

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
Division of Biostatistics (HFM-215)

STATISTICAL REVIEW AND EVALUATION

Type/Application ID/Amendment #: BLA 125105/708

Applicant: Baxter

Product Name: IGIV, 10% given Subcutaneous

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Clinical/Product Reviewer: Hon Sum Ko, Ph. D.

Supervisory Concurrence:

1st Level Review

Supervisor Name: Jessica Kim, Ph. D.

Supervisor Title: Team Leader

Concur _____ Not Concur _____

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Review Project Manager: Nannette Cagungun.

Cc:

Original/HFM-380/Hon Sum Ko, Ph. D.

HFM- 215 /Chronological File

HFM-215/Henry Hsu, Ph. D.

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1. EXECUTIVE SUMMARY

The primary objective of Study 160601 was to determine the tolerability and pharmacokinetic (PK) equivalence in terms of area under the IgG plasma concentration versus time curve (AUC) per week between intravenous (IV) and subcutaneous (SC) administration of IGSC, 10% for the subjects with Primary Immunodeficiency Diseases (PID). The statistical review was focused on a further aim to evaluate the protective effect against infection of SC in terms of acute serious bacterial infections. The original submission did not provide reference sources of data required in the analysis-ready datasets which correspond to the tables of results reported in the submission to facilitate the review. Information Request letters were conveyed regarding to these analysis-ready datasets, questions of the clinical study report, and the labeling. Based on Baxter's responses with re-submitted analysis-ready datasets, the results of serious infection and protective effect against infection were verified.

2. BACKGROUND

PIDs are heritable disorders of immune system function primarily associated with single gene defects. Defective antibody formation is the most common abnormality in the majority of primary immunodeficiency (PID) diseases. It is most often reflected by a decrease in serum immunoglobulins, which in turn leads to increased susceptibility to bacterial infections especially of the sinopulmonary tract.

The manufacturing process of IGSC is the same as for Baxter's currently licensed GAMMAGARD LIQUID Immune Globulin Intravenous (Human), 10% Solution (IGIV, 10%) product.

The primary objective of the study was to determine the pharmacokinetic (PK) equivalence in terms of area under the IgG plasma concentration versus time curve (AUC) per week between intravenous (IV) and subcutaneous (SC) administration of IGSC, 10%. Maintenance of high IgG trough levels after SC treatment presumably results in a protective effect against infection comparable to that afforded by IV treatment. A further aim of this study is to evaluate the protective effect against infection of SC in terms of acute serious bacterial infections.

3. STATISTICAL EVALUATION

The primary objective of the study is to determine the efficacy based on the PK equivalence between IV and SC of IGSC, 10%. Therefore, statistical review is focused on the evaluation of protective effect against infection of IGSC in terms of acute serious bacterial infections.

Demographic analysis is performed for this study. It shows that (1) 22 subjects are female and 27 are male; (2) 35 subjects are 12 years and older (4 are between 12 and 16) and 14 subjects are between 2 and 12 years old; (3) 46 subjects are Caucasian, 2 are black, and 1 is Hispanic. The results of demographic analysis are in the appendix. This analysis confirms the sponsor's demographic report.

For the primary safety endpoint of serious infection, statistical analysis was performed using the analysis-ready dataset (sabactsm.xpt) provided in sponsor's responses. With 3 serious validated bacterial infections (all bacterial pneumonia) during SC therapy reported in the submission, the annual rate of serious infection per subject year for administration of IGSC, 10 % is 0.06. The upper 99% confidence limit is 0.133 which meets FDA's criterion that annual rate of serious infection must be less than 1 per subject year.

During the mid-cycle review, the statistical analyses were also performed to verify the results of any infections and associated events, presented in Table 14.2.2-14 and Table 14.2.2-15 in the Full Clinical Study Report as well as the summary results shown in the labeling in the submission.

However, the data source for acute serious bacterial infection and the annual infection rate of parameters of associate events were not submitted as analysis-ready datasets in the original submission. The information of infections and other information related to labeling were scattered in the CRT file. Consequently, the reference sources of data to verify the results were not available. Without the adequate analysis-ready datasets, it was not possible to confirm the results. The statistical comments were conveyed to the review committee as: *In order to perform statistical analysis and to verify the results stated in clinical study report and the labeling, the reference sources of data are required in the analysis-ready datasets which correspond to the tables of results reported in the submission. Therefore, the sponsor should submit analysis-ready files of **individual datasets** that provide infection data that correspond to tables of infection rates (such as Tables 14.2.2-14, 14.2.2-15) in the Clinical Study Report, and the datasets that correspond to the summary table of infections and associated events in the Labeling of the submission. In addition, please submit the datasets for the Poisson model in SAS program (i.e. "sabactsum" and "infsum1a").*

An IR letter regarding to these comments was issued on December 17, 2010. CBER received Baxter's responses on December 27, 2010. With sponsor's re-submitted analysis ready datasets, statistical analyses were able to be performed to confirm the results, mainly reported in the summary table 12 of package insert. Based on Poisson model, the annual rates (per subject year) with the corresponding confidence intervals (CI) for any infection and for different parameters of associate events were estimated using SAS procedure of PROC GENMOD.

These analyses revealed that the total numbers of observation days are not the same for different associated events shown in Table 12 of package insert. By analyzing the provided analysis-ready dataset, the discrepancies of total number of observation time among three associate events are indicated on 7 out of 47 subjects. In the clinical reviewer's opinion, these observation days should be consistent because they are diary records. Consequently, another IR letter was issued to Baxter on January 6, 2011 for this concern. Baxter responded to this request with an explanation on January 14, 2011. These two IR letters and Baxter's responses are included in the following section.

In Baxter's responses, it stated that the discrepancy on total observation days is due to missing data. This response is acceptable. Subsequently, using the updated total number of subject years in the response, the statistical analysis was performed and verified for the annual rates (with 95% confidence intervals) of three associate events: Any infection, Antibiotic use, and Days out of work/school.

However, in the same response letter dated January 14, 2011, Baxter also stated an issue (with explanation) that the result of 5 hospitalizations was changed to 0 in the revised Table 12. The justification of the change is requested by CBER clinical reviewer.

On January 26, 2011, the clinical reviewer received Baxter's responses to his information request about the explanation, and informed this statistical reviewer by e-mail as:

"Baxter has submitted information on the cases with hospitalization. Among the three subjects who had hospitalization, two were in the IV phase of the study, and the one hospitalized in the SC phase had chest pain and was not hospitalized for infection. The original Table with 5 hospitalizations also included cases with outpatient procedures which are now excluded.

Therefore, I agree that hospitalization due to infection in the IGSC treatment phase is zero."

Consequently, with this addition information, this statistical reviewer verified all the results presented in the revised Table 12.

3.1 INFORMATION REQUEST (IR) AND SPONSOR'S RESPONSE RELATED TO STATISTICAL CONCERNS

A) IR on December 17, 2010

Please submit the analysis-ready files of the datasets that support the following information provided in Table 7 “Summary of Infections and Associated Events” (now Table 12) in the latest version of the proposed package insert:

- *Annual rate of any infections*
- *Antibiotic use (prophylactic or treatment) [Total # of subject days, # of subjects (%), Annual rate]*
- *Days out of work/school/day care or unable to perform normal activities [Total # of subject days, # of subjects (%), # of days (%), Annual rate]*
- *Hospitalizations due to infections [Total # of subject days, # of subjects (%), # of days (%), Annual rate]*

Baxter Responses dated January 10, 2011

A list of analysis-ready files of individual datasets replacing the previously submitted was provided: infectrt.xpt, infectsm.xpt, seasonsm.xpt, infect365.xpt, sabact.xpt, sabactsm.xpt, and infumla.xpt. The response also included the SAS program. In addition, an analysis-ready file for infection and associated events (abhosp.xpt) was also included in the sponsor's responses.

B) IR on January 6, 2011

1. The total number of subject days for “Antibiotic use”, “Days out of work/school/day care or unable to perform normal activities” and “Hospitalizations due to infection” in Table 12 of the package insert are 16,236, 16,005 and 16,040, respectively. These numbers should be the same considering 7 subjects out of 47 for each event, however they indicate a discrepancy. The computation using the data from the “abhosp” file provided by Baxter matches the results shown in Table 12. Please explain the discrepancy in the total number of subject days.

2. Please include in Table 12 of the package insert the confidence intervals for the annual rates for the other events (e.g. Antibiotic use, Days out of work/school/day care unable to

perform normal activities and Hospitalizations due to infection) as was provided for “Annual rate of any infections”.

Baxter Responses dated January 14, 2011

1. The different numbers of observation days (subject days) for “Antibiotic use”, “Days out of work/school/day care or unable to perform normal activities” and “Hospitalizations due to infection” in Table 12 are due to occasional missing data in the case report forms. While it is unlikely that any events would have occurred in these periods when a data clarification request did not reveal any, it was felt not appropriate to include these periods in the denominator in the absence of documentation. Baxter proposes to alternatively present the observation days as “subject years” ($16,236/365.2425 = 44.453$; $16,005/365.2425 = 43.837$; $16,040/365.2425 = 43.910$), i.e. rounded to “44” integer years), which will provide a consistent number. This new number of “44 subject years” has been included as well as the “# of days (%)” have been removed in the revised [Table 12](#) below.

2. The confidence intervals for the annual rates for “Antibiotic use”, “Days out of work/school/day care or unable to perform normal activities” and “Hospitalizations due to infection” have been included in the revised [Table 12](#).

Baxter noted that there were 5 hospitalizations listed in Table 12 during SC therapy plus there were 2 during the IV part of the study. In further reviewing the data, 3 of these “hospitalizations” were outpatient procedures for unrelated AEs and thus were not actually hospitalizations and a fourth was a coding error. Thus, the correct total number of hospitalizations for both the SC and IV parts of the study is 3. One was for infection (sinusitis), but it occurred during IV treatment. Table 12 was intended to list only events related to infection, and therefore in the corrected Table 12 the number of hospitalizations for infection during SC therapy is 0.

Revised Table 12. Summary of Infections and Associated Events	
Number of subjects (efficacy phase)	47
Total number of subject years	44
Annual rate of any infections	4.1 (95% CI 3.2 to 5.1) infections/subject year
Antibiotic use [§] (prophylaxis or treatment)	
Number of subjects (%)	40 (85.1%)
Annual rate	50.2 (95% CI 33.4 to 71.9) days/subject year
Days out of work/school/ day care or unable to perform normal activities	
Number of subjects (%)	25 (53.2%)
Annual rate	4.0 (95% CI 2.5 to 6.1) days/subject year
Hospitalizations due to infections	
Number of subjects (%)	0 (0.0%)
Annual rate	0.0 (95% CI 0.0 to 0.1) days/subject year

[§] Included systemic and topical antibacterial, anti-fungal, anti-viral, and anti-protozoal antimicrobials.

4. Comments for the ADaM-like files in this submission

This submission includes ADaM (data tabulation of analysis model) files of SDTM for the pilot project of CDISC. Based on the experience of this submission, sponsor's ADaM-like files are only the subsets of SDTM and they are not **analysis-ready datasets** corresponding specifically to the statistical analyses stated in the SAP. Therefore, ADaM may have benefits for Meta analysis using different datasets after approval but would not facilitate the statistical review process for product approvals.

5. Conclusion

Based on Baxter's responses to IR with re-submitted analysis-ready datasets, statistical analyses were performed and confirmed that the annual rate of serious bacterial infection meets

FDA criterion for IGSC. In addition, the results of other protective effect shown in the summary table of package insert were also verified.

APPENDIX

SEX

Level	Count	Prob
F	22	0.44898
M	27	0.55102
Total	49	1.00000

AGEGRP1

Level	Count	Prob
Subjects aged 12 years and older	35	0.71429
Subjects aged 2 to <12 years	14	0.28571
Total	49	1.00000

AGEGRP2

Level	Count	Prob
Subjects aged 12 to <16 years	4	0.08163
Subjects aged 16 years and older	31	0.63265
Subjects aged 2 to <5 years	1	0.02041
Subjects aged 5 to <12 years	13	0.26531
Total	49	1.00000

RACE

Level	Count	Prob
BLACK	2	0.04082
CAUCASIAN	46	0.93878
HISPANIC	1	0.02041
Total	49	1.00000