Statistical Review and Evaluation, August 27, 2009 - Gammaplex

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Statistical Review and Evaluation

BLA
BLA/Supplement Number: 125329/0
Product Name: Gammaplex
Indication(s): Primary Immunodeficiency Disease
Applicant: Bio Products Laboratory
Date(s): 11/17/08
Review Priority: Standard
Statistical Branch: Therapeutics Evaluation Branch
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5. EXECUTIVE SUMMARY

This is an original BLA application submitted by Bio Product Laboratory (BPL) for Gammaplex in treating Primary Immunodeficiency Disease (PID). Gammaplex is an immune globulin product intended for intravenous (IV) administration.

This submission includes one Phase 3, single- arm, open-label, multi-center study. The objective of the study is to evaluate the efficacy, safety, and pharmacokinetics of Gammaplex. The primary efficacy endpoint is serious, acute, bacterial infection rate. The one-sided 99% upper confidence limit for the rate needs to be less than 1 to meet the FDA's efficacy requirement. In addition, an important safety endpoint is the proportion of infusions with 1 or more temporally associated Adverse Events (AEs). To meet the FDA's safety requirement, the one-sided 95% upper confidence limit for the proportion needs to be less than 40%.

The study enrolled 50 subjects all of which had at least one infusion of the study drug. The study results show that Gammaplex meets both FDA's efficacy and safety requirements listed above. No serious, acute, bacterial infection was observed during the study period. With zero mean infection rate per subject year, the one-sided 99% upper confidence limit was 0.101 per subject year using the exact method implemented in --(b)(4)--, which is less than FDA's efficacy threshold value of 1. The one-sided 95% upper confidence limit for the proportion of infusions with at least one AE up to 72 hours after the infusion is 23.9%, which is less than FDA's safety threshold value of 40%. Based on all the necessary statistical evaluations, this reviewer has no objection to the licensure approval of this product.

However, please note that for the one-sided 99% upper confidence limit for the serious, acute, bacterial infection rate, there is a discrepancy between the sponsors's reported value (0.088) in their draft Package Insert (PI) and this reviewer's calculated value (0.101).

2.INTRODUCTION

2.1 Overview

Gammaplex is an immune globulin intravenous (human) indicated for the treatment of PID. It is manufactured by BPL, UK using pooled plasma from healthy U.S. donors. There is only one pivotal study (GMX01) in this submission. Besides this pivotal study, there is a PK study (GMX03).

The pivotal trial (GMX01) is a single-arm, open-label, multi-center study. The objective of the study is to evaluate the efficacy, safety, and pharmacokinetics of Gammaplex. The primary efficacy endpoint is serious, acute, bacterial infection rate. FDA requires the one-sided 99% upper confidence limit for the infection rate to be less than 1 to meet the efficacy criteria. In addition, an important safety endpoint is the proportion of infusions with 1 or more temporally associated AEs. To meet FDA's safety requirement, the one-sided 95% upper confidence limit for the proportion needs to be less than 40%.

2.2 Data Sources

The materials reviewed include relevant parts of **PI Section 14.1 clinical study in patients** and **Section 5.3.5.2.1** of the BLA submission, **GMX01 Clinical Study Report**.

Data sets analyzed are: Ae2m.xpt (STN 125328\0\5, DATS Log Number 458173) Diaryq.xpt, diarytmp.xpt, antibi_m.xpt, Visits.xpt, Expoinf.xpt, and Demo.xpt (STN 125328\0\4, DATS Log Number 456130)

3.STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study Design and Endpoints

The pivotal study (GMX01) is a multi-center, single-arm, open-label study to evaluate the efficacy, safety, and pharmacokinetics of Gammaplex in PID. The primary efficacy endpoint is serious, acute, bacterial infection rate.

The secondary efficacy endpoints include:

- Number and proportion of subjects with trough IgG levels that were [redacted]600 mg/dL from Week 15 onwards;
- Number of days of work/school missed because of infection per subject year;
- Number of days of hospitalization because of infection per subject year;
- Number of visits to physicians for acute problems and/or number of visits to hospital emergency rooms per subject year;
- Other infections documented by fever, a positive result on a radiograph, and/or culture;
- Number of infectious episodes per subject per year;
- Number of days on therapeutic antibiotics.

Patient Disposition, Demographic and Baseline Characteristics

Fifty subjects were enrolled in the study and received Gammaplex infusions every 21 days or 28 days for up to 12 months. All subjects received at least 1 infusion of Gammaplex. They were all included in the intent-to-treat (ITT) population. The ITT population was used for all safety and efficacy analyses.

Among the 50 subjects enrolled, 45(90%) completed the study and returned for both follow-up visits. Five (10%) subjects discontinued treatment: 3 discontinued because of adverse events, 1 lost to follow-up and 1 withdrew consent. The IDs of the discontinued subjects and their days on the study (from date of first infusion to date of last visit excluding the second follow-up visit) are: Subjects --(b)(6)-- (49 days), --(b)(6)-- (346 days), --(b)(6)-- (29 days), Subject --(b)(6)-- (308 days), Subject --(b)(6)-- (156 days). (See Statistical Methodologies section for how such subjects are counted in the primary efficacy analysis).

The following table shows the demographic characteristics of ITT population.

Category	Statistics
Age	
Mean	44.0
SD	19.10
Median	44.5
Range	9-78
[redacted]	12(24%)
	38(76%)
< 60	
Gender	
Male	26(52%)
Female	24(48%)
Race	
Caucasian	46(92%)
African-American	2(4%)
	2(4%)

Category	Statistics
Hispanic	

Statistical Methodologies

In the protocol the sponsor proposed the following methodologies:

----------(b)(4)----------

For subjects who completed the study, first follow-up visit (F1) will be the last visit. If subjects dropped out, the date of last visit was when he/she was last seen during the study. The number of subject years was calculated by summing the total subject days and dividing by 365.

The one-sided 99% upper confidence limit was estimated by using the generalized linear model for Poisson regression with log link. The analysis procedure was implemented in -(b)(4)- with procedure --(b)(4)--.

The secondary efficacy variables were analyzed using descriptive statistics. The sponsor followed their proposed methodologies when analyzing the data as they planned.

This reviewer used an alternative methodology, the exact method from the --(b)(4)-- software (one sample Poisson rate), to calculate the one-sided 99% upper confidence limit for infection rate to take care of zero outcome (no serious acute bacterial infection) case. For detailed explanation, see Section **Results and Conclusions**.

Results and Conclusions

Sponsor's results

The study showed no serious acute bacterial infection during the study period. Consequently, the mean event rate of serious acute bacterial infections per subject per year was zero, which resulted in the one-sided 99% upper confidence limit being Not-Applicable (NA). At the clinical reviewer’s request, the sponsor later used an alternative method to calculate the confidence limit and reported .088 in their draft PI.

FDA Statistical Reviewer’s findings

The one-sided 99% upper confidence limit is 0.101 using the exact method implemented in --(b)(4)-- (one sample Poisson rate).

3.2 Evaluation of Safety

The sponsor reported that of the 703 infusions, 149(21.2%) are associated with at least one AE up to 72 hours after the infusion. The one-sided 95% upper confidence limit for the proportion is 23.9%, which is less than FDA’s safety threshold value 40%. The results are confirmed by the statistical reviewer.

For some AEs, the information on the time when it happened is missing, so a worst case analysis was conducted; all AEs happened on the same day of an infusion or within 4 days after the infusion are included in the analysis. This sensitivity analysis shows that the proportion of infusions with an AE is 25.7%. The corresponding one-sided 95% upper confidence limit is 28.6% (< 40%).

3.3 Gender, Race, Age and Other Special/Subgroup Populations

Primary efficacy results across subgroups:

1. Age group

Age	Infection Rate	*Upper Confidence Limit
	0	0.401
< 60	0	0.134

2. Gender

Gender	Infection Rate	*Upper Confidence Limit
Male	0	0.184
Female	0	0.222

*: One-sided 99% upper confidence limit

3. Race.

Race	Percentage
Caucasian	46(92%)
African-American	2(4%)
Hispanic	2(4%)

As can be seen from the above table, 92% of subjects are Caucasian. Both African-American and Hispanic subgroup sizes are too small for any valid subgroup analyses. So subgroup analysis by race was not conducted.

Safety results across subgroups:

Only subgroup analysis by gender was performed and results are the following:

AEs*				Product-related AEs*			
Males n=26		Females n=24		Males n=26		Females n=24	
#subjects	#AEs	#subjects	#AEs	#subjects	#AEs	#subjects	#AEs
26 (100%)	257	24 (100%)	375	8 (30.8%)	43	16 (66.7%)	147

*Any AEs

	Males #Infusions (n=382)	Males # subjects (n=26)	Males #AE	Females #Infusions (n=321)	Females # subjects (n=24)	Females #AE	
Infusions with AEs **	59 (15.4%)	21 (80.8%)	86	90 (28.0%)	22 (91.7%)	151	
Infusions with product-related AEs **	14 (3.7%)	6 (23.1%)	25	50 (15.6%)	16 (66.7%)	90	

** AEs reported up to 72 hours after the infusion.
From the tables we can see that females tend to have more AEs and product-related AEs than males.

4. SUMMARY AND CONCLUSIONS

Statistical Issues and Collective Evidence

The study results show that Gammaplex meets FDA's associated efficacy and safety requirements. No serious, acute, bacterial infection was observed during the study period. With zero mean infection rate per subject year, the one-sided 99% upper confidence limit was 0.101 per subject year using the exact method implemented in --(b)(4)--, which is less than FDA's efficacy threshold value of 1. The one-sided 95% upper confidence limit for the proportion of infusions with at least one AE up to 72 hours after the infusion is 23.9%, which is less than FDA's safety threshold value of 40%. Based on all the necessary statistical evaluations, this reviewer has no objection to the licensure approval of this product.

However, please note that for the one-sided 99% upper confidence limit for the serious, acute, bacterial infection rate, there is a discrepancy between the sponsors' reported value (0.088) in their draft Package Insert and this reviewer's calculated value (0.101).

Letter Ready Comments

The one-sided 99% upper confidence limit is 0.101 using the exact method implemented in --(b)(4)-- (one sample Poisson rate). You reported a different value, 0.088. Please provide details of your calculation including method and software you used.