2. SYNOPSIS

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<th>Name of Sponsor/Company:</th>
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<th>Individual Study Table Referring to part of the Dossier</th>
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<td>Name of Finished Product:</td>
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<td>Volume:</td>
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<td>Immunoglobulin intravenous (human)</td>
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**TITLE OF STUDY:**
Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of IGIV3I GRIFOLS [Immune Globulin Intravenous (Human)] for Replacement Therapy in Primary Immunodeficiency Diseases (PID)

**INVESTIGATORS AND STUDY CENTERS:**
Multi-center. A complete list of Investigators is given in Appendix 16.1.4.

**STUDY DATES:**
From: 11-Nov-2002 To: 20-May-2004

**PHASE OF DEVELOPMENT:**
Phase III

**OBJECTIVES:**
To determine if IGIV3I GRIFOLS 5% is safe, has pharmacokinetics comparable with intact immunoglobulin G (IgG), and is efficacious as determined by the Food and Drug Administration (FDA) minimal requirements (no more than 1 serious bacterial infection per patient per year).

**METHODOLOGY:**
Multi-center clinical, open-label, and historically controlled trial designed to assess the safety, pharmacokinetics, and therapeutic efficacy of IGIV3I GRIFOLS 5%.

**NUMBER OF PATIENTS:**
Enrolled: 46 patients Completed Study: 41 patients In detailed PK analysis: 20 patients

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:**
Patients aged greater than 3 years were eligible for the study if they weighed at least 27 pounds (based on blood volume required for testing); had a PID, which has as a significant component hypogammaglobulinemia and/or antibody deficiency (i.e., common variable immunodeficiency, X-linked and autosomal forms of agammaglobulinemia, hyper-immunoglobulin M [IgM] syndrome, Wiskott-Aldrich syndrome, isolated deficiency of a single IgG subclass, without hypogammaglobulinemia per se, did not qualify for inclusion); had been receiving IGIV replacement therapy at a dose that has not changed by ± 50% of the mean dose for at least 3 months prior to study entry; and had maintained a trough level of at least 300 ± 10% mg/dL above baseline serum IgG levels.
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**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION, cont’d.:**

Patients were ineligible for the study if they had a history of severe anaphylactic reactions to blood or any blood-derived product; had selective immunoglobulin A (IgA) deficiency or demonstrable antibodies to IgA; were known to be intolerant to any component of the product such as sorbitol; were receiving or had received any investigational agents within the prior 3 months, except Flebogamma®; had been exposed to blood or any blood product or derivative other than a commercially available IGIV, or other forms of commercially available and licensed Immune Serum Globulin (ISG) or an ISG product that was in Phase II or IIIB trials within the 3 months prior to study entry; required pre-medication for IGIV infusion other than aspirin, acetaminophen or other non-steroidal anti-inflammatory drug, or antihistamine; were positive for hepatitis B surface antigen (HBsAg), hepatitis C virus ribonucleic acid [RNA (HCV PCR)], or human immunodeficiency virus RNA (HIV PCR) at screening; had renal or hepatic abnormalities; had a history of drug or alcohol abuse in the previous 12 months; had a history of deep vein thrombosis or thrombotic complications of IGIV therapy; had an acquired medical condition known to cause secondary immune deficiency; were receiving steroids (long-term, daily, ≥ 1 mg/kg/day), immunosuppressive drugs, or immunomodulatory drugs; were pregnant or nursing an infant child; or if female, were sexually active and unwilling to commit to practicing contraception by a method of proven reliability for the duration of the study.

**TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER:**
IGIV3I GRIFOLS 5%; 300-600 mg/kg/infusion; Lot numbers IAGJ2NG001, IBGJ2MC001, and IBGJ3T3001

**DURATION OF TREATMENT:**
All patients in this study received IGIV3I GRIFOLS 5% every 3 or 4 weeks for 12 months.

**REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER:**
None

**CRITERIA FOR EVALUATION:**

**Efficacy:**

Primary Efficacy Endpoint:
The number of episodes of the following serious bacterial infections: bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscesses, and bacterial meningitis.

Secondary Efficacy Endpoints:
- Number of days of work/school missed
- Number and days of hospitalizations
- Number of visits to physicians for acute problems and/or number of visits to hospital emergency rooms per patient year
- Other infections documented by positive radiograph and fever per patient year
- Number of infectious episodes per patient year, which includes both serious bacterial infections and other infections
- Number of days of therapeutic antibiotic use per patient year
### CRITERIA FOR EVALUATION, cont’d.

#### Safety:
Safety was assessed by the recording of vital signs; the nature, severity, and frequency of adverse events (AEs); effects on hepatic, renal and hematological function; transmission of hepatitis B, hepatitis C, and HIV; and administration of the Coombs’ test.

#### Pharmacokinetics:
A detailed pharmacokinetic (PK) analysis was performed on a subset of 20 patients. PK samples were collected at baseline and after the 5th month after initiation of treatment (after the 5th infusion for patients on a 28-day infusion schedule, and after the 7th infusion for patients on a 21-day infusion schedule).

The PK analysis included the following parameters:

- maximum observed concentration ($C_{\text{max}}$)
- time to occurrence of $C_{\text{max}}$ ($t_{\text{max}}$)
- elimination rate constant ($\lambda_z$)
- serum half-life ($t_{1/2}$)
- area under the concentration-time curve from time 0 to the time of the last post-dose quantifiable serum concentration ($\text{AUC}_{(0-\text{last})}$)
- area under the concentration-time curve from time 0 to infinity ($\text{AUC}_{(0-\text{inf})}$)
- clearance (CL, only for total IgG)
- volume of distribution ($V_d$, only for total IgG)

Unless otherwise specified, these parameters were estimated or derived for total IgG, IgG subclasses, and IgG antibodies against specified antigens by using non-compartmental methods. Trough levels were compared with those before the trial.

#### STATISTICAL METHODS:
The primary efficacy variable was the number of episodes of serious bacterial infections per patient per year. To estimate the infection rate and develop the appropriate 1-sided 99% upper confidence bound, a generalized linear model for Poisson regression was used. Infection rates for individuals were calculated by dividing the number of events for that individual by the total amount of follow-up time. The distribution of these rates across individuals was presented by using a histogram.

Rates for secondary efficacy endpoints were calculated by dividing the total number of events observed for the individual in the study (e.g., days of work/school missed, visits to a doctor, etc.) by the total number of patient years of follow-up.

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STATISTICAL METHODS, cont’d.:

For safety analysis, the number and percent of infusions with at least 1 AE temporarily associated with the infusion is presented. The upper bound of the 1-sided 95% confidence interval (CI) for the percent was calculated by using the normal approximation. If the upper bound was less than 40%, the safety of IGIV3I GRIFOLS 5% was declared. The number and percent of patients who reported any AE at least possibly related to the study medication, together with the 95% CI for percents was presented. Adverse events that occurred during an infusion or within 1, 24, 48, or 72 hours of an infusion were also summarized.

For all intent-to-treat (ITT) patients, trough IgG levels, IgG subclasses, and IgG antibodies against specific antigens (e.g., tetanus toxoid, CMV, hepatitis B, and specified S. pneumoniae subtypes) were summarized descriptively by visit. Trough IgG levels and levels of IgG subclasses were compared with those before the trial.

For patients included in the detailed PK analysis, levels of total IgG and IgG subclasses were plotted on a log scale against time; antibody titers to specific antigens (e.g., tetanus toxoid, pneumococcal polysaccharides, Hepatitis B) were also plotted on a log scale against time. The parameters $C_{\text{max}}$, $t_{\text{max}}$, $\lambda_z$, $t_{\frac{1}{2}}$, $AUC(0-\text{last})$, $AUC(0-\text{inf})$, CL, and $V_d$ of total IgG, IgG subclasses, and IgG antibodies against specified antigens were measured or derived by using non-compartmental methods and summarized descriptively.

An interim analysis was planned to occur when at least 15 patients had been treated for 6 months, including patients who would have completed the PK study. The purpose of this review was to ensure that the experimental treatment was not associated with unacceptable outcomes regarding the primary efficacy endpoint, as well as to review toxicity. Consideration was to be given to closing the study if the experimental treatment had a significantly higher event rate (i.e., serious bacterial infection rate) than 1 per patient per year, at the level of $p=0.001$. Since the study would not have stopped even if therapeutic efficacy of the experimental treatment had been demonstrated, the final analysis was not adjusted for the interim analysis.
### SUMMARY OF RESULTS AND CONCLUSIONS:

#### Efficacy and Pharmacokinetic:
- Patients who received IGIV3I GRIFOLS 5% infusions of 300-600 mg/kg had a serious bacterial infection rate of 0.021 infections/patient/year (1 serious bacterial infection reported; 98% CI = 0.001-0.112), which satisfies the FDA efficacy criterion of ≤1 serious bacterial infection/patient/year.
- The mean rates of patients missing work/school, missing normal activities, being hospitalized, or visiting a physician/ER, were low in patients treated with IGIV3I GRIFOLS 5%. There were no other infections documented by positive radiograph or fever. The number of all infectious episodes per patient year was similar to that which could reasonably be expected in a patient population with PIDs regularly treated with IGIV.
- For Total IgG for patients on the 21-day and 28-day infusion schedules, the mean estimated serum half-lives were 29.9 days and 32.1 days, respectively; the mean values of estimated clearance were 138.6 mL/day and 108.5 mL/day; and the mean estimated volumes of distribution were 5.5 L and 4.9 L. Overall, the patterns observed in the PK behavior for Total IgG levels, IgG subclass levels, and the IgG antibody levels to specified antigens were similar.
- Trough total IgG and IgG subclass concentrations were maintained throughout the treatment period with IGIV3I GRIFOLS 5%, as evidenced by both the relatively small changes in these parameters observed over the course of the study and the absence of any patients with decreases from screening or first infusion in trough total IgG that were > 50%.

#### Safety:
- The most common AEs were sinusitis NOS, pyrexia, headache, headache NOS or sinus headache, upper respiratory tract infection NOS, combined bronchitis, wheezing or asthma aggravated and cough or productive cough, diarrhea NOS, pharyngitis, injection site reaction NOS, arthralgia, and nasal congestion. The most common treatment-related AEs were headache, pyrexia, injection site reaction NOS, diarrhea NOS and rigors, and urticaria NOS.
- Of the 706 infusions administered, 10% (1-sided 95% CI upper bound = 12.4%) were associated with an AE suspected to be related to IGIV3I GRIFOLS 5% that occurred during the infusion or within 72 hours after infusion completion.
- No patients died, 1 patient withdrew from the study because of an AE that was not related to study drug, and 3 patients experienced 6 SAEs that were considered not related to study drug.
- No patients tested positive for HBsAg, HBV, HCV, or HIV. Seven patients had positive Coombs’ test results after baseline.
- Assessments of laboratory values, vital signs, and trough IgG levels did not indicate any safety concerns for patients receiving IGIV3I GRIFOLS 5% infusions at a dose of 300-600 mg/kg.
- Based on these results of safety data, the safety and tolerability profile of IGIV3I GRIFOLS 5% in this study is consistent with that reported in Grifols-04 and that which could be reasonably expected for a patient population with PID.
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### CONCLUSIONS:
- The observed serious bacterial infection rate was 0.021 infections/patient/year, and the efficacy of IGIV3I GRIFOLS 5% at a dose of 300-600 mg/kg can be considered acceptable under the FDA efficacy criterion of ≤1 serious bacterial infection/patient/year.
- The mean rates of patients missing work/school, being hospitalized, or visiting a physician/ER, were low in patients treated with IGIV3I GRIFOLS 5%.
- Efficacy and safety results for 3 pediatric patients (those ≤16 years old) appeared to be generally similar to those for the overall patient population. Two patients aged 17 years old were enrolled, and the results for these patients also appeared to be similar to those for the overall population.
- The PK behavior of IGIV3I GRIFOLS 5% appears to be generally similar to that of Flebogamma® (as demonstrated in the study Grifols-04) and similar to that presented in the literature both for healthy patients and patients with PIDs, and half-life estimation was not influenced by truncating the sampling period at 28 days.
- Trough levels of Total IgG and IgG subclasses were maintained at or near pre-study levels throughout the treatment period with IGIV3I GRIFOLS 5%.
- IGIV3I GRIFOLS 5% at a dose of 300-600 mg/kg appears to be safe and well-tolerated and does not put patients at increased risk of any AEs other than those that could reasonably be expected in PID patients who are receiving any IGV infusion.

### DATE OF REPORT:
14-Sep-2005