overall change in haematology or biochemistry parameters before and after participation in the study. There were no clinically relevant changes in individual haematology or biochemistry parameters that were considered to be related to Subgam®.

There was no evidence of the transmission of HIV, Hepatitis B virus, Hepatitis C virus or Parvovirus B19.

***Conclusion:***

Subgam® was safe and well tolerated and was effective in increasing and maintaining serum IgG levels with only moderate dose increases required over time. The incidence of bacterial infections remained low during long-term treatment with Subgam®. The majority of patients in the study preferred Subgam® treatment to their previous treatments.

***Date of Report:*** 27 April 2007

**This study was conducted in compliance with GCP CPMP/ICH/137/95.**