SUMMARY BASIS FOR APPROVAL

I. General Information

Licensed Product Name: Immune Globulin Subcutaneous (Human)

Proprietary Product Name: Vivaglobin®

Name and Address of Sponsor: ZLB Behring GmbH
35002 Marburg, Germany
US License No. 1708

Biologics License Application (BLA) Tracking Number: STN 125115/0

Date of Submission: October 27, 2004

Date of Filing: December 15, 2004

Review Designation: Priority Review

Date of Licensure: January 9, 2006

II. Indication and Usage

Immune Globulin Subcutaneous (Human), Vivaglobin® is indicated for the treatment of patients with primary immune deficiency (PID).

III. Dosage Form, Route of Administration and Recommended Dosage

Vivaglobin® is supplied as a sterile liquid to be administered by the subcutaneous route. It is a 16% (160 mg/mL) protein solution, with a content of at least 96% immunoglobulin G (IgG). The distribution of IgG subclasses is similar to that present in normal human plasma. Vivaglobin® contains 2.25% glycine, 0.3% sodium chloride, and water for injection, U.S.P. The pH of Vivaglobin® is 6.4 to 7.2. Vivaglobin® contains no preservative.

When stored at 2 – 8 °C, Vivaglobin® is stable for the period indicated by the expiration date on its label.

A usual recommended dose of Vivaglobin® is 100 to 200 mg/kg body weight administered subcutaneously weekly. Doses may be adjusted over time to achieve the desired clinical response and serum IgG levels. In the clinical study with Vivaglobin®, a volume of 15 mL per injection site at a rate of 20 mL per hour per site was not exceeded. Doses over 15 mL were divided and infused into several sites using an infusion pump.

IV. Chemistry, Manufacturing and Controls

A. Overview of Manufacturing Process

Vivaglobin® is manufactured by ZLB Behring GmbH, under U.S. License Number 1708. Vivaglobin® is currently manufactured entirely at the Marburg, Germany facility from Source Plasma through storage, testing, inspection, packaging and labeling of final product.

All plasma used in the manufacture of Vivaglobin® is tested using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 (HIV-1/2) as well as FDA-licensed Nucleic Acid Testing (NAT) for HCV and HIV-1 and found to be nonreactive (negative). For hepatitis B virus (HBV), an investigational NAT procedure is used and the plasma found to be negative. However, the significance of a negative result has not been established. In addition, the plasma has been tested by NAT for hepatitis A virus (HAV) and parvovirus B19 (B19). Only plasma that passes virus-screening is used for production and the limit for B19 in the fractionation pool is set not to exceed 10^4 IU of B19 DNA per mL.

Vivaglobin® is prepared by modified Cohn Fractionation procedures. --------------------------------
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Filling into final containers is performed under aseptic conditions. Immediately after completion of the filling process vials are automatically stoppered and sealed with crimp caps. The sealed containers are visually examined for freedom from particulates followed by labeling and packaging. The finished drug product containers are stored at 2 to 8 °C until distribution. All lots of finished product meet the requirements of 21 CFR § 610 for potency, safety, sterility, purity, and identity and the established specifications for Vivaglobin®.

Vivaglobin® is available as:

- Box of ten 3 mL vials,
- Single 10 mL vial,
- Box of ten 10 mL vials,
- Single 20 mL vial, and
- Box of ten 20 mL vials.

B. Validation

------- conformance lots were manufactured in support of this application. Process validation was performed during conformance lot manufacturing.

Validation of Assays Used to Release Final Product

The final product specifications include Protein, Immune globulin G, ---, ---, Glycine, Sodium Chloride, ----------, Appearance, ----------, ----------, ----------, Sterility, ----------, ----------, pH, ----------, ----------, General Safety, ----------. Validation protocols and validation reports have been provided for these assays.

Validation of Manufacturing

The critical steps of the manufacturing process have been identified. The criticality of process control parameters has been evaluated and ranges have been defined for these parameters in order to assure consistent product quality. Acceptance criteria were based on experience with the manufacturing process and operating ranges were validated.

Clinical trials were performed with Vivaglobin® manufactured at production scale. Impurity profiles of clinical trial material and full-scale material from the final manufacturing plant were compared and showed no differences. One part of the manufacturing process was relocated to Marburg after clinical trials were completed. The process was subsequently revalidated, and the equivalence of the produced material has been demonstrated with regard to purity, potency, efficacy, safety, and stability.

Validation of Viral Safety

In addition to serological and NAT screening of Source Plasma, the manufacturing procedure of Vivaglobin® includes multiple processing steps that reduce the risk of virus transmission. To assure the safety of Vivaglobin®, the viral reduction processes were validated to ensure that possible infectious viral contaminants are removed or reduced. Experiments were performed to evaluate the manufacturing process for its capacity to eliminate or inactivate various viruses. The viruses were selected to cover a wide range of physicochemical properties of viruses (see Table 1, below).

The virus reduction capacity of two steps was evaluated in a series of *in vitro* spiking experiments; the steps were ethanol - fatty alcohol/pH precipitation and pasteurization in aqueous solution at 60 °C for 10 hours. Total mean cumulative virus reductions ranged from 9.0 to ≥ 14.1 $\log_{10}$ as shown in Table 1.

Table 1: Mean Virus Reduction Factors

Virus Studied:	Ethanol - Fatty Alcohol/pH Precipitation [$\log_{10}$]	Pasteurization [$\log_{10}$]	Total Cumulative [$\log_{10}$]
Enveloped Viruses			
HIV-1	≥ 6.2	≥ 6.5	≥ 12.7
BVDV	≥ 5.3	≥ 8.7	≥ 14.0
WNV	≥ 4.4	≥ 9.3	≥ 13.7
PRV	≥ 6.2	≥ 7.9	≥ 14.1
Non-enveloped Viruses			
PEV	≥ 6.7	3.7	≥ 10.4
CPV	6.7	2.3*	9.0

HIV-1: Human immunodeficiency virus type 1, model for HIV types 1 and 2
BVDV: Bovine viral diarrhea virus, model for HCV and WNV
WNV: West Nile virus
PRV: Pseudorabies virus, model for large enveloped DNA viruses (e.g., herpes virus)
PEV: Porcine enterovirus, model for HAV (in an immunoglobulin product)
CPV: Canine parvovirus, model for parvovirus B19
* Reduction of parvovirus B19 (evaluated using porcine IgG) by pasteurization was ≥ 3.5 $\log_{10}$.

C. Stability

Stability studies were conducted on more than ---- lots manufactured in support of Vivaglobin® final- container product stability (Study # *STP-403-025*). Stability data available thus far support storage of product for up to 24 months at 2 – 8 °C. Accelerated testing was conducted for --- months at --- °C. Under these stress conditions, statistical evaluation of the stability data shows that Vivaglobin® was stable for at least --- months.

Based on the 5 and --- °C data presented in the 24-month stability report, an initial shelf life of 24 months at 2 – 8 °C can be supported.

D. Labeling

The package insert, container, and package labels are in compliance with 21 CFR § 201.57, 610.60, 610.61, 610.62, and 610.67. The trade name, Vivaglobin®, is not known to be in conflict with the trademark of any other product.

E. Establishment Inspection

A pre-approval inspection was conducted at the ZLB Behring facility in Marburg, Germany from 02 March through 10 March 2005 by an inspector from the Center for Biologics Evaluation and

Research (CBER), FDA. The Marburg, Germany production facility is the only current manufacturing site for both the active substance and the finished product, and it was the subject of the inspection. The establishment was found to be in compliance with current Good Manufacturing Practices.

F. Environmental Assessment

A request for a categorical exclusion according to 21 CFR § 25.31 (c) Human drugs and biologics was granted.

V. Pharmacology and Toxicology

The nonclinical testing strategy for subcutaneous administration of Vivaglobin® took into consideration the history of the product as it was initially approved (outside of the U.S.) for intramuscular administration in 1953. Accordingly, the initial preclinical program evaluated intramuscular administration. The new subcutaneous route of administration required additional preclinical evaluation.

As proteins of human origin are immunogenic to animals, long-term or repeated administration of Vivaglobin® to animals would not generate useful data. Preclinical toxicity testing consisted of acute toxicity studies after single doses in rodents (mice and rats), safety pharmacology studies in dogs and local tolerance investigations in rabbits. Due to the fact that immunoglobulins are naturally occurring molecules in humans, no testing on genotoxicity, carcinogenicity or embryotoxicity was performed. The ---------- resulting from the ---------- procedure was evaluated in a rabbit neoantigenicity study.

A. Pharmacokinetics

Pharmacokinetic investigations addressed the mode and extent of absorption from the subcutaneous space in rabbits. Bioavailability after subcutaneous or intramuscular administration in rabbits was calculated by comparing the areas under the (concentration versus time) data curve (AUDC), extrapolated to infinity. One limitation of these models, however, is that human proteins undergo rapid clearance in animals resulting in a shortened half-life as compared to the half-life in human beings.

To study bioavailability, an immune globulin preparation was manufactured using ---------- ---------- plasma ---------- Immune Globulin) employing the identical procedure used to manufacture Vivaglobin®. After intravenous administration of ---------- Immune Globulin, elimination followed a two-phase exponential curve corresponding to an open two-compartment model. A mean distribution half-life of 0.1 days and a mean elimination half-life of 4.4 days were observed after intravenous administration. ---------- Immune Globulin was well absorbed from the intramuscular compartment, maximum plasma levels (C_{max}) were observed after 2.9 days (mean). The bioavailability, as measured by AUDC, of intramuscular versus intravenous was 70% (90% CI: 57% to 87%). After subcutaneous administration, ---------- Immune Globulin was absorbed slightly more slowly with a mean time to reach maximum concentration (T_{max}) of 3.2 days. The bioavailability, calculated using AUDC, for

subcutaneous compared to intravenous administration was 47% (90% CI: 39% to 57%), which is about 30% less than the respective bioavailability for intramuscular administration.

B. General Safety

General safety investigations were performed in male and female beagle dogs. Treatment was started with a subcutaneous placebo injection, followed three days later by a single subcutaneous administration of 400 mg/kg Vivaglobin®. The results of this study showed that Vivaglobin®, administered subcutaneously, was well tolerated in dogs. In another study, dogs were given an intramuscular injection of either 160 mg/kg or 480 mg/kg. No relevant adverse effects were caused by the treatment with Vivaglobin®.

Single dose acute toxicity studies were performed in two rodent species, mice and rats.

In an acute toxicity study, Vivaglobin® was administered subcutaneously to mice at a dose of 600 mg/kg. Control mice were treated with placebo. The mice were periodically observed for clinical symptoms, weighed and autopsied at the end of the 14 days of observation. No deaths occurred after single subcutaneous administration to mice of both sexes, observed over a period of 14 days. At this dose level, Vivaglobin® was tolerated without adverse reactions. A dose of 600 mg/kg Vivaglobin® provides a safety margin of a factor at least 3 to 6 when compared to a usual human dose.

Vivaglobin® was also administered intramuscularly to three groups of mice at dose levels of 2.0, 4.0 and 8.0 g/kg with 8.0 g/kg being the highest dosage technically possible. The mice were periodically scored for their clinical symptoms, weighed and autopsied at the end of the 14-day observation period. At all dose levels, Vivaglobin® was tolerated without adverse reactions. The highest technically feasible dose of 8.0 g/kg provides a safety margin of at least 40 to 80 when compared to a usual human dose.

In another acute toxicity study, Vivaglobin® was administered subcutaneously to rats. Vivaglobin® was tested in one group at a dose level of 600 mg/kg. Six control rats were treated with placebo. The rats were periodically scored for their clinical symptoms, weighed and autopsied at the end of the 14 days of observation. No deaths occurred after single subcutaneous administration to rats of both sexes, observed over a period of 14 days. At this dose level, Vivaglobin® was tolerated without adverse reactions. A dose of 600 mg/kg Vivaglobin® provides a safety margin of a factor of at least 3 to 6 when compared to a usual human dose.

An acute intramuscular toxicity study was also performed in rats. Vivaglobin® was administered at dose levels of 0.4, 0.8 and 1.6 g/kg. The rats were periodically scored for their clinical symptoms, weighed and autopsied at the end of the 14 days of observation. Vivaglobin® was tolerated without adverse reactions at all dose levels. A dose of 1.6 g/kg Vivaglobin® provides a safety margin of a factor of at least 8 to 16 when compared to a usual human dose.

Local tolerance studies were performed in rabbits. Vivaglobin® was administered subcutaneously at a dose of 80 mg per rabbit (0.5 mL/rabbit). Reactions were assessed after three days and eight days after injection. Neither clinical observation nor gross pathological or

histopathological examination revealed relevant alterations. Vivaglobin® was regarded as locally tolerable after subcutaneous injection.

In another study, four rabbits were injected intramuscularly with 80 mg Vivaglobin® per rabbit (0.5 mL/rabbit) into the thigh. Contralateral intramuscular injections with 80 mg unpasteurized Vivaglobin® per rabbit of served as control. Reactions were assessed two or seven days after injection. The only finding was a local hemorrhage and mild muscle fiber degeneration on Day 2 with an almost complete recovery on Day 7. Vivaglobin® was regarded as locally tolerable after intramuscular injection.

C. Neoantigenicity

The potential for ---------- resulting from the ---------- step included in the manufacturing process of Vivaglobin® was evaluated in rabbits and guinea pigs. These studies revealed no evidence for the existence of neoantigens in pasteurized Vivaglobin® samples.

D. Conclusion

The results of the preclinical toxicological and safety studies suggested sufficient tolerance and safety of Vivaglobin® in human patients to support clinical trials with subcutaneous administration. Vivaglobin® was well tolerated in toxicological studies at doses representing multiples of the anticipated clinical dose after subcutaneous administration.

VI. Medical

A. Summary of Clinical Studies

ZLB Behring sponsored the following two open-label, prospective, multicenter, multinational clinical studies that evaluated the pharmacokinetics, efficacy, safety and tolerability of Immune Globulin Subcutaneous (Human), Vivaglobin®, in adult and pediatric subjects with primary immune deficiency (PID):

- A pivotal Phase 2/3 open-label, prospective, multicenter efficacy study conducted in the United States and Canada (Study CE1200_3001) and associated Pharmacokinetic (PK) Sub-study CE1200_3001, and
- A non-IND Phase 3 open-label, prospective, multicenter efficacy study conducted in Europe (Germany, Poland, Spain, Sweden, and Austria) and Brazil (Study CE1200_3002) and associated PK Sub-study CE1200_3002.

Furthermore, ZLB Behring also previously sponsored two additional clinical studies with the same study medication, but, in these studies, the immune globulin was administered intramuscularly (IM):

- A Phase 1 study (IM) in healthy male volunteers (BI 61.013/7D--101IP)
- A Phase 2 study (IM) in subjects with PID and in healthy volunteers (BI 61.013/7D--201IP-A)

Data from all the above studies were used to evaluate the safety of Vivaglobin®. Data to support the efficacy of Vivaglobin® were derived from the pivotal Study CE1200_3001 and associated PK Sub-study CE1200_3001.

Pivotal Subcutaneous Study

Pivotal Study CE1200_3001, conducted in United States and Canada, was designed to evaluate the pharmacokinetics (PK Sub-study CE1200_3001), efficacy, safety, and tolerability of subcutaneously administered Vivaglobin® in subjects with PID. Subjects enrolled were males and non-pregnant females at least 2 years of age (and at least 10 kg body weight) who were previously treated with IGIV prior to the start of the study. Subjects enrolled in the study were treated weekly with subcutaneous infusions of Vivaglobin® for approximately 15 months.

One week after subjects had received their regularly scheduled IGIV dose, they began the wash-in/wash-out (W/W) phase and received an initial weekly Vivaglobin® dose of approximately 120% (on a mg/kg basis) of their weekly-equivalent IGIV dose. Vivaglobin® doses administered in the efficacy phase of Study CE1200_3001 were derived from the results of PK Sub-study CE1200_3001, which was conducted concurrently in a subset of subjects. A determination was made of the average dose adjustment for Vivaglobin® by comparing the AUC from the previous IGIV treatment to the adjusted area under the curve (AUC) of IgG concentrations during Vivaglobin® therapy. The subcutaneous weekly dose of Vivaglobin® administered in the study was to achieve an AUC that was non-inferior to the AUC achieved during the previous IGIV therapy.

The primary objective in the efficacy phase (12-month treatment period) of Study CE1200_3001 was to evaluate whether the mean number of clinically documented serious bacterial infections (SBIs) was less than one per subject year. Determination of the number, type, and duration of all types of infections, as well as other secondary objectives, was also performed.

Previous Intramuscular Studies

Study BI 61.013 / 7D--101IP was a placebo-controlled, dose-ranging, single-blind Phase 1 study in 26 healthy male volunteers, performed between August 1986 and September 1987 to assess the tolerability and virus safety of single-dose IM administration of the same formulation used for Vivaglobin®. Tolerability was assessed by measurement of vital signs, laboratory parameters, physical examination, and adverse events (AEs).

Study BI 61.013 / 7D--201IP-A was an open-label, multicenter, uncontrolled Phase 2 single- or multiple-dose study conducted between January 1991 and July 1991 in 147 subjects to assess safety and tolerability of single- and multiple-dose IM administration of the same formulation used for Vivaglobin®. Tolerability was assessed by measurement of vital signs, laboratory parameters, physical examination, and AEs.

B. Human Pharmacokinetics and Bioavailability

The United States and Canada PK Sub-study CE1200_3001 was specifically designed to determine the subcutaneous Vivaglobin® dose required to provide the intravascular exposure

(i.e., AUC) standardized to seven days that is non-inferior to the AUC provided by the subject's previous IGIV during a one-month treatment period. The dosing regimen for IGIV is about monthly (every 3 or 4 weeks), whereas dosing of Vivaglobin® is weekly. Average trough concentrations during subcutaneous Vivaglobin® treatment and adjusted AUC values (standardized to the respective sampling period) of IgG concentrations measured during the initial IGIV treatment period were compared to determine the appropriate dose for weekly subcutaneous Vivaglobin® therapy.

For the PK Sub-study, 24 subjects with PID and with at least 3 months of prior treatment with IGIV were enrolled for the pharmacokinetic evaluation. Twenty subjects completed the W/W period. Nineteen of these subjects were evaluable per-protocol. The average starting dose of Vivaglobin® was approximately 120% of the weekly equivalent IGIV dose. Subsequently, the dose of Vivaglobin® was adjusted individually for each PK subject to provide 100% of the AUC for the subject's previous IGIV treatment. The individual subject's (body weight adjusted) weekly dose of Vivaglobin® was derived at the end of the W/W period, based on the difference between actual and target trough IgG levels. The PK Sub-study subjects continued with this dose of Vivaglobin® during the efficacy phase.

The objective to determine a dose to provide non-inferiority of AUC for Vivaglobin® ($AUC_{Vivaglobin}$) vs. AUC for IVIG (AUC_{IGIV}) was met. For the 19 per-protocol subjects completing the W/W phase, the average adjusted Vivaglobin dose in mg/kg body weight in comparison to the previous IGIV dose was 137% (range: 103% to 192%). This corresponded to a mean weekly Vivaglobin® dose of 165 mg/kg (range: 63 to 319 mg/kg). Following 10-12 weeks of treatment with Vivagloblin® at this adjusted dose, the final steady-state AUC determinations were made. The standardized steady-state geometric mean ratio of $AUC_{Vivaglobin}$ to the AUC_{IGIV} was 94.5% (range 71.4 to 110.1%) with a lower 95% confidence limit of 89.8% for the per-protocol population (n = 17). Table 2 summarizes additional pharmacokinetic parameters for this study including dosing and serum IgG peak and trough levels following treatment with IGIV and Vivaglobin®.

Table 2: Summary of Additional Pharmacokinetics Parameters – US and Canada PK Sub-study – Per-protocol Subjects

	IGIV	**Vivaglobin®**
Number of Subjects	17	17
Dose*		
Mean	120 mg/kg	165 mg/kg
Range	55 – 243 mg/kg	63 – 319 mg/kg
IgG peak levels		
Mean	1735 mg/dL	1163 mg/dL
Range	1110 – 3230 mg/dL	743 – 2240 mg/dL
IgG trough levels		
Mean	883 mg/dL	1064 mg/dL
Range	430 – 1600 mg/dL	547 – 2140 mg/dL

* For IGIV: weekly-equivalent dose

The time course of serum IgG levels after IGIV treatment is well known and characterized by a typical pronounced ratio of peak to trough IgG concentrations while subcutaneous treatment was shown to be associated with much more stable IgG levels and much less of a difference between peak and trough concentrations.

In conclusion, data derived from this PK Sub-study showed that subcutaneous Vivaglobin®, administered at an average of 137% of the IGIV weekly-equivalent dose, yielded an equivalent intravascular exposure to IGIV with respect to AUC of IgG levels over time.

C. Summary of Efficacy

In the pivotal study conducted in the United States and Canada (Study CE1200_3001), 65 adult and pediatric PID subjects previously treated monthly with Immune Globulin Intravenous (Human) (IGIV) were switched to weekly subcutaneous administrations of Vivaglobin® for 12 months. The pharmacokinetic phase of this study established the Vivaglobin® dose that provided an IgG intravascular exposure (area under the curve; AUC) that was not inferior to the AUC of the weekly-equivalent IGIV dose. The per-protocol efficacy analysis included 51 subjects. Subjects received a weekly mean Vivaglobin® dose of 158 mg/kg body weight (range: 34 to 352 mg/kg), which was 136% (range: 99 to 188%) of their previous weekly-equivalent IGIV dose.

The primary endpoint of the study, the annual rate of SBIs, defined as bacterial pneumonia, meningitis, sepsis, osteomyelitis, and visceral abscesses, was 0.04 infections per subject year (one-sided upper 99% confidence interval: 0.14) for the per-protocol set (n = 51). Pneumonia was reported in two subjects. The annual rate of any infections, a secondary endpoint, was 4.4 infections per subject year.

The IgG subclass levels observed in this study were consistent with a physiologic distribution pattern (mean values) IgG_1: 703 mg/dL, IgG_2: 278 mg/dL, IgG_3: 36 mg/dL, IgG_4: 30 mg/dL.

Table 3 summarizes the dosing and annual rate of infections for the efficacy phase of this study.

Table 3: Dose and Annual Rate of Infections with Vivaglobin® – Per-protocol Subjects Efficacy Phase of the US and Canada Study

Number of Subjects (Efficacy)	51
Vivaglobin® Dose Mean % Previous IGIV Dose (range): Mean: Range:	 136% (99 – 188%) 158 mg/kg b.w. 34 – 352 mg/kg b.w.
Annual Rate of Serious Bacterial Infections:	0.04 infections/subject year
Annual Rate of Any Infections:	4.4 infections /subject year

b.w.: body weight

Table 4 provides a summary of missed school or work and hospitalization due to infection, which were secondary endpoints.

Table 4: Summary of Secondary Efficacy Variables – Per-protocol Subjects Efficacy Phase of the US and Canada Study

Number of Subjects	51
Total Number of Subject Days	18,949
Total Number of Days Missed School/Work Due to Infection (%)	192 (1.0%)
Annual Rate Missed School/ Work Due to Infection (days/ subject year)	3.70
Total Number of Days Hospitalized Due to Infection (%)	12 (< 0.1%)
Annual Rate of Hospitalization (days/subject year)	0.23

Table 5 provides a summary of additional secondary efficacy endpoints for the US and Canada study. This includes analyses of infections of all types, fever, antibiotic use, and hospitalization or missed school or work due to infection.

Table 5: Summary of Secondary Efficacy Analyses: Per-Protocol Set for the US and Canada Study

Secondary Endpoint			**Study CE1200_3001 (N=51)**
Total Number of Subject Days			18,949
Infections of all types	Annualized infection rate (# infections/subject year)		4.43
	Annualized infection days rate (# infection days/subject year)		118.04
	Annualized Rate of Infection Severity (# infections/subject year)	Mild	2.16
		Moderate	1.75
		Severe	0.35
Fever	Annualized fever rate (# fever episodes/subject year)		0.17
	Annualized fever days rate (# fever days/subject year)		0.23
Antibiotic use	Annualized antibiotic use rate (# days antibiotic use/subject year)		120
Hospitalization	Total Number of Days Hospitalized Due to Infection (%)		12 (< 0.1%)
	Annualized hospitalization rate (# days hospitalized/subject year)		0.23

Efficacy Results in Subpopulations

In order to determine whether differences in treatment effects occurred within distinctive subpopulations, several subgroup analyses of infections and IgG trough concentrations were conducted and revealed no conspicuous pattern in any of the subpopulations. Vivaglobin® was evaluated in children (n=6) and adolescents (n=4) in the US and Canada study and in 16 children and 6 adolescents in the non-IND study. There were no apparent differences in the safety and

efficacy profiles as compared to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and efficacy of Vivaglobin® was not studied in pediatric subjects under two years of age.

Clinical studies of Vivaglobin® did not include sufficient numbers of subjects 65 and over to determine whether they response differently than younger subjects. Subgroup analysis by ethnic groups was too small to draw reliable conclusions.

Vivaglobin® use in other special populations (e.g., pregnant or lactating mothers) has not been sufficiently examined in clinical studies, and Vivaglobin® should be used at the discretion of the attending physician.

Statistical Review and Evaluation

Study CE1200_3001: The primary efficacy analysis was based on the number of documented SBIs per year. The null hypothesis for the primary analysis was that the rate of serious bacterial infection episodes was greater than one per subject-year. This rate along with its one-sided 99% upper confidence interval (CI) was estimated using Poisson regression. The primary analysis was based on the per-protocol data set, which contained only subjects who had completed the 12-month efficacy phase. The null hypothesis was to be rejected if the upper 99% CI was less than one.

Different approaches were used to evaluate the sensitivity of the analysis of SBIs and any infections with regard to the handling of drop-outs and the underlying assumption of the Poisson distribution. All analyses were performed for the full analysis set and the per-protocol set. The safety analysis included all subjects that had received Vivaglobin® and safety variables were assessed using descriptive statistics.

Statistical methods for the PK sub-study were descriptive analyses of Vivaglobin® dose adjustments. AUC was calculated according to the trapezoidal rule, with outliers not considered. PK non-inferiority of Vivaglobin® could be concluded if the lower 95% confidence limit of the geometric mean of the AUC ratios standardized to a 7-day period exceeded the value of 0.8.

D. Safety Summary Across Studies

In the US and Canada clinical study, the safety of Vivaglobin® was evaluated for 15 months in 65 subjects with PID. Table 6 summarizes subjects reporting treatment-emergent adverse events (AEs) occurring after the start of Vivaglobin® administration.

Table 6. Summary of Subjects with Adverse Events after Vivaglobin® Administration in the US and Canada Study

	CE1200_3001	
	N	**%**
Subjects treated	65	100.0 %
Subjects with adverse events (AEs)	65	100.0 %
Subjects with related AEs	63	96.9 %
Subjects with serious AEs	9	13.8 %
Subjects with related serious AEs	0	0
Subjects who died due to AEs	0	0
Subjects who died due to related AEs	0	0
Study drug permanently discontinued due to AEs	5	7.7 %
Study drug permanently discontinued due to related AEs	4	6.2 %

AE = adverse event, N = number of subjects

The most frequent adverse reaction was local reaction at the injection site. Table 7 summarizes the most frequent adverse events by subject reported in the clinical study, and Table 8 summarizes the most frequent adverse events by infusion.

Table 7: Most Frequent Adverse Events by Subject *Irrespective* of Causality* in the US and Canada Study

Adverse Events (≥ 10% of subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site:	60 (92%)
Non-Injection Site Reactions:	
Headache	31 (48%)
Gastrointestinal disorder	24 (37%)
Fever	16 (25%)
Nausea	12 (18%)
Sore throat	11 (17%)
Rash	11 (17%)
Allergic reaction	7 (11%)
Pain	6.7 (10%)†
Diarrhea	6.7 (10%)†
Cough increased	6.7 (10%)†

*Excluding infections

† Due to missing subject diary information, values listed are estimates.

Table 8: Most Frequent Adverse Events by Infusion *Irrespective* of Causality* in the US and Canada Study

Adverse Events (≥ 1% of infusions) (Number of Infusions: 3656)	**No. of Adverse Events** (Rate**)
Adverse Events at the Injection Site:	1789 (49%)
Mild	1112 (30%)

Moderate	601 (16%)
Severe	65 (2%)
Unknown Severity	11 (< 1%)
Non-Injection Site Reactions:	
Headache	159 (4%)
Gastrointestinal disorder	40.3 (1%)†

*Excluding infections; **Rate = number of reactions/infusion
† Due to missing subject diary information, values listed are estimates.

Table 9 summarizes the most frequent related adverse events by subject reported in the clinical study, and Table 10 summarizes the most frequent related adverse events by infusion.

Table 9: Most Frequent Related Adverse Events by Subject* in the US and Canada Study

Related Adverse Event (≥ 2 subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site:	60 (92%)
Non-Injection Site Reactions:	
Headache	21 (32%)
Nausea	7 (11%)
Rash	4 (6%)
Asthenia	3 (5%)
Gastrointestinal disorder	3 (5%)
Fever	2 (3%)
Skin disorder	2 (3%)
Tachycardia	2 (3%)
Urine abnormality	2 (3%)

*Excluding infections

Table 10: Most Frequent Related Adverse Events by Infusion* in the US and Canada Study

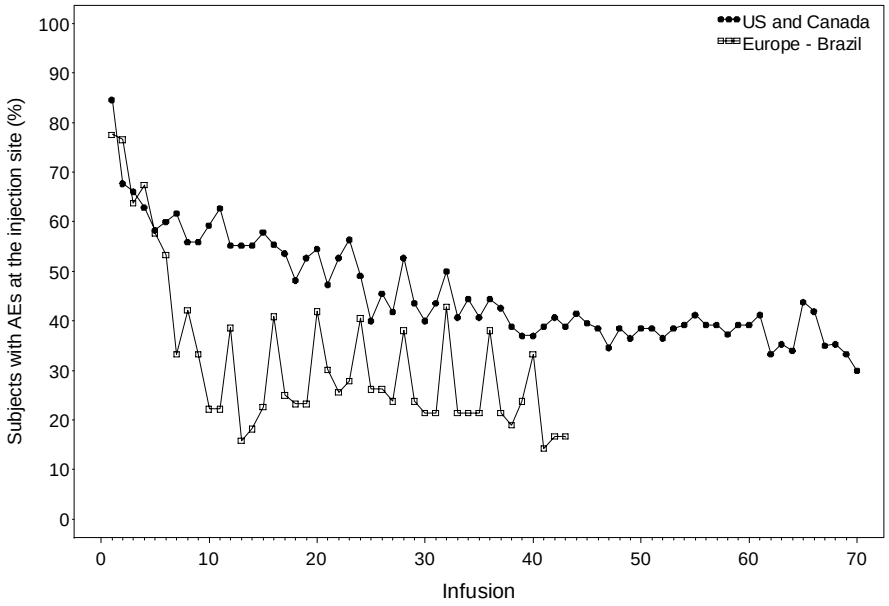
Related Adverse Event (≥ 2 AEs) (Number of Infusions: 3656)	**No. of AEs (Rate**)**
Adverse Events at the Injection Site:	1787 (49%)
Non-Injection Site Reactions:	
Headache	59 (1.6%)
Rash	9 (0.2%)
Nausea	9 (0.2%)
Nervousness	4 (0.1%)
Asthenia	3 (0.1%)
Gastrointestinal disorder	3 (0.1%)
Skin disorder	3 (0.1%)
Urine abnormality	3 (0.1%)
Fever	2 (0.1%)
Dyspnea	2 (0.1%)
Gastrointestinal pain	2 (0.1%)
Tachycardia	2 (0.1%)

*Excluding infections; **Rate = number of reactions/infusion

In the non-IND Europe and Brazil clinical study, the safety of Vivaglobin® was evaluated for 10 months in 60 subjects with PID. The adverse events and their rates reported in this study were similar to those reported in the US and Canada study, with two notable exceptions for the related adverse events. These events were 59 episodes of headache (1.6%) and 2 episodes of fever (0.1%) in the US and Canada Study and no episodes of headache and 18 episodes of fever (0.8%) in the Europe and Brazil study.

Local (Injection Site) Reactions - Local injection site reactions consisting of mostly mild or moderate swelling, redness and itching, were observed with the use of Vivaglobin®. No serious local site reactions were observed. The majority of injection site reactions resolved within four days. Additionally, the number of subjects reporting local injection site reactions decreased substantially after repeated use (see Figure 1). Only three subjects in the US and Canada study and one subject in the Europe and Brazil study discontinued due to local site reactions.

Figure 1: Subjects Reporting Local Site Reactions By Infusion



Note: Analysis is confined to 70 infusions.

During clinical trials, no cases of infection due to hepatitis A, B, or C virus, parvovirus B19, or HIV were reported with the use of Vivaglobin®.

Previous Intramuscular Studies

In IM Study BI 61.013 / 7D--101IP, vital signs were assessed as a measure of immediate tolerability. Vital signs that deviated from normal ranges were classified as AEs; no other AEs were recorded. There was no relationship between dose and AEs. The product was well tolerated and neither local nor intravascular reactions were recorded. There was no evidence of transmission of any viral infection (human immunodeficiency virus [HIV], hepatitis B virus [HBV], or hepatitis C virus [HCV]) as assessed for up to 1 year in 16 subjects.

In IM Study BI 61.013/7D--201IP-A, 19 (13%) of 147 subjects exhibited at least one AE; a total of 26 events were reported. The most common AE was injection site pain, reported by 10 (7%) subjects. Seven of the 10 AEs were classified as mild, and three AEs were classified as moderate intensity. All other AEs occurred only infrequently (2% or fewer subjects), and none required any intervention. There were no serious AEs.

E. Conclusion

Safety: The most common AEs after administration of Vivaglobin® are local reactions at the injection site. These reactions are predominantly mild and self-limiting reactions and are mostly related to the volume administered. In contrast, non-injection site reactions occur at a much lower rate of 0.13 per infusion. Over time, the incidence and rate of all treatment-emergent AEs decrease. This applies in particular to AEs at the injection site (0.01 per infusion). Based on the findings in clinical studies and the spontaneous reports from market surveillance in countries where Vivaglobin® is available, it can be concluded that treatment with Vivaglobin® is judged to be safe and well tolerated.

Efficacy: The efficacy of Vivaglobin® was demonstrated by the pivotal study of 51 subjects treated for 12 months. In accordance with the CBER/FDA consensus, presented to the 65th Blood Products Advisory Committee held on 17 March 2000, CBER/FDA considers an Immune Globulin preparation to be efficacious if the infection rate is <1 serious bacterial infections (defined as bacterial pneumonia, meningitis, sepsis, osteomyelitis, or visceral abscess) per subject year. In Vivaglobin® treated subjects, the rate of serious bacterial infections was 0.04 per subject year.

VII. Post-Licensure Commitments

1. ----------
2. ----------

VIII. Marketing History

Vivaglobin® is currently approved in Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Great Britain, Hungary, Ireland, Netherlands, Norway, Portugal, and Sweden.

LICENSING REVIEW COMMITTEE

Mei-ying W. Yu, Ph.D. (Scientific Lead)	Paul Aebersold, Ph.D. (Clinical Safety and Efficacy)
Angela Shen (CMC/Establishment)	Bhanu Kannan, M.S. (Bioresearch Monitoring)
Douglas Frazier (CMC/Product)	Pei Zhang, M.D. (CMC/Product)
Weishi (Vivian) Yuan, Ph.D. (Statistic Evaluation)	Michael Wiack (Regulatory Project Manager)