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Application Type	BLA
STN	125590
CBER Received Date	July 31, 2015
PDUFA Goal Date	July 29, 2016
Division / Office	OBE/DB
Committee Chair	Pei Zhang. Ph.D.
Clinical Reviewer(s)	Charles Maplethorpe, M.D., Ph.D.
Project Manager	Yu Do, M.S.
Priority Review	No
Reviewer Name(s)	Boris Zaslavsky, Ph.D., Dr.Sc.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renee Rees, Ph.D. Team Leader, OBE/DB/TEB
Branch Chief	Boguang Zhen, Ph.D. Branch Chief, OBE/DB/TEB
Division Director	Estelle Russek-Cohen, Ph.D. Division Director, OBE/DB
Applicant	ADMA Biologics, Inc.
Established Name	Immune Globulin Intravenous (Human), 10% Liquid (RI-002)
(Proposed) Trade Name	(b) (4)
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Intravenous
Dosing Regimen	300-800 mg/kg every 3-4 weeks
Indication(s) and Intended Population(s)	Indicated for the treatment of primary humoral immunodeficiency (PIDD)

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GLOSSARY

CMV	Cytomegalovirus
CVID	Common Variable Immunodeficiency
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGIV	Intravenous Immunoglobulin
ITT	Intent-To-Treat
IV	intravenous
kg	kilogram
mg	milligram
mL	milliliter
mITT	modified ITT population
PIDD	Primary Immunodeficiency Disease
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SBIs	Serious Bacterial Infections
SQ	Subcutaneous
TAAEs	Temporally Associated Adverse Events
TEAEs	Treatment Associated Adverse Events

1. EXECUTIVE SUMMARY

RI-002 is an Immune Globulin Intravenous (Human), 10% Liquid (IGIV) product intended for the treatment of primary immunodeficiency diseases (PIDD) in adults and children.

Study ADMA-003 was a Phase III, multicenter, single arm, open-label study in subjects with PIDD intended to evaluate the pharmacokinetics, efficacy, and safety of RI-002. This study, the only pivotal study for RI-002, enrolled 59 subjects (48 adults and 11 pediatric subjects). The primary efficacy endpoint was the rate of serious bacterial infections (SBI) meeting the FDA Guidance for Industry (2008) criteria. There were no infections experienced during the course of this study meeting the criterion defined for SBIs. The 99% upper one-sided confidence limit for the observed annual SBI rate per subject was 0.066, meeting the success criterion of <1. During the study, 43 (72.9%) subjects experienced at least one temporally associated AE (TAAE), and TAAEs were experienced with 113 of 793 (14.2%) of study infusions. The upper one-sided 95% confidence limit for the observed proportion of infusions with TAAEs (the total number of infusions with TAAEs divided by total number of infusions administered in the study) was 0.164, meeting the FDA criterion of <0.40 (FDA Guidance for Industry (2008), page 4) .

The statistical results of Study ADMA-003 appear to support the use RI-002 in subjects with PIDD for control of SBIs.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

PIDDs are genetically determined disorders of the immune system resulting in greatly enhanced susceptibility to infectious disease, autoimmunity and malignancy. PIDDs include agammaglobulinemia, hyper Immunoglobulin M (IgM) syndromes, common variable immunodeficiency (CVID) as well as other deficiencies of antibody production (hyper IgE syndromes, Wiskott-Aldrich Syndrome and specific antibody deficiency) (Buckley et al., 1991). While individual PIDDs are rare, as a group, it is estimated that between 1:2,000 and 1:10,000 live births are affected by a PIDD. However the National Institutes of Health (NIH) have estimated that there are in excess of 500,000 cases of undiagnosed PIDD in the US. Moreover, PIDDs can present at any age, from birth to adulthood, posing a considerable challenge for the practicing physician to know when and how to evaluate a subject for a possible immune defect. Typical clinical presentations for subjects with PIDDs are:

- antibody deficiency and recurrent bacterial infections
- T lymphocyte deficiency and opportunistic infections
- other lymphocyte defects causing opportunistic infections
- neutrophil defects causing immunodeficiency
- complement deficiencies.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Replacement therapy with Immunoglobulin G (IgG) purified from pools of plasma from multiple donors has been used since the early 1950s, as intramuscular and more recently, as intravenous (IV) immunoglobulin (IGIV), and subcutaneous (SQ) injections. IGIV is indicated to reduce the susceptibility to infections in subjects with primary immunodeficiencies affecting the quantity and/or quality of humoral immunity. Subjects with marked antibody deficiencies are dependent on IGIV therapy for survival.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

On November 06, 2014, FDA sent ADMA the Type B pre-BLA meeting summary with comments regarding the analyses for the primary efficacy endpoint, safety endpoints, and subgroups. The applicant agreed to these changes and submitted a revised Statistical Analytical Plan to IND 15308 (Amendment 20).

On June 26, 2015, FDA sent ADMA an acknowledgement stating we have reviewed and agreed with ADMA's revised initial pediatric study plan. In addition, the Agency acknowledged ADMA's plan to request a deferral of the submission of pediatric data/assessments for children aged 2 to <6 years, 6 to <12 years, and 12 to <16 years and a partial waiver of the requirement for pediatric assessments for neonates (birth to 1 month) and infants (1 month to 2 years).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The applicant submitted data from one completed clinical study (IND 15308; Study ADMA-003). The provided material was the basis for the statistical review.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following documents (module numbers) from the original submission for BLA 125590 were used in this review:

1.14 Labeling
1.2 Cover Letter
2.2 RI-002 Introduction
2.7.3 Summary of Clinical Efficacy (RI-002)
2.7.4 Summary of Clinical Safety (RI-002)
2.7.6 Synopsis of Individual Studies
2.5 Clinical Overview
5.2 Tabular Listing of all Clinical Studies
5.3.5.2 ADMA-003 Clinical Study Report
5.3.5.2 ADMA-003 Documentation of Statistical Methods and Interim Analysis Plan

5.3 Table of Studies/Clinical Trials

Table 1: Listing of RI-002 (ADMA-003) Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	ADMA-003	5.3.5.2	Long-term efficacy and safety; PK analysis	Open-label, Single-arm, Multicenter	RI-002, planned 300-800 mg/kg (actual 284-1008 mg/kg) every 3- or 4-weeks, IV	59	Patients with PIDD	12 months	Complete; Full

IV-Intravenous, PK-Pharmacokinetic, PIDD- Primary Immunodeficiency Diseases
Source: BLA 125590, 5.2 Tabular Listing of All Clinical Studies, Table 1

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 ADMA-003

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective is to demonstrate that RI-002 reduces the frequency of SBIs, as defined by the FDA Guidance for Industry (Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency, 2008), in subjects with PIDD.

The secondary objectives are as follows:

1. To evaluate incidence of all infections (serious and non-serious) per patient-year
2. To evaluate the number of days lost from work/school/usual activities per patient-year due to infections and their treatment
3. To evaluate the number of unscheduled visits to physician/ER due to infections per patient-year
4. To evaluate the time to resolution of infections
5. To evaluate the number of hospitalizations and days of hospitalizations due to infections per patient-year
6. To evaluate the number of days of antibiotic therapy (prophylactic and treatment) per patient-year
7. To evaluate the relationship among dose of RI-002, trough level, and risk of serious and non-serious infections
8. To evaluate trough total IgG and specific antibody levels at regular intervals
9. To evaluate pharmacokinetic profile of total IgG and specific antibody levels.

6.1.2 Design Overview

This is a Phase III, multicenter, single arm, open-label study of RI-002 in subjects with PIDD. Once registered, the subjects were to receive an intravenous infusion of RI-002 on Study Day 1 and every 21 to 28 days thereafter for 1 year according to their current interval of IGIV treatment.

6.1.3 Population

Male and female subjects, aged 3 to 74 years, have confirmed clinical diagnosis of PIDD including hypogammaglobulinemia or agammaglobulinemia, have received licensed IGIV which was maintained at a steady dose (± 50% of the mean dose) for at least 3 months prior to study entry, and have maintained a trough IgG level of at least 500 mg/dL recorded prior to receiving RI-002.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The subject received an intravenous infusion of RI-002 on Study Day 1 (required to be within 28 days of screening) and every 21 or 28 days thereafter for 1 year. Subjects received RI-002 at the same dose as their pre-entry IGIV treatment or higher dose if medically appropriate (300-800 mg/kg). Any increases in dose of administration were at the discretion of the investigator and could be made if trough serum levels of IgG fell

below 500 mg/dL. Dose increases above 800 mg/kg required approval of the ADMA Medical Director. Additional doses were not administered between the scheduled infusions.

6.1.6 Sites and Centers

The study was conducted in nine centers located in the USA.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint:
The primary efficacy endpoint is the rate of SBIs (as defined by the Diagnostic Criterion for Serious Infection Types in the FDA Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency, 2008) such that the 99% upper one-sided confidence limit for the observed SBI rate per subject per year is less than 1.0 (as specified in the 2008 FDA Guidance).

Secondary Efficacy Endpoints:
1. The number of days of antibiotic therapy (prophylactic and treatment) per subject-year
2. The number of days lost from work/school/usual activities per subject-year due to infections and their treatment
3. The number of unscheduled physician/ER visits due to infection per subject-year
4. The number of hospitalizations and days of hospitalizations due to infections per subject-year
5. The time to resolution of infection
6. The incidence of infections (serious and non-serious) per subject-year
7. The relationship among dose of RI-002, trough level, and risk of serious and non-serious infections
8. Trough total IgG and specific antibody levels at regular intervals

Safety Endpoints:

1. Incidence of adverse events that occurred during or within 1 hour, 24 hours and 72 hours of completion of an infusion. Temporally associated AEs (TAAEs) were AEs occurring within 72 hours of RI-002 infusion. The success criterion for TAAEs, per the FDA 2008 Guidance, is such that the upper one-sided 95% confidence limit is less than 0.4.
2. Incidence of serious adverse events (SAEs) and related SAEs
3. Incidence Treatment Emergent Adverse events (TEAEs) and related TEAEs
4. Incidence of discontinuation of study treatment
5. Incidence of all-cause mortality and PIDD related deaths
6. Change in vital signs before and after administration of study treatment
7. Incidence of infusion site reactions
8. Proportion of infusions with one or more temporally-associated AEs

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size:
The sample size was calculated based on a historically-based standard, which suggests that untreated patients with primary humoral immunodeficiency experience approximately four or more SBIs per year (the 2008 FDA Guidance). This is in contrast to a SBI rate of 0.5 per patient-year for subjects receiving regular (generally every 3 to 4 weeks) administration of IGIV (the 2008 FDA Guidance, Page 7). Based on this Guidance, a statistical demonstration of a SBI rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy. Assuming the true SBI rate was no higher than 0.58 for IGIV treated subjects, a minimum of 40 evaluable subjects was needed to ensure more than 80% power to reject the null hypothesis that the SBI rate is greater than or equal to 1.0 per person-year, using a one-sided 0.01 level test. A 20% dropout rate was estimated; therefore approximately 60 subjects were planned to be enrolled in order to achieve approximately 40 evaluable subjects. Evaluable was defined as a subject who received 1 year of treatment.

Analysis Populations:
The intent-to-treat (ITT) population includes all subjects enrolled and eligible to receive study drug. The safety population includes all ITT subjects who received at least one infusion of the study drug. This safety population is also referenced as the modified ITT population (mITT). The mITT population was the primary population for efficacy and safety evaluations.

Statistical Methods:
A generalized linear model for Poisson regression using the log link function was planned to be used to estimate the confidence intervals for the primary endpoint. Summary statistics were computed for each secondary endpoint. Such statistics included simple frequency counts, proportions and confidence intervals for binary outcome endpoints and descriptive statistics of mean, standard deviation, median, and confidence intervals for the mean and median of the continuous endpoints.

For the safety endpoint TAAE, the 2-sided 90% confidence interval was constructed. All safety endpoints were summarized with descriptive statistics (N, mean, median, minimum, maximum, and standard deviation) for continuous outcomes and frequency counts for binary outcomes.

Missing Data:
No imputation of missing data for early terminations was performed.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 59 subjects were enrolled and treated with RI-002. All of them were included in ITT, mITT and safety populations.

6.1.10.1.1 Demographics

A total of 59 subjects, 28 male and 31 female, were enrolled. The majority of subjects were white (98.3%), and ranged in age from 3 to 74 years (mean 41.8 years). Subjects were more commonly receiving IGIV on a 4-week dosing cycle (n=40) compared to a 3-week cycle (n=19). The study included 48 adult subjects (> 16 years of age), and 11 pediatric subjects. Of the 48 adult subjects, 11 subjects were ≥ 65 years. Of the 11 pediatric subjects, 2 were aged 2-6 years, 4 were aged 7-11 years, and 5 were aged 12-16 years. A summary of demographic data for the mITT population is given Table 2.

Table 2: Summary of Demographic Data for mITT Population

	Total (N=59)	**3-Week Cycle (N=19)**	**4-Week Cycle (N=40)**
Age – Mean (SE)	41.8 (2.84)	38.6 (4.94)	43.3 (3.48)
Subjects ≤16 years – n (%)	11 (18.6)	3 (15.8)	8 (20.0)
Subjects 17 to 64 years – n (%)	37 (62.8)	12 (63.2)	25 (62.5)
Subjects ≥65 years – n (%)	11(18.6)	4 (21.0)	7 (17.5)
Sex –n (%)			
Male	28 (47.5)	7 (36.8)	21 (52.5)
Female	31 (52.5)	12 (63.2)	19 (47.5)
Race – n (%)			
White	58 (98.3)	19 (100)	39 (97.5)
Black/African American	1 (1.7)	0	1 (2.5)
Ethnicity – n (%)			
Non-Hispanic or Latino	56 (94.9)	19 (100)	37 (92.5)
Hispanic or Latino	3 (5.1)	0	3 (7.5)
PIDD Type – n (%)*			
CVID	45 (76.3)	17 (89.5)	28 (70.0)
X-Linked Agammaglobulinemia	7 (11.9)	0	7 (17.5)
Autosomal Agammaglobulinemia	1 (1.7)	0	1 (2.5)
Antibody Deficiencies	13 (22.0)	6 (31.6)	7 (17.5)
Other	10 (16.9)	6 (31.6)	4 (10.0)
Years since diagnosis - Mean (SE)	8.66 (1.1)	6.87 (1.4)	9.51 (1.5)
Weight (kg) – Mean (SE)	67.37 (2.647)	62.84 (4.288)	69.53 (3.311)
BMI – Mean (SE)	24.52 (0.709)	23.37 (0.961)	25.07 (0.936)
Final Status – n (%)			
Completed Study	54 (91.5)	16 (84.2)	38 (95.0)
Discontinued Early	5 (8.5)	3 (15.8)	2 (5.0)
PK Study Subjects	30 (50.8)	10 (52.6)	20 (50.0)

*Subjects were able to be included in more than one category
Source: BLA 125590, Adapted from 5.3.5.2 Study Report Body, Table 11

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
All subjects had at least one medical history finding at the screening visit. Among ongoing medical conditions, only one condition was considered not controlled during the

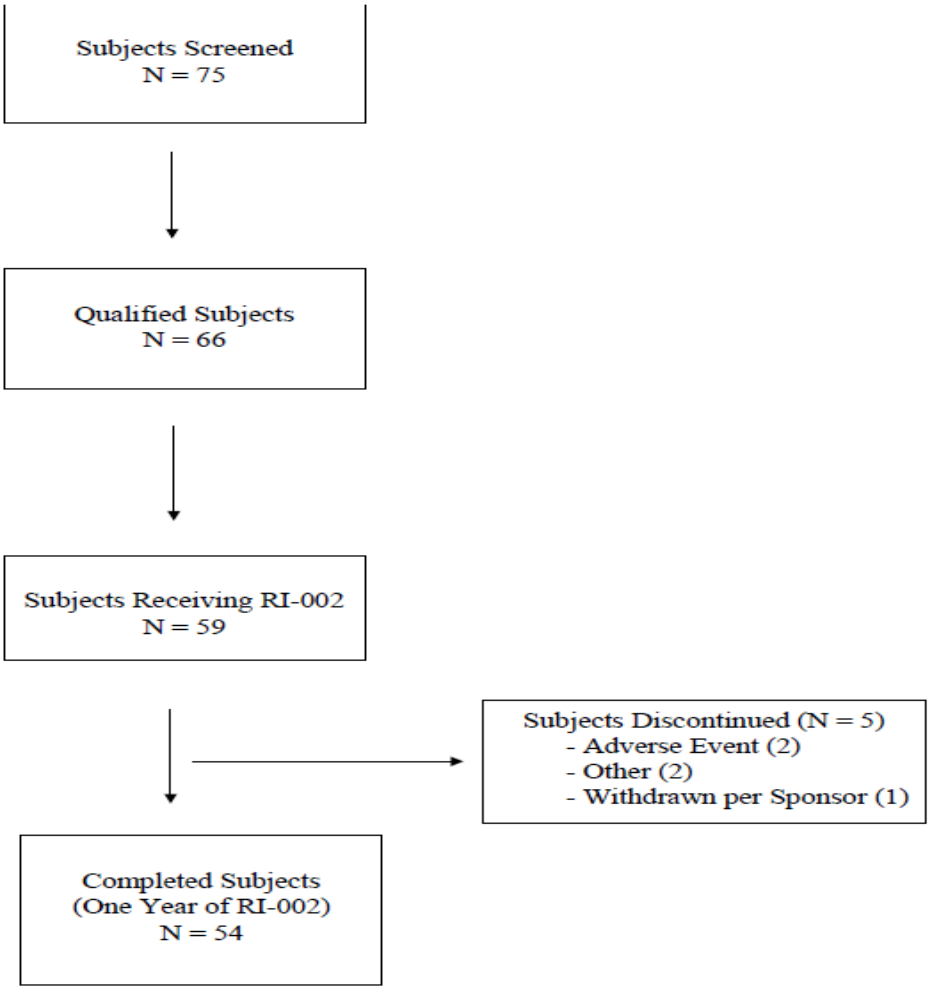
course of the study, which was an incidence of dental caries. All subjects had at least one concomitant medication documented at screening or during the course of the study.

A summary of the subjects' PIDD type is given in Table 2. The majority of subjects had CVID.

6.1.10.1.3 Subject Disposition

Fifty four of 59 subjects completed the study while five discontinued early. A 45 year old female discontinued because of a sponsor decision. Two withdrew due to adverse events (one was 12 years old male and the other was 64 years old male). One was a 27 year old female that was pregnant. A 55 year old female subject relocated. Subject disposition is illustrated in figure 1.

Figure 1: Subject Disposition



Source: BLA 125590, 5.3.5.2 Study Report Body, Figure 1.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

There were no infections experienced during the course of this study meeting the criterion defined for SBIs. With zero SBIs in 55.88 person years of treatment with RI-002, the study had a rate of 0.0 SBIs per subject per year (upper one-sided 99% confidence limit 0.066), and therefore was successful in achieving the success criterion since the upper one-sided 99% confidence limit for the observed SBI rate per subject per year is <1.0.

Reviewer Comment: I calculated the 99% confidence bound using StatXact 10. The applicant did not calculate this confidence limit using PROC GENMOD in SAS as planned, or using any other method. The planned Poisson regression analysis for the primary efficacy endpoint was not conducted because no SBI incidence was reported in the study (Module 5.3.5.2, Documentation of Statistical Methods and Interim Analysis Plan, Statistical Analysis Plan, page 42.)

6.1.11.2 Analyses of Secondary Endpoints

Days of Antibiotic Therapy for Treatment of Infection:
In total, 22 of the 59 subjects (37.3%) did not require the use of antibiotics for the treatment of infection during the course of the study. The total number of days of antibiotic treatment for infection during the study was 1839, with 55.8 subject-years, yielding a rate of 32.91 days of treatment per subject per year. The number of days of antibiotic treatment for infection per subject per year was numerically greater in the 4-week cycle compared with the 3-week cycle, 38.58 versus 17.30 days respectively. The mean number of days of antibiotic therapy for treatment of an infection per subject per infusion cycle ranged from 1.14 to 5.50 days. The number of days of antibiotic therapy for treatment of infection is summarized in Table 3.

Table 3: Summary of Days of Antibiotic Use for Treatment of Infection

Summary Category	**Total (N=59)**	**3-Week Cycle (N=19)**	**4-Week Cycle (N=40)**
Antibiotic Use for Treatment of Infection			
Total Days on Antibiotic Therapy	1839	713	1126
Total person-years	55.88	17.30	38.58
Days on Antibiotic Therapy per person per year	32.912	41.219	29.187
Subjects with no antibiotic therapy; n (%)	22 (37.3)	7 (36.8)	15 (37.5)

Source: BLA 125590, Adapted from 5.3.5.2 Study Report Body, Table 15.

The number of days of antibiotic use (treatment and prophylactic) is summarized by age and gender in Table 4.

Table 4: Summary of Total Days of Antibiotic Therapy by Age and Sex

Group	Summary Category	Total	3-Week Cycle	4-Week Cycle
Overall	Number of Subjects	59	19	40
	Days of antibiotics per subject-year	53.135	83.190	39.659
	Subjects using no antibiotics (%)	19 (32.2)	5 (26.3)	14 (35.0)
Age 2-11	Number of Subjects	6	2	4
	Days of antibiotics per subject-year	82.094	222.044	11.782
	Subjects using no antibiotics (%)	1 (16.7)	0	1 (25)
Age 12-16	Number of Subjects	5	1	4
	Days of antibiotics per subject-year	23.746	20.405	24.801
	Subjects using no antibiotics (%)	2 (40)	0	2 (50)
Age > 16	Number of Subjects	48	16	32
	Days of antibiotics per subject-year	27.293	17.326	31.824
	Subjects using no antibiotics (%)	19 (39.6)	7 (43.8)	12 (37.5)
Male	Number of Subjects	28	7	21
	Days of antibiotics per subject-year	22.012	22.685	21.771
	Subjects using no antibiotics (%)	13 (46.4)	3 (42.9)	10 (47.6)
Female	Number of Subjects	31	12	19
	Days of antibiotics per subject-year	42.638	53.713	36.676
	Subjects using no antibiotics (%)	9 (29)	4 (33.3)	5 (26.3)

Source: BLA 125590, 5.3.5.2 Study Report Body, Table 16.

Days Lost from Work/School/Daycare or Normal Activities:

A total of 243 days were lost from school/daycare, work, or normal activities due to infection, equating to an incidence of 4.349 days per subject per year (55.8 subject-years). The rate of days lost was similarly distributed between the 4-week and 3-week treatment cycle subjects at 4.432 and 4.162 days respectively. The number of days lost due to infection for an individual subject ranged from 0 to 48 days. A summary of days lost from work/school/daycare and normal activities is provided in Table 5.

Table 5: Summary of Combined Days Lost from Work/School/Daycare and Normal Activities

Summary Category	Total (Subjects=59)	3-Week Cycle (Subjects=19)	4-Week Cycle (Subjects=40)
Days Lost due to Infection			
Subjects with no days lost; n (%)	29 (49.2%)	9 (47.4%)	20 (50.0%)
Total Days Lost	243	72	171
Days Lost per person per year	4.349	4.162	4.432
1-Sided 95% Upper Bound	4.833	5.053	5.027
Median	1.0	1.0	0.5

Source: BLA 125590, Adapted from 5.3.5.2 Study Report Body, Table 17

Additional analysis was performed to separate the number of days lost from work, school and/or daycare from the days missed from normal activities. In total, 39% (23 of 59) of subjects lost at least one day from work/school/daycare due to infection, with an overall rate of 1.66 (93 days/55.8 subject-years) days lost per subject per year. A summary of days lost from work/school/daycare due to infection is provided in Table 6.

Table 6: Summary of Days Lost from Work/School/Daycare (Ad-Hoc)

Statistics	Total (N=59)	3-Week Cycle (N=19)	4-Week Cycle (N= 40)
Days Lost Due to Infection			
Total days missed in the study	93	27	66
Total person-years	55.88	17.30	38.58
No. of days missed per person per year	1.66	1.56	1.71
1-sided 95% Upper Bound	1.97	2.14	2.09
Subjects with no missed days; n (%)	36 (61.0)	12 (63.2)	24 (60.0)

Source: BLA 125590, Adapted from 5.3.5.2 Study Report Body, Table 18.

Unscheduled Medical Visits:
A total of 54 unscheduled medical visits, including doctor and hospital visits, due to infection, were reported, equating to a rate of 0.966 (54 visits/55.8 subject-years) visits per subject per year. The rate of unscheduled medical visits due to infection was distributed between the 4-week and 3-week treatment cycle subjects at 0.933 and 1.041 visits respectively. The mean number of unscheduled medical visits due to infection by infusion cycle ranged from 0.0 to 0.13 visits per subject. A summary of unscheduled medical visits is provided in Table 7.

Table 7: Summary of Unscheduled Medical Visits

Summary Category	Total (N=59)	3-Week Cycle (N=19)	4-Week Cycle (N=40)
Unscheduled Medical Visits Due to Infection			
Subjects with no unscheduled visits; n (%)	35 (59.3%)	10 (52.6%)	25 (62.5%)
Total Visits in the study	54	18	36
Visits per person per year	0.966	1.041	0.933
1-Sided 95% Upper Bound	1.209	1.533	1.227
Median	0.0	0.0	0.0

Source: BLA 125590, Adapted from 5.3.5.2 Study Report Body, Table 20.

Hospitalizations:

In total, one (1.7%) subject of 59 infected was hospitalized due to infection for five days. The overall rate of hospitalizations due to infection per subject per year was 0.018. A summary of hospitalizations due to infection is provided in Table 8.

Table 8: Summary of Hospitalizations Due to Infection

Summary Category	Total (N=59)	3-Week Cycle (N=19)	4-Week Cycle (N=40)
Total Hospitalizations	1	0	1
Total subject-years in study	55.88	17.30	38.58
Hospitalizations per subject per year	0.018	0	0.026
Number of days of Hospitalization	5	0	5
Days hospitalized per subject per year	0.089	0	0.130

Source: BLA 125590, 5.3.5.2 Study Report Body, Table 22.

6.1.11.3 Subpopulation Analyses

There were no SBIs experienced during the course of this study among all subpopulations.

6.1.11.4 Dropouts and/or Discontinuations

Estimated or derived data were not used to deal with missing data. The analyses of annualized SBI rate were done per subject-year for all mITT subjects, and thus included an adjustment for length of time each subject was followed. Therefore no imputation of missing data for early terminations was performed.

6.1.11.5 Exploratory and Post Hoc Analyses

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

There were two SAEs (one instance each of postoperative wound infection and migraine in the 4-week cycle), and neither was associated with study drug. Each event was experienced with a single occurrence in a single subject.

6.1.12.5 Adverse Events of Special Interest (AESI)

During the study, 43 (72.9%) of the 59 subjects experienced at least one TAAE, and TAAEs were experienced with 113 (14.2%) of the 793 study infusions. The upper one-sided 95% confidence limit of observed proportion of infusions with TAAE was 0.164 which met the success criterion of < 0.4.

The overall incidence of TAAEs is summarized in Table 9.

Table 9: Summary of TAAEs

	Total (N=59)	3-Week Cycle (N=19)	4-Week Cycle (N=40)
Number of Infusions with TAAEs	113	36	77
Total Number of Infusions	793	294	499
Proportion of Infusions with TAAEs	0.142	0.122	0.154
Upper 1-sided 95% confidence limit	0.164	0.156	0.182
Total Number of TAAEs	158	47	111
Mean Number of TAAEs per Infusion	0.199	0.160	0.222
Subjects with No TAAE	16 (27.1%)	4 (21.1%)	12 (30.0%)

Source: BLA 125590, 5.3.5.2 Study Report Body, Table 38.

Reviewer Comment: I verified the CI using the exact method using StatXact 10.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Only one pivotal study was implemented (IND 15308; Study ADMA-003). According to the original statistical plan, the planned enrollment was 60 subjects in order to achieve 40 evaluable subjects. A total of 59 subjects were enrolled, 28 male and 31 female. Of these 59 subjects, 40 subjects were on a 4-week infusion cycle and 19 subjects were on a 3-week infusion cycle, with 54 subjects completing the study.

All 59 enrolled subjects received at least one infusion of RI-002 so they were included in the mITT population, the pre-specified population for the primary efficacy analysis. With no subjects experiencing a SBI during the study, RI-002 achieved the primary efficacy endpoint success criteria: the observed SBI annual rate of 0.0 has a 99% upper one-sided

confidence bound of 0.066 which is less than 1.0. Secondary efficacy endpoints further demonstrated the benefits of RI-002 in the low incidence of infection, therapeutic antibiotic use, days missed from work/school/daycare, and unscheduled medical visits and hospitalizations.

No deaths occurred during the conduct of the study. Two subjects had a single occurrence of an SAE (postoperative wound infection and migraine). The upper one-sided 95% confidence limit of observed proportion of infusions with TAAE (14.2%) was 0.164 which met the success criterion of < 0.4.

10.2 Conclusions and Recommendations

There were no statistical issues in this submission. The confidence intervals were calculated correctly. Results of Study ADMA-003 appear to support the use RI-002 in subjects with PIDD for control of SBIs.