Application Type	Original Application
STN	125590/0
CBER Received Date	July 31, 2015
PDUFA Goal Date	July 30, 2016
Division / Office	DHRR /OBRR
Priority Review	No
Reviewer Name(s)	Charles M. Maplethorpe M.D., Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	ADMA Biologics, Inc.
Established Name	Immune Globulin Intravenous (Human), 10% Liquid
(Proposed) Trade Name	(b) (4) ASCENIV
Pharmacologic Class	Immune Globulin (liquid) 10%
Formulation(s), including Adjuvants, etc	245 ± 45 mM glycine, 120 ± 20 mM sodium choride, 0.2 ± 0.05% polysorbate 80 in Water for Injection (WFI) at a pH of 4.3 ± 0.3.
Dosage Form(s) and Route(s) of Administration	Injectable Solution, Intravenous
Dosing Regimen	300 to 800 mg/kg body weight every 3 to 5 weeks
Indication(s) and Intended Population(s)	Treatment of primary humoral immunodeficiency (adults and adolescents)
Orphan Designated (Yes/No)	No

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Glossary

AE	Adverse event
AUC	Area under the concentration-time curve
AUC0-∞	AUC from time 0 to infinity
CFR	Code of Federal Regulations
CMC	Chemistry, manufacturing and controls
Cmax	peak (maximum) observed plasma drug concentration
IGIV	Immune Globulin Intravenous
PIDD	Primary Immunodeficiency Disease
RI-002	The investigational new drug ASCENIV
RSV	Respiratoy syncytial virus

1. Executive Summary

ADMA, Inc. has submitted STN125590/0 to license its Immune Globulin (human) product ASCENIV® (submitted as (b) (4) ®) for treatment of patients with primary immunodeficiency. ASCENIV is a 10% liquid immune globulin product in an excipient containing 245 ± 45 mM glycine, 120 ± 20 mM sodium choride, 0.2 ± 0.05% polysorbate 80 in Water for Injection (WFI) at a pH of 4.3 ± 0.3. The product was referred to as RI-002 during the investigational phase of product development.

The product is made from plasma collected from donors with (b) (4) this is apparently the reason for the proposed proprietary name (b) (4), which was rejected by FDA as promoting an off-label use. The applicant proposed the new proprietary name ASCENIV, which is acceptable.

The indication sought is as follows:

> (b) (4) ASCENIV (10%) is an Immune Globulin Intravenous (Human) indicated for the treatment of patients with primary humoral immunodeficiency (PI).
>
> This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID).

A pre-BLA meeting was held on October 7, 2014 (CRMTS #9487). A letter acknowledging the agreed initial pediatric study plan (iPSP) was sent on June 25, 2015, under IND 15308.

Phase 3 study ADMA-003 was a multicenter open-label study of the use of the investigational product RI-002 (ASCENIV) dosed intravenously every 3 or 4 weeks (depending on patient custom) for one year for routine prophylaxis in 59 patients with primary immunodeficiency. ADMA-003 was designed according to current minimum FDA standards for this indication. The primary endpoint was the number of serious bacterial infections over a 12 month treatment and observation period (see Appendix 1 for details on the primary endpoint).

There were no serious bacterial infections among the 59 subjects reported in study ADMA-003.

There were 616 adverse events reported in 58 subjects. The adverse reactions occurring in more than 3 (5%) of the subjects were headache, sinusitis, diarrhea, viral infections, nausea and vomiting, fatigue, muscle and joint pain, fever, itching and rashes, and fever. There were 2 serious adverse events, migraine headache and post-operative wound infection, in 2 subjects 20 and 33 days after the previous dose of the product; these adverse events were not attributed to the product.

A post-hoc analysis to examine the effect of product age on the observance of adverse events was triggered by the finding of particles by visual inspection after 6 months storage in product lot 3-FIN-1500. This post-hoc analysis shows that other product lots, that do not have particle formation by visual detection, have increased adverse events when administered after 6 months storage (see section 6.1.11.5 Exploratory and Post Hoc Analyses). Therefore, it may be the case that all product lots form particles after storage for several months, and these particles may not be detectable by visual inspection but may nevertheless cause an increased rate of certain adverse events.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Study ADMA-003: Sex and Race Demographics

	Black or African American	**White**			**Total**
	Not Hispanic or Latino	**Hispanic or Latino**	**Not Hispanic or Latino**		
Age Group	M	M	F	M	
2-6 years				2	2
7-11 years		1	1	2	4
12-16 years		1		4	5
>16 years	1	1	30	16	48
Grand Total	1	3	31	24	59

M = male, F = female
Source: analysis of STN125590/0 database ADSL

Recommendation.

The study ADMA-003 met the standard for licensure by ruling out 1 serious bacterial infection per subject over 12 months. Although there is evidence for an increased rate of adverse events in subjects treated with product more than 6 months after the filling date, the safety profile is acceptable in that it does not differ appreciably from the safety profile of other licensed immune globulin products. ASCENIV may be licensed for routine prophylaxis in patients with primary immunodeficiency. The indication should specify the indicated population as 'adults and adolescents' based on the study enrollment.

At this time, a Complete Response (CR) letter is being sent based on CMC issues. Final product labeling is dependent on response to the CR letter.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Study ADMA-003 enrolled subjects with a diagnosis of primary immunodeficiency.

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

The following table lists Immune Globulin products licensed to treat patients with primary immunodeficiency:

Trade Name	Manufacturer
HYQVIA	Baxter Healthcare Corporation, Baxter BioScience
Carimune® NF, Nanofiltered	CSL Behring AG
Flebogamma DIF 5%	Instituto Grifols, SA
Gammaplex	Bio Products Laboratory
OCTAGAM	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Gamunex-C	Grifols Therapeutics Inc
Bivigam	Biotest Pharmaceuticals Corporation
Privigen	CSL Behring AG
Gammagard Liquid	Baxter Healthcare Corp
Hizentra	CSL Behring AG
Vivaglobin	CSL Behring GmbH

2.4 Previous Human Experience with the Product (Including Foreign Experience)

None.

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

Date	Item
August 25, 2015	First committee meeting
September 14, 2015	Filing meeting
April 13, 2016	Late cycle meeting
June 14, 2016	PeRC meeting to present PSP
June 27, 2016	Meeting with applicant to discuss FDA refusal to include mention of (b) (4) in labeling

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was of adequate quality and completeness for review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

There were no issues with Good Clinical Practice or submission integrity.

3.3 Financial Disclosures

Covered clinical study (name and/or number): ADMA-003		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 10		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

See the CMC review. A significant CMC issue is the observation by visual inspection of particle formation in product lo (b) (4) after 6 months storage. CMC concerns have led to the issuance of a CR letter.

4.3 Nonclinical Pharmacology/Toxicology

There was no nonclinical pharmacology/toxicology section in the submission related to the primary immunodeficiency indication. See the April 16, 2016, memo of Evi Struble, Ph.D., for a review of a nonclinical study in cotton rats to support (b) (4) labeling, which was determined insufficient to support such labeling by Dr. Struble.

Dr. Struble's memo also notes the comparatively high level of polysorbate 80 in the final product, and makes the following conclusion:

> "Based on the excipient profile of (b) (4) the possibility exists for cardiovascular adverse events in the clinic. From the nonclinical toxicology data, it is recommended that the BLA be approved for the proposed indication with a post marketing commitment for assessing PS80 related toxicity."
>
> ***Reviewer comment:*** CMC reviewers have required a post-marketing study to look for adverse events from high levels of polysorbate 80 in another Immune Globulin product. This reviewer does not object to such a requirement, but I have not found clinical results from study ADMA-003 to support such a requirement.

FDA reviewers objected to the product labeling, which appeared to promote off-label use by mentioning the (b) (4)
These (b) (4) are based on selection criteria for the plasma units used in manufacturing. The applicant said the labeling should mention these (b) (4) because ASCENIV could interfere with the licensed (b) (4) monoclonal antibody (b) (4) . The applicant submitted technical report TEC-16-015-RPT-01, which (b) (4)

(b) (4) . FDA said the study was inadequate for the following reasons:

- The assays used were (b) (4)
  - At a June 27, 2016, meeting the applicant said ASCENIV reverses the activity of (b) (4) in an (b) (4) assay"
- (b) (4), another monoclonal against (b) (4), was shown to compete with (b) (4) in the (b) (4)
- (b) (4) was shown to compete with ASCENIV in the (b) (4), but ASCENIV was not shown to compete with (b) (4). Either they did not do this experiment or else it did not work.
- The experiments did not involve using appropriate controls, e.g. a non-relevant mAb, non-relevant IGIV preparation or other proteins.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Immune Globulin products raise the plasma levels of immunoglobulin G subclass in patients with primary immunodeficiency (PIDD).

4.4.3 Human Pharmacokinetics (PK)

See the Clinical Pharmacology review. Pharmacokinetic parameter estimates were calculated from data obtained from 30 subject in study ADMA-003 (10 subjects on 3-week cycle dosing, 20 subjects on 4-week cycle dosing). The following table from the study report (page 119) shows the reported results:

Total IgG Pharmacokinetic Parameter Estimates (PK Population)

	3-Week Cycle (N=10)		**4-Week Cycle (N=20)**	
Statistic	**Mean ± SD (n)**	**CV%**	**Mean ± SD (n)**	**CV%**
Cmax (mg/dL)	2427±452 (10)	18.63	2227±584 (20)	26.21
Cmin (mg/dL)	1152±308 (10)	26.73	954±245 (20)	25.65
Tmax (h)a	2.93 [1.80,4.52] (10)	NA	2.78 [1.43,99.08] (20)	NA
AUCtau (day·mg/dL)	32128±7020 (10)	21.85	35905±9351 (20)	26.04
t½ (d)	28.47±4.38 (6)	15.38	39.70±11.57 (13)	29.13
CL (mL/kg/d)	1.68±0.43 (10)	25.42	1.47±0.50 (20)	33.63
Vss (dL/kg)	76.79±13.45 (6)	17.52	89.57±26.16 (13)	29.21

AUCtau = steady-state area under the plasma concentration versus time curve with tau = dosing interval; CL = total body clearance; Cmax = maximum concentration; Cmin = minimum concentration; CV = coefficient of variation; n = number of subjects; NA = not applicable; SD = standard deviation; Tmax = time of maximum concentration; t½ = terminal half-life; Vss = Volume of distribution steady-state.
a Units median [Range] (n)
Source: STN125590/0 clinical study report page 119

Reviewer comment: The reported pharmacokinetic results appear to be typical of Immune Globulin products.

4.5 Statistical

See the May 10, 2016, statistical review of Boris Zaslavsky, Ph.D. The review concludes the following:

> "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."

4.6 Pharmacovigilance

There are no clinical issues resulting from the bioresearch monitoring inspection.

5. Sources of Clinical Data and Other Information Considered in the Review

STN125590/0.38, submitted July 8, 2016, contained data from a (b) (4) assay using (b) (4) antigens, a murine (b) (4) monoclonal antibody, and ASCENIV to argue for inclusion of (b) (4) language in the label. See section 4.3 Nonclinical Pharmacology/Toxicology.

5.1 Review Strategy

This review is based on analysis of databases submitted in STN125590/0. The analysis focused on product stability issues and their relation to adverse event rates. See section 6.1.11.5 Exploratory and Post Hoc Analyses.

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

- STN125590/0 and supplements
- IND 15308 (for meeting minutes)

5.3 Table of Studies/Clinical Trials

ADMA-003 is the only submitted clinical study.

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

None.
5.4.2 External Consults/Collaborations

Questions related to the inclusion of (b) (4) language in the label were consulted with Judy Beeler, M.D., CBER/OBRR, Division of Viral Products. See Dr. Beeler's May 19, 2016, memo for details.

5.5 Literature Reviewed (if applicable)

1. (b) (4)

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 ADMA-003 "AN OPEN LABEL, MULTICENTER STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY AND SAFETY OF RI-002 (IGIV) IN SUBJECTS WITH PRIMARY IMMUNODEFICIENCY DISEASES (PIDD)"

6.1.1 Objectives (Primary, Secondary, etc)

Primary objective:

- to demonstrate that RI-002 (IGIV) reduces the frequency of serious bacterial infections, as defined by the Diagnostic Criteria for Serious Infections Types guideline in subjects with primary humoral immunodeficiency

Secondary objectives:

- to evaluate incidence of infections other than serious bacterial infections
- to evaluate the number of days lost from work/school/usual activities per year due to infections and their treatment
- T to evaluate the number of unscheduled visits to physician/ER due to infection
- to evaluate the time to resolution of clinically significant symptoms of infections
- to evaluate the episodes of fever per year
- to evaluate the number of hospitalizations and days of hospitalizations per patient-year for PIDD related infections
- to evaluate the number of days of antibiotic therapy (prophylactic and treatment)
- to evaluate the relationship among dose of RI-002, trough level, and risk of serious and non-serious bacterial infections
- to evaluate trough total IgG and specific antibody levels at regular intervals
- to evaluate the pharmacokinetic profile of total IgG and specific antibody levels

6.1.2 Design Overview

Study ADMA-003 was a multicenter open label repeat-dose 1-year phase 3 study of the use of RI-002 (immune globulin) to prevent serious bacterial infections in IGIV-experienced primary immunodeficiency patients aged 2-75 years.

6.1.3 Population

From protocol ADMA-003:

Inclusion criteria:

1. Able to understand the study procedures, have agreed to participate in the study and have voluntarily signed an IEC/IRB approved written informed consent. The consent form or a specific assent form, where required, will be signed and dated by minors.
2. Have confirmed and documented clinical diagnosis of primary immunodeficiency disease including but not limited to: common variable immunodeficiency, X-linked and autosomal forms of agammaglobulinemia, hyper-IgM syndrome, or antibody deficiencies.
3. Be male or female, and ≥ 2 years and ≤ 75 years at the time of informed consent by subject or legal guardian.
4. Have body weight ≥ 12 kg at screening.
5. Have been receiving IGIV replacement therapy at a dose that has not changed by ±50% of the mean dose on a mg/kg basis for at least 3 months prior to study entry and has maintained a trough level ≥ 500 mg/dL on the previous 2 assessments prior to receiving RI-002. The trough level must be at least 300 mg/dL above the pre-treatment serum IgG level.
6. Have trough levels of IgG, dose of IGIV, treatment intervals and trade name of the IGIV products used for two doses documented before the first infusion in this study.
7. For female subjects, be of non-childbearing potential or have a negative pregnancy test prior to study start and be deemed not at risk of becoming pregnant by adherence to a reliable contraceptive method for the duration of the study. Females of non-childbearing potential are defined as prepubertal girls, women who have had a hysterectomy, bilateral oophorectomy, tubal ligation or who have been post-menopausal for at least two years, or are considered to be sterile due to recent chemotherapy.

Exclusion criteria:

1. Have a known hypersensitivity to immunoglobulin or any excipient in RI-002.
2. Have a history of a severe anaphylactic or anaphylactoid reaction to blood or any blood-derived product.
3. Have a specific Immunoglobulin A (IgA) deficiency (IgA ≤ 5 mg/dL and normal IgG and IgM), history of allergic reaction to products containing IgA or has demonstrable antibodies to IgA.
4. Have uncompensated hemodynamically significant congenital or other heart disease.

5. Have a medical condition that is known to cause secondary immune deficiency, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, HIV infection, or AIDS.
6. Have a significant T-cell deficiency or deficiency of granulocyte number (chronic or recurrent neutropenia [absolute neutrophil count <1000 x 10^9/L]) or function.
7. Have severe renal impairment (defined as serum creatinine > 2 x ULN or BUN > 2.5 x ULN); be on dialysis or expected to receive dialysis during the course of the study; or have a history of acute renal failure.
8. Have abnormal liver function, defined as ALT or AST ≥ 2.5 x ULN.
9. Be receiving chronic anti-coagulation therapy.
10. Have a history of DVT, thrombotic or thrombo-embolic complications due to Immunoglobulin therapy.
11. Current daily use of the following medications:
    - corticosteroids (> 7.5 mg (or equivalent dose on a mg/kg basis) of prednisone equivalent per day for > 30 days)
      Note: Intermittent corticosteroid use during the study is allowable, if medically necessary and approved by the ADMA Medical Director: i.e. 1 mg/kg twice a day for ten days to a maximum of 40 mg per dose
    - immunomodulatory drugs (e.g. TNF-α inhibitors –Enbrel, Humira, etc.)
    - immunosuppressive drugs (excluding topical pimecrolimus (Elidel) and tacrolimus (Protopic))
12. Administration of a hyperimmune or specialty high titer Immunoglobulin product (e.g. Cytogam, VZIG, HBIG, etc.) within 30 days of screening, or expectation that a hyperimmune Immunoglobulin product will be given during the course of the study.
13. Have uncontrollable arterial hypertension.
14. Have anemia at screening (hemoglobin <10 g/dL).
15. Have an active viral or bacterial infection or symptoms/signs consistent with such an infection, excluding chronic sinusitis or bronchiectasis, within the two weeks prior to the initial dose of investigational product. Subjects may be receiving antibiotics as long as signs/symptoms of infection have been absent for two weeks prior to the initial infusion of IP.
16. Have received any blood product (other than Immunoglobulin G) within 3 months prior to screening.
17. Have received any RSV specific products, including palivizumab (Synagis®) within 3 months prior to screening.
18. Have abused alcohol, opiates, psychotropic agents, or other chemicals or drugs within the past 12 months.
19. Have an acute or chronic medical condition that, in the opinion of the investigator, may interfere with the conduct of the study.
20. Have any condition judged by the investigator to preclude participation in the study, including any psychological disorder, which might hinder compliance.
21. Have any laboratory assessment result that, in the opinion of the investigator, warrants exclusion from participation in the study.
22. Are currently pregnant or nursing.
23. Have hepatitis A, B, or C.

24. Have received an investigational product within 4 weeks of the anticipated first infusion of RI-002.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were dosed every 21 or 28 days, according to the subject's previous routine. The dose was 300-800 milligrams per kilogram bodyweight according to the subject's previous routine.

The applicant states RI-002 contains 100 mg IgG/mL formulated with 120 ± 20 mM sodium chloride, 245 ± 45 mM glycine, 0.2 ± 0.05% polysorbate 80 at a pH 4.3 ± 0.3. RI-002 IGIV (b) (4) The distribution of the four IgG subclasses falls in the following ranges: IgG1: (b) (4); IgG2: (b) (4); IgG3: (b) (4); IgG4: (b) (4). The content of IgA is stated to be lower than 200 µg/mL and (b) (4) . RI-001 is stored at 2-8 ºC.

The protocol states RI-002 is to be administered by intravenous infusion through an (b) (4) filter within (b) (4) of dose preparation. Pre-medication was not to be given according to the protocol.

There were 6 product lots used in the study as shown in the following table:

Lot No.	Date of mfr from 1º report of fill date	Date of mfr from Stability Summary
3-FIN-1500	(b) (4)	
3-FIN-1740		
3-FIN-1742		
3-FIN-1744		
3-FIN-1915		
3-FIN-1917		

6.1.5 Directions for Use

6.1.6 Sites and Centers

Site Number	Investigator	Study Center
101	Richard L. Wasserman, MD, PhD	Dallas Immunology Allergy Research Dallas, TX 75230
102	William Lumry, MD	AARA Research Center Dallas, TX 75231
103	Roger Kobayashi, MD	Midlands Pediatrics Papillion, NE 68046

Site Number	Investigator	Study Center
104	James Harris, MD	The South Bend Clinic South Bend, IN 46617
105	Robyn Levy, MD	Family Allergy & Asthma Center Atlanta, GA 30342
106	Mark Stein, MD	Allergy Associates of the Palm Beaches North Palm Beach, FL 33408
107	Lisa Forbes, MD	Baylor Texas Children's Hospital, Feigin Center
108	Charlotte Cunningham-Rundles, MD	Icahn School of Medicine at Mount Sinai New York, NY 10029
109	John Vanchiere, MD	LSU Health Science Center - Shreveport, Shreveport, LA
111	Isaac Melamed, MD	IMMUNOe Health Center Centennial, CO 80112

6.1.7 Surveillance/Monitoring

Table 2: Schedule of Assessments for Subjects on 3-Week (21 Day) Infusion Schedule

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit**
Type of Visit	Screening[1]	Infusion 1	Study Day 7	Infusion 2	Infusion 3	Infusion 4	Infusion 5	Infusion 6	Infusion 7	Infusion 8	Infusion 9
PROCEDURES[8]											
Eligibility confirmed	X	X									
Consent signed	X										
Medical History	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X		X	X	X	X	X	X	X	X
Vital Signs[2]	X	X		X	X	X	X	X	X	X	X
Subject Diary		X	X	X	X	X	X	X	X	X	X
Assess Concomitant Medications,	X	X	X	X	X	X	X	X	X	X	X
Assess Adverse Events		X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS											
HCG urine test	X			X		X		X		X	
Routine	X	X		X	X	X	X	X	X	X	X
Viral Transmission Tests[4]	X	X				X				X	
Trough IgG	X	X		X	X	X	X	X	X	X	X
IgG Subclasses (predose)	X	X				X				X	
IgA, IgM	X										
Specific antibody levels[10]		X[5]				X				X	
Direct Coombs Test and Tests of	X	X[11]		X[11]							
Urinalysis	X	X			X		X		X		X
C-Reactive Protein	X	X				X				X	
Pharmacokinetics[7]											X

[1] 1 Screening Visit within 28 days of dosing.
[2] 2 See Protocol Section 9.5.2.4 for additional information on requirements for collection of vital signs.

[3] 3 See Protocol Section 9.5.2.5 for a complete list of analytes to be tested. Please note that differentials were to be provided in percent.
[4] 4 Viral Transmission Tests included NAT and serological tests for HCV, HBV, HAV, HIV 1 & 2 and Parvovirus B19. Serological tests for HAV and Parvovirus B19 were only required at screening. Testing for Parvovirus B19 was not required if the subject had a positive result prior to the first infusion of RI-002.
[5] 5 Blood draw prior to Infusion 1.
[6] 6 Serum haptoglobin, plasma-free hemoglobin, urine hemosiderin, and direct anti-globulin (DAT, Coombs)
[7] 7 See Table 4: Schedule of Assessments for Subjects in the Pharmacokinetic Portion of the Study, backup samples were to be archived for future analysis (see Protocol Section 9.5.1.1).
[8] 8 There was to be a ± 1 day window for Visit 3. There was to be a ± 3 day window for all subsequent treatment visits 4-17 and End of Study/Early Termination.
[9] 9 Review diary for SAEs remotely.
[10] 10 Specific antibody levels were to include Streptococcus pneumoniae (including serotypes), Haemophilus influenzae type B, CMV, measles, RSV, and tetanus.
[11] 11 To be performed 24-72 hours after RI-002 infusion

Table 2: Schedule of Assessments for Subjects on 3-Week (21 Day) Infusion Schedule (continued)

	Visit 12	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**	**End of Study/ Early Term**
Type of Visit	Infusion 10	Infusion 11	Infusion 12	Infusion 13	Infusion 14	Infusion 15	Infusion 16	Infusion 17	30 days post last
PROCEDURES[8]									
Eligibility confirmed									
Consent signed									
Medical History	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X
Vital Signs[2]	X	X	X	X	X	X	X	X	
Subject Diary		X	X	X	X	X	X	X	
Assess Concomitant Medications,	X	X	X	X	X	X	X	X	X

Assess Adverse Events		X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS									
HCG urine test									
Routine	X	X	X	X	X	X	X	X	X
Viral Transmission Tests[4]								X	X
Trough IgG	X	X	X	X	X	X	X	X	X
IgG Subclasses (predose)			X				X	X	
IgA, IgM									X
Specific antibody levels[10]			X				X		X
Direct Coombs Test and Tests of									X
Urinalysis		X		X	X	X		X	X
C-Reactive Protein			X			X	X		X

[1] Screening Visit within 28 days of dosing.
[2] See Section 7.4 of protocol for additional information on requirements for collection of vital signs.
[3] See Section 7.5 of protocol for a complete list of analytes to be tested. Please note that differentials should be provided in percent.
[4] Viral Transmission Tests include HCV and HIV NAT, and serological tests for HBsAg, HCV and HIV 1& 2. Parvovirus B19 NAT will also be tested at Visit 2 and Visit 3.
[5] Blood draw prior to Infusion 1.
[6] Serum haptoglobin, plasma-free hemoglobin, urine hemosiderin, and direct anti-globulin (DAT, Coombs)
[7] See Table 4: Schedule of Assessments for Subjects in the Pharmacokinetic Portion of the Study
[8] There is a ± 1 day window for Visit 3. There is a ± 3 day window for all subsequent treatment visits 4-17 and End of Study/Early Termination.
[9] Specific antibody levels to include Streptococcus pneumoniae (including subtypes), Haemophilus influenzae type B, CMV, measles, RSV, and tetanus

Table 3: Schedule of Assessments for Subjects on 28-Day Infusion Schedule

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Type of Visit	Screenin	Infusion	Study	Infusion	Infusion	Infusio	Infusion	Infusion	Infusion	Infusion	Infusion
PROCEDURES[8]											
Eligibility confirmed	X	X									
Consent signed	X										
Medical History	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X		X	X	X	X	X	X	X	X
Vital Signs2	X	X		X	X	X	X	X	X	X	X
Subject Diary		X	X9	X	X	X	X	X	X	X	X
Assess Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Assess Adverse Events		X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS											
HCG urine test	X										
Routine hematology/chemistry3	X	X		X	X	X	X	X	X	X	X
Viral Transmission Tests4	X	X		X					X		
Trough IgG	X	X		X	X	X	X	X	X	X	X
IgG Subclasses (predose)	X	X				X				X	
IgA, IgM	X										
Specific antibody levels10		X5				X				X	
Direct Coombs Test and Tests of Hemolysis6	X	X		X							
Urinalysis	X	X			X		X		X		X
C-Reactive Protein	X	X				X				X	
Pharmacokinetics[7]									X		

[1] Screening Visit within 28 days of dosing.
[2] See Section 7.4 of protocol for additional information on requirements for collection of vital signs.

[3] See Section 7.5 of protocol for a complete list of analytes to be tested. Please note that differentials should be provided in percent.
[4] Viral Transmission Tests include HCV and HIV NAT, and serological tests for HBsAg, HCV and HIV 1& 2. Parvovirus B19 NAT will also be tested at Visit 2 and Visit 3.
[5] Blood draw prior to Infusion 1.
[6] Serum haptoglobin, plasma-free hemoglobin, urine hemosiderin, and direct anti-globulin (DAT, Coombs)
[7] See Table 4: Schedule of Assessments for Subjects in the Pharmacokinetic Portion of the Study
[8] There is a ± 1 day window for Visit 3. There is a ± 3 day window for all subsequent treatment visits 4-17 and End of Study/Early Termination.
[9] Review diary for SAEs remotely.
[10] Specific antibody levels to include Streptococcus pneumoniae (including subtypes), Haemophilus influenza type B, CMV, measles, RSV, and tetanus

Table 3: Schedule of Assessments for Subjects on 28-Day Infusion Schedule (continued)

	Visit 12	**Visit 13**	**Visit 14**	**Visit 15**	**Endof Study/ Early**
Type of Visit	Infusion 10	Infusion 11	Infusion 12	Infusion 13	30 days post last
PROCEDURES[8]					
Eligibility confirmed					
Consent signed					
Medical History	X	X	X	X	X
Physical Exam	X	X	X	X	X
Vital Signs2	X	X	X	X	
Subject Diary	X	X	X	X	
Assess Concomitant Medications	X	X	X	X	X
Assess Adverse Events		X	X	X	X

LABORATORY ASSESSMENTS					
HCG urine test	X				
Routine hematology/chemistry3	X	X	X	X	X
Viral Transmission Tests4				X	X
Trough IgG	X	X	X	X	
IgG Subclasses (predose)			X	X	
IgA, IgM					X
Specific antibody levels10			X		X
Direct Coombs Test and Tests of Hemolysis6					X
Urinalysis		X		X	X
C-Reactive Protein			X		X

[1] Screening Visit within 28 days of dosing.
[2] See Section 7.4 for additional information on requirements for collection of vital signs.
[3] See Section 7.5 for a complete list of analytes to be tested. Please note that differentials should be provided in percent.
[4] Viral Transmission Tests include HCV and HIV NAT, and serological tests for HBsAg, HCV and HIV 1& 2. Parvovirus B19 NAT will also be tested at Visit 2 and Visit 3.
[5] Blood draw prior to Infusion 1.
[6] Serum haptoglobin, plasma-free hemoglobin, urine hemosiderin, and direct anti-globulin (DAT, Coombs)
[7] See Table 4: Schedule of Assessments for Subjects in the Pharmacokinetic Portion of the Study
[8] There is a ± 1 day window for Visit 3. There is a ± 3 day window for all subsequent treatment visits 4-17 and End of Study/Early Termination
[9] Specific antibody levels to include Streptococcus pneumoniae (including subtypes), Haemophilus influenzae type B, CMV, measles, RSV, and tetanus

Table 4: Schedule of Assessments for Subjects in the Pharmacokinetic Portion of the Study

	Time before start of infusion	**Time after end of infusion[1]**									
	-5 mins	*0 min*	*60 min*	*2 hours*	*24 hours*	*48 hours*	*4 days*	*7 days*	*14 days*	*21 days*	*28 days*[3]
IgG	X	X	X	X	X	X	X	X	X	X	X
Specific Antibody Levels[2]	X	X	X	X	X	X	X	X	X	X	X
Reserve sample	X	X	X	X	X	X	X	X	X	X	X

[1] Samples will be drawn after Infusion 7 for subjects on a 28-day schedule, and after infusion 9 for subjects on a 21-day schedule.

[2] Specific antibody levels to include Streptococcus pneumoniae (including subtypes), Haemophilus influenzae type B, CMV, measles, RSV, and tetanus.

[3] This visit to be conducted only in subjects receiving treatment on a 28 day dosing schedule

1

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint is the rate of serious bacterial infections, as defined by the criteria in Appendix 1.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study ADMA-003 planned to enroll 60 subjects based on the assumption of 4 serious bacterial infections (SBI) per year in untreated patients, and on the assumption that the observed point estimate for SBIs would not excede 0.58 per patient per year; a 20 percent dropout rate was also assumed, to result in an analysis population of at least 40 subjects. The sample size is based on 80 percent power, using one-sided significance testing at a level of 0.01, to reject a null hypothesis that the 0.58 SBI rate would be surpassed.

6.1.10 Study Population and Disposition

Subject Disposition by Analysis Population

Analysis Population	**Total**	**3-Week Cycle**	**4-Week Cycle**
Screened	75	-	-
ITT	66	-	-
mITT/Safety	59	1	40
PK	30*	1	20

Source: STN125590/0 ADMA-003 study report p.93

- 75 subjects were screened
  - yielding 66 qualified subjects,
    - of which 56 subjects were enrolled and treated with RI-002.
    - Three subjects who did not meet all inclusion/exclusion criteria received exception from sponsor to participate the study
- 59 subjects were included in the safety /mITT population
  - with 31 of these subjects participating in the pharmacokinetic portion of the study
  - 54 subjects completed one year of dosing
    - with five subjects being discontinued prior to one year of treatment due to adverse event (2), other (2; pregnancy, relocation), and sponsor decision (1).

6.1.10.1 Populations Enrolled/Analyzed

The following table describes the various analysis populations:

Intent-To-Treat (ITT) population	all screened subjects who fulfilled eligibility for RI-002 treatment, including signed the informed consent

	form
Safety Population/Modified ITT Population	all ITT subjects who received at least one RI-002 infusion
PK Population	all safety/mITT subjects who had sufficient plasma samples to derive PK parameters

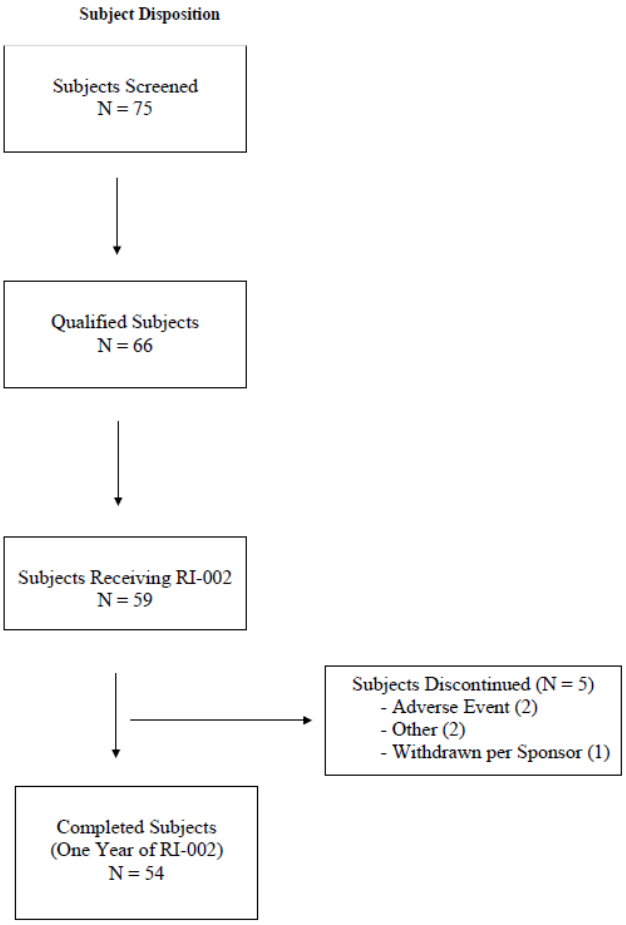
6.1.10.1.1 Demographics

	Black or African American	**Hispanic or Latino**	**White not Hispanic or Latino**		**Total**
Age Group	Male	Male	Female	Male	
2-6 years				2	2
7-11 years		1	1	2	4
12-16 years		1		4	5
Older than 16 years	1	1	30	16	48
Total	1	3	31	24	59

Source: Analysis of STN125590/0 database ADSL

6.1.10.1.3 Subject Disposition

The following chart shows the subject disposition in study ADMA-003:



6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

There were no serious bacterial infections (primary endpoint); therefore, the null hypothesis was rejected.

6.1.11.2 Analyses of Secondary Endpoints

Secondary endpoints:

- **Incidence of infections other than serious bacterial infections**

  The following table summarizes the incidence of infections:
  Summary of Incidence of Infections

Summary Category	Total (Subjects=59)		3-Week Cycle (Subjects=19		4-Week Cycle (Subjects=40	
	Episodes	Subjects N (%)	Episodes	Subjects N (%)	Episodes	Subjects N (%)
All Infections of any Kind/Seriousness						
Subjects with ≥1 Infections	192	51 (86.4)	62	16 (84.2)	130	35 (87.5)
Rate per person per	3.436		3.584		3.370	
1-Sided 95% Upper Bound	3.869		4.417		3.893	
All Serious Infections of Any Kind						
Subjects with ≥1 Infections	1	1 (1.7)	0	0	1	1 (2.5)
Rate per person per	0.018		0.000		0.026	
1-Sided 95% Upper Bound	0.093		NA		0.134	
All Non-Serious Infections of Any Kind						
Subjects with ≥1 Infections	191	51 (86.4)	62	16 (84.2)	129	35 (87.5)
Rate per person per	3.418		3.584		3.344	
1-Sided 95% Upper Bound	3.850		4.417		3.865	

Source: STN125590/0 Clinical Report p. 100

- Number of days lost from work/school/usual activities per year due to infections and their treatment

    - The number of days lost from work/school/usual activities per year was 4.3, and this rate was similary in both treatment schedule arms.

- Number of unscheduled visits to physician/ER due to infection
    - From the submission: “A total of 54 unscheduled medical visits, including doctor and hospital visits, due to infection were reported during the study, equating to a rate of 0.966 days 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”
- Time to resolution of clinically significant symptoms of infections

  - From the submission: "The average (±SD) duration of a single infection was 16.7 (±27.83) days, with a range of 1 to 243 days (median 9.0 days). The duration of a single infection was numerically greater in subjects receiving RI-002 on a 4-week cycle compared with a 3-week cycle, 18.5 (±32.46; range 1 to 243) versus 12.9 (±13.26; range 1 to 61) days respectively.
  - On a per subject basis, the average (±SD) total duration of infections was 62.7 (±86.60) days, with a range of 3 to 472 days per subject (median 31.0 days). The average total duration of an infection per subject was numerically greater in subjects receiving RI-002 on a 4-week cycle compared with a 3-week cycle, 68.7 (±99.12; range 5 to 472) versus 49.8 (±49.67; range 3 to 167) days respectively."
- Number of hospitalizations and days of hospitalizations per patient-year for PIDD related infections
  - Subject (b) (6) was hospitalized for 5 day for a wound infection at the site of a left shoulder replacement.
- Number of days of antibiotic therapy (prophylactic and treatment)
  - From the submission: "The total number of days of antibiotic treatment for infection during the study was 1839, yielding a rate of 32.912 days of treatment per subject per year. In total, 22 subjects (37.3%) did not require the use of antibiotics for the treatment of infection during the course of the study, and 22 (37.3%) subjects required 1-25 days of treatment. 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."
- Relationship among dose of RI-002, trough level, and risk of serious and non-serious bacterial infections
  - From the submission: "The relationship between trough IgG concentrations and study outcomes were evaluated using Pearson linear correlation coefficients. In general, the correlation between IgG levels and study endpoints were not strong. No significant correlation was identified using forward or backward analysis."
- Trough total IgG and specific antibody levels at regular intervals
  - See the review of Iftekhar Mahmood, Ph.D. and section 4.4.3 Human Pharmacokinetics (PK)
- Pharmacokinetic profile of total IgG and specific antibody levels
  - See the review of Iftekhar Mahmood, Ph.D. and section 4.4.3 Human Pharmacokinetics (PK)

6.1.11.4 Dropouts and/or Discontinuations

From the submission: "Five subjects discontinued, or were terminated, from participating in the study. Two discontinuations were due to AEs (b) (6) , adverse drug reaction;

(b) (6), wound infection), two discontinued due to other causes (b) (6) , pregnancy; (b) (6), relocation), and one discontinuation due to sponsor decision (b) (6) "

6.1.11.5 Exploratory and Post Hoc Analyses

Stability Problems Associated with Increased Rate of Adverse Events.

On December 21, 2015, CMC reviewer Dr. Yonggang Wang contacted this reviewer by e-mail stating there is a stability problem with Lot 3-FIN-1500 in which particle formation has occurred after 6 months storage. Dr. Wang asked if there are adverse events associated with this product lot.

To address this question, I examined the manufacturing dates for the main lots used in study ADMA-003, and assembled the following data:

Manufacturing Dates of Study ADMA-003 Product Lots

Lot No.	Date of mfr from filling report	Date of mfr from Stability Summary
3-FIN-1500	(b) (4)	
3-FIN-1740		
3-FIN-1742		
3-FIN-1744		
3-FIN-1915		

It can be seen that the dates from the filling reports and the dates from the stability reports are similar, differing by at most 30 days for Lot 3-FIN-1742.

I then determined which product lot was administered to each subject for each routine prophylaxis infusion. From the above table of dates of manufacture, I classified each infusion as occurring less than 6 months from the date of manufacture, or occurring more than 6 months from the date of manufacture. This partition was suggested by the observation of particle formation in Lot 3-FIN-1500 that occurred only after 6 months of storage. The following table shows the results of this bipartite classification of the infusions:

1	Denotes an infusion using product manufactured less than 180 days before the infusion
2	Denotes an infusion using product manufactured more than 180 days before the infusion

	Infusion Number																
Subject	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
ADMA-003-(b) (6)	2	2	2	2	2	2	2	2	2	2	2	2	1				
ADMA-003-	2	2	2	2	2	2	2	2	2	2	2	2	1				
ADMA-003-	2	2															
ADMA-003-	2	2	2	2	2	2	2	2	2	2	2	2	1				
ADMA-003-	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1
ADMA-003-	2	2	2	2	2	2	2	2	2	2	2	2	2				
ADMA-003-	2	2	2	2	2	2	2	2	2	2	2	1	1				
ADMA-003-	2	2	2	2	2	1	1	1	2	1	1	2	2				
ADMA-003-	2	2	2	2	2	1	2	2	1	2	2	2	1				
ADMA-003-	2	2	1	2	2	2	2	2	1	1	1	2	1				
ADMA-003-	2	2	2	2	2	1	2	2	2	1	1	1	1				
ADMA-003-	2	2	2	2	2	2	2	2	1	1	2	1	1				
ADMA-003-	2	2	2	2	2	2	1	1	2	1	1	2	2				
ADMA-003-	2	2	2	2	2	2	1	1	1	1	1	2	2				
ADMA-003-	2	2	2	2	2	2	2	2	1	2	2	2	1				
ADMA-003-	2	2	2	2	2	2	2	2	1	2	2	2	2				
ADMA-003-	2	2	2	2	2	2	1	2	2	2	2	2	1				
ADMA-003-	2	2	2	2	2	1	2	2	2	2	2	2	1				
ADMA-003-	2	2	2	1	2	2	2	2	2	1	1	2	2				
ADMA-003-	2	2	2	1	2	2	2	2	2	1	1	2	2				
ADMA-003-	2	2	2	1	2	1	1	1	2	2	2	2	2				
ADMA-003-	2	2	2	2	2	2	2	2	2	2	1	2	2				

1	Denotes an infusion using product manufactured less than 180 days before the infusion
2	Denotes an infusion using product manufactured more than 180 days before the infusion

	Infusion Number																
Subject	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
ADMA-003-(b) (6)	2	2	2	2	2	2	2	1	1	2	2	2	2	1	2	2	1
ADMA-003-	2	2	2	2	2	2	1	2	2	1	2	1	1				
ADMA-003-	2	2	2	2	2	1	2	2	2	1	2	2	1				
ADMA-003-	2	2	2	2	1	2	2	2	2	1	2	2	1	1	1	1	1
ADMA-003-	1	2	2	2	1	1	2	1	1	1	1	1	1	1	1	2	2
ADMA-003-	1	2															
ADMA-003-	2	2	1	2	2	1	1	1	1	1	1	2	2				
ADMA-003-	2	2	2	2	2	1	1	1	1	1	1	2	2				
ADMA-003-	2	2	2	2	2	2	2	2	2	2	2						
ADMA-003-	2	2	2	2	1	1	1	1	2	2	1	1	1	1	1	1	1
ADMA-003-	2	2	2	2	1	1	1	1	2	2	1	1	1	1	1	1	1
ADMA-003-	2	2	2	2	2	2	1	1	1	1	1	1	2				
ADMA-003-	2	2	1	1	2	2	2	1	1	1	1	2	1	1	1	2	2
ADMA-003-	2	2	2	2	2	2	1	1	1	1	2	2	1				
ADMA-003-	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2	2	2
ADMA-003-	2	2	2	2	2	2	2	2	1	1	1	1	1	2	2	2	1
ADMA-003-	2	2	2	1	1	1	2	2	2	2	1	2	2				
ADMA-003-	2	2	2	2	1	1	2	2	2	1	2	2	2				
ADMA-003-	2	2	2	1	1	1	2	2	2	1	1	2	2				
ADMA-003-	1	1	1	2	2	2	1	2	2	1	2	2	2				
ADMA-003-	1	1	1	2	2	2	1	2	2	1	2	2	2				
ADMA-003-	1	1	1	2	2	2	1	2	2	1	2	2	2				
ADMA-003-	1	1	1	2	2	2	2	2	1	1	1	2	2				

1	Denotes an infusion using product manufactured less than 180 days before the infusion
2	Denotes an infusion using product manufactured more than 180 days before the infusion

	Infusion Number																
Subje(b) (6)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
ADMA-003	1	1	1	2	2	2	2	2	2	2	2	1	1	2	2	2	2
ADMA-003	1	2	2	2	2	2	1	1	1	2	2	1	2				
ADMA-003	2	2	2	2	2	1	1	2	2	2	2	2	2				
ADMA-003	2	2	2	2	2	1	1	1	2	1	1	2	2				
ADMA-003	2	2	2														
ADMA-003	1	1	1	1	2	1	1	1	2	1	1	2	2				
ADMA-003	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	2	2
ADMA-003	1	1	1	1	1	2	1	1	1	1	1	2	1	1	1	2	2
ADMA-003	1	1	1	1	1	2	1	1	1								
ADMA-003	1	1	1	1	1	2	2	2	2	1	1	2	2	1	1	2	2
ADMA-003	1	1	1	1	1	2	1	1	1	1	2	1	1	1	2	2	2
ADMA-003	1	1	1	1	2	1	1	1	✕	1	1	2	2				
ADMA-003	1	1	1	1	2	1	1	1	1	2	1	1	1	2	2	2	2
ADMA-003	1	1	1	1	2	2	1	1	1	1	2	1	1	1	2	2	2

✕ Denotes a single infusion of Lot 3-FIN-115 to subject ADMA-003-(b) (6) on the 9th visit
Source: derived from STN125590/0 tabulation database EX

These data can be summarized as infusions by lot number by the following table:

Study ADMA-003: Number of Infusions by Lot Number and Lot Age at Infusion:

		Total	**3-FIN-1500**	**3-FIN-1740**	**3-FIN-1742**	**3-FIN-1744**	**3-FIN-1915**
Lots manufactured ≤ 6 months before dosing	subjects	55	0	16	33	49	28
	infusions	296	0	19	96	113	68
Lots manufactured > 6 months before dosing	subjects	59	35	38	48	24	23
	infusions	496	191	118	92	44	51
All Lots dosed	subjects	59	35	38	50	49	29
	infusions	793	191	136	189	157	119

It can be seen that subjects commonly received infusions from product lots in both groups: group 1) less than 6 months from the date of manufacture, and group 2) more than 6 months from the date of manufacture. Therefore, the analysis of adverse events by the age of the product lot would need to be on an 'infusion basis' as opposed to a 'subject basis', which is the usual method of analysing adverse events.

I then determined which product lot was administered to each subject immediately prior to every adverse event reported for each subject. For a given adverse event, I determined the time from the date of manufacture of the associated product lot to the date of the adverse event.

The following table shows adverse event rates by body system when normalized by the number of infusions in category 1 or 2 (i.e. less or more than six months from the date of product lot manufacture).

Adverse Event Rate per Infusion by Dosed Product Age (less than, more than 6 months from manufacturing date)

	Dosed less than 6 months from Lot Mfr date			**Dosed more than 6 months from Lot Mfr date**			**Ratio of Events per infusion**
Body System	**Events**	**Subjects**	**Infusion N = 296**	**Events**	**Subjects**	**Events per Infusion**	**(> 6 months over < 6 months)**
Blood and lymphatic system disorders	1	1	0.003	4	4	0.008	2.39
Cardiac disorders	1	1	0.003	2	2	0.004	1.19
Ear and labyrinth disorders	1	1	0.003	5	5	0.01	2.98
Eye disorders	2	1	0.007	4	4	0.008	1.19
Gastrointestinal disorders	18	17	0.061	54	51	0.109	1.79
General disorders and administration site conditions	14	10	0.047	41	31	0.083	1.75
Immune system disorders				4	3	0.008	
Infections and infestations	55	50	0.186	137	125	0.276	1.49
Injury, poisoning and procedural complications	6	5	0.02	20	19	0.04	1.99

Investigations	2	2	0.007	10	10	0.02	2.98
Metabolism and nutrition disorders	1	1	0.003	3	3	0.006	1.79
Musculoskeletal and connective tissue disorders	4	4	0.014	41	36	0.083	6.12
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2	0.007	4	4	0.008	1.19
Nervous system disorders	14	12	0.047	52	38	0.105	2.22
Psychiatric disorders	2	2	0.007	5	5	0.01	1.49
Renal and urinary disorders	1	1	0.003	3	3	0.006	1.79
Reproductive system and breast disorders	1	1	0.003	3	3	0.006	1.79
Respiratory, thoracic and mediastinal disorders	17	17	0.057	50	41	0.101	1.76
Skin and subcutaneous tissue disorders	6	6	0.02	24	21	0.048	2.39
Vascular disorders	1	1	0.003	1	1	0.002	0.60
Grand Total	149	135	0.503	467	409	0.942	1.87

Source: derived from STN125590/0 tabulation databases EX and AE

The blue background highlights subjectively-determined ‘high adverse event rates’ that are more than 50 percent higher when comparing category 1 vs. category 2 within a body system. (These ‘high adverse event rates’ body systems are selected based on the large number of subjects in these categories compared to other categories with similarly increased rates, but having fewer subjects.)

It can be seen that all such ‘high adverse event rates’ are in category 2, the product lots that are more than six months from the date of manufacture. These ‘high adverse event rates’ are in the body system categories Gastrointestinal Disorders, General Disorders and Administration Site Conditions, Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, Nervous System Disorders, Respiratory Thoracic and Mediastinal disorders , and Skin and Subcutaneous Tissue Disorders.

A fair criticism of this analysis -- which shows an increase in adverse events for product lots administered more than 6 months from the date of manufacture -- would be that the analysis includes Lot 3-FIN-1500 that is known to form particles after 6 months of storage, and that these

adverse event rate differences could be solely attributable to results from Lot 3-FIN-1500. Therefore, I have repeated the analysis after excluding adverse events that occurred after dosing by Lot 3-FIN-1500. The following table presents these results:

Adverse Events by Dosed Lot Age (less than or more than 6 months of manufacture) excluding Lot 1500

	Dosed less than 6 months from date of mfr			Dosed more than 6 months from date of mfr			Ratio of Events per infusion
Body System	**Events**	**Subjects**	**Events per Infusion (N = 296 infusion)**	**Events**	**Subjects**	**Events per Infusion (N = 305 infusions)**	**(> 6 months over < 6 months)**
Blood and lymphatic system disorders	1	1	0.003	3	3	0.010	2.91
Cardiac disorders	1	1	0.003	1	1	0.003	0.97
Ear and labyrinth disorders	1	1	0.003	2	2	0.007	1.94
Eye disorders	2	1	0.007	3	3	0.010	1.46
Gastrointestinal disorders	18	17	0.061	27	26	0.089	1.46
General disorders and administration site conditions	14	10	0.047	21	15	0.069	1.46
Immune system disorders			0.000	2	2	0.007	
Infections and infestations	55	50	0.186	93	88	0.305	1.64
Injury, poisoning and procedural complications	6	5	0.020	7	7	0.023	1.13
Investigations	2	2	0.007	9	9	0.030	4.37
Metabolism and nutrition disorders	1	1	0.003	1	1	0.003	0.97
Musculoskeletal and connective tissue disorders	4	4	0.014	23	20	0.075	5.58
Neoplasms benign, malignant and	2	2	0.007	3	3	0.010	1.46

	Dosed less than 6 months from date of mfr			Dosed more than 6 months from date of mfr			Ratio of Events per infusion
Body System	**Events**	**Subjects**	**Events per Infusion (N = 296 infusion)**	**Events**	**Subjects**	**Events per Infusion (N = 305 infusions)**	**(> 6 months over < 6 months)**
unspecified (incl cysts and polyps)							
Nervous system disorders	14	12	0.047	27	22	0.089	1.87
Psychiatric disorders	2	2	0.007	4	4	0.013	1.94
Renal and urinary disorders	1	1	0.003	1	1	0.003	0.97
Reproductive system and breast disorders	1	1	0.003	1	1	0.003	0.97
Respiratory, thoracic and mediastinal disorders	17	17	0.057	26	21	0.085	1.48
Skin and subcutaneous tissue disorders	6	6	0.020	11	11	0.036	1.78
Vascular disorders	1	1	0.003	1	1	0.003	0.97

Source: derived from STN125590/0 tabulation databases EX and AE

As was done previously, the right-hand column of the above table gives the ratio of the infusion-normalized adverse event ratios (events-per-infusion from lots older than 6 months divided by events-per-infusion from lots younger than 6 months from the date of product lot manufacture). The blue background highlights ratios that were highlighted in the previous table. Even after eliminating data from Lot 3-FIN-1500, the table shows large differences between time period categories 1 and 2, in all cases showing higher rates for category 2 (i.e. product lots more than 6 months from the date of lot manufacture).

Therefore, it is reasonable to conclude that product lots of ASCENIV that are older than 6 months at the time of administration are associated with elevated adverse event rates in

the following body system categories (each body system followed by a listing of the adverse events reported under the body system):

1. Gastrointestinal Disorders
    - abdominal discomfort, abdominal pain, abdominal pain upper, coeliac disease, constipation, dental caries, diarrhoea, dyspepsia, food poisoning, gastritis, gastrointestinal disorder, gastrooesophageal reflux disease, nausea, odynophagia, salivary gland pain, stomatitis, toothache, vomiting
2. General Disorders and Administration Site Conditions
    - adverse drug reaction, chest discomfort, chills, fatigue, influenza like illness, infusion site extravasation, non-cardiac chest pain, oedema peripheral, pain, pyrexia
3. Infections and Infestations
    - abscess oral, acute sinusitis, bacteriuria, bronchitis, cellulitis, conjunctivitis viral, cystitis, diverticulitis, ear infection, eczema herpeticum, eye infection viral, fungal infection, gastroenteritis, gastroenteritis viral, gingival infection, H1N1 influenza, impetigo, infected bites, influenza, laryngitis, nasopharyngitis, otitis externa, otitis media, paronychia, periodontitis, pharyngitis streptococcal, postoperative wound infection, pulpitis dental, sinusitis, sinusitis fungal, upper respiratory tract infection, urinary tract infection, viral pharyngitis, viral upper respiratory tract infection, vulvovaginal mycotic infection
4. Musculoskeletal and Connective Tissue Disorders
    - arthralgia, arthritis, back pain, bursitis, flank pain, muscle spasms, myalgia, neck pain, osteoarthritis, pain in extremity, rotator cuff syndrome, tendonitis
5. Nervous System Disorders
    - amnesia, aphonia, dizziness, dysgeusia, headache, hypoaesthesia, migraine, parosmia, poor quality sleep, sinus headache
6. Respiratory Thoracic and Mediastinal disorders
    - asthma, cough, dysphonia, dyspnoea, eosinophilic rhinitis, epistaxis, nasal congestion, nasal polyps, nasal septum deviation, oropharyngeal pain, rhinitis allergic, rhinorrhoea, sinus congestion, upper-airway cough syndrome, vasomotor rhinitis, wheezing

Reviewer comment: One explanation for the finding of higher adverse event rates for product lots administered more than 6 months after the date of manufacture would be that these older product lots form particles (b) (4) – as was seen with Lot 3-FIN-1500 – and that these particles are responsible for the increased adverse event rates in the listed body systems. The reported particle formation for Lot 3-FIN-1500 is base on visual inspection, and other product lots may also form particles that are below the limit of visual detection. It should be noted that the adverse events observed in the body systems Gastrointestinal Disorders, General Disorders and Administration Site Conditions, Musculoskeletal and Connective Tissue Disorders, Nervous System Disorders, Respiratory Thoracic and Mediastinal disorders are typically reported for other Immune globulin product, leading to the possibility that protein aggregates are contributory to the causation of these adverse events in the use of other Immune Globulin

products, as well as in the use of ASCENIV. The observation of increase adverse events in the body system category Infections and Infestations is difficult to interpret, unless this reflects decrease potency in product lots with particle formation. It should be noted that ASCENIV is manufactured by Biotest using (b) (4) procedures for the manufacture of the Biotest licensed product Bivigam [Immune Globulin Intravenous (Human), 10 Percent Liquid]. On April 5, 2013, FDA announced that Biotest had withdrawn Bivigam lot number (b) (4) due to the presence of visible particles.

6.1.12 Safety Analyses

6.1.12.1 Methods

The database AE from STN125590/0 was analyzed for adverse event frequency by categories.

6.1.12.2 Overview of Adverse Events

Adverse events that were reported in more than 5 percent of subjects, in decreasing frequency, were the following: headache, sinusitis, nasopharyngitis, diarrhoea, nausea, acute sinusitis, bronchitis, gastroenteritis viral, upper respiratory tract infection, fatigue, viral upper respiratory tract infection, migraine, myalgia, cough, oropharyngeal pain, abdominal pain upper, urinary tract infection, arthralgia, pyrexia, epistaxis, vomiting, adverse drug reaction, gastroenteritis, pain in extremity, rash, nasal congestion, abdominal pain, gastrooesophageal reflux disease pain, influenza, vulvovaginal mycotic infection, contusion, back pain, muscle spasms, rhinitis allergic, and rhinorrhoea.

The underlined adverse events were more than twice as frequent (per infusion) in the product lots manufactured more than 6 months prior to the time of dosing compared to the rates for lots manufactured less than 6 months prior to the time of dosing.

6.1.12.3 Deaths

There were no deaths in study ADMA-003.

6.1.12.4 Nonfatal Serious Adverse Events

Subject (b) (6) (on a 4-week infusion cycle), a 64-year old white male non-Hispanic or Latino, experienced a post-operative wound infection 33 days after the previous infusion and 31 days after undergoing left shoulder replacement surgery. Wound exhudate was postive for *Pasteurella Multocida*; the infection was treated with ceftriaxone. The subject was discontinued from study ADMA-003.

Subject (b) (6) (on a 4-week infusion cycle), with a history of migraines, experienced a SAE migraine (b) (6) days after the previous infusion, resulting in hospitalization. This subject was not discontinued from study ADMA-003.

6.1.12.5 Adverse Events of Special Interest (AESI)

6.1.12.6 Clinical Test Results

The number of abnormally high or low lab results, and the number of subjects with these abnormal results are shown in the following table:

Abnormally High Lab Results			**Abnormally Low Lab Results**		
Lab Test	**Events**	**Subjects N = 59**	**Lab Test**	**Events**	**Subjects N = 59**
Hepatitis A G/M	60	58	Alanine Aminotransferase	482	45
Parvovirus B19 IgG Antibody	58	57	Specific Gravity	191	45
Monocytes/Leukocytes	225	45	Protein S*	214	38
Protein (urinalysis)	130	42	Estimated GFR	343	35
Specific Gravity (urinalysis)	118	40	Sodium	140	34
Plasma-Free Hemoglobin	67	38	Lymphocytes/Leukocytes	139	30
Eosinophils/Leukocytes	150	33	Neutrophils/Leukocytes	106	30
Estimated GFR	205	31	Glucose	67	28
Amorphous Crystals	45	27	Hemoglobin	136	25
C Reactive Protein	59	22	Leukocytes	75	25
Lactate Dehydrogenase	55	22	Hematocrit	115	20
Blood Urea Nitrogen	71	20	Neutrophils	31	20
Leukocytes	45	19	Aspartate Aminotransferase	130	18
Blood	59	18	Creatinine	117	15
Neutrophils	41	18	Erythrocytes	69	12
Glucose	70	17	Bilirubin	54	12
Leukocyte Esterase	51	17	Lactate Dehydrogenase	56	11
Bacteria	39	17	Calcium	17	9
Direct Coombs	44	16	Platelets	46	8
Alkaline Phosphatase	104	14	Lymphocytes	33	7
Haptoglobin	26	14	Potassium	16	7
Lymphocytes/ Leukocytes	43	13	Haptoglobin	10	6
Neutrophils/Leukocytes	33	12	Phosphate	7	5

Abnormally High Lab Results			Abnormally Low Lab Results		
Lab Test	**Events**	**Subjects N = 59**	**Lab Test**	**Events**	**Subjects N = 59**
Monocytes	28	12	Alkaline Phosphatase	12	3
Phosphate	37	10	Blood Urea Nitrogen	2	2
Potassium	27	10	Albumin	5	1
Eosinophils	19	10	Monocytes/Leukocytes	1	1
Hemoglobin	33	9			
Basophils/Leukocytes	10	9			
Hematocrit	26	7			
Erythrocytes	16	7			
Albumin	15	6			
Aspartate Aminotransferase	13	6			
Mucous Threads	11	6			
Calcium	7	6			
Creatinine	28	5			
Lymphocytes	11	5			
Bilirubin	8	5			
Alanine Aminotransferase	3	3			
Ketones	3	3			
Nitrite	8	2			
Elution	3	2			
Hbv Dna Qnt Pcr Log (Cpy/Ml)	2	2			
Platelets	2	2			
Sodium	2	2			
Crystals	1	1			
Hepatitis B Virus Dna By Pcr	1	1			
Hepatitis C Virus Antibody	1	1			
Parvovirus B19 Dna, Qn Pcr	1	1			
Sediment Examination	1	1			
Spermatozoa	1	1			
Yeast Cells	1	1			

*The database AE uses the term “Protein S” to refer to serum protein, not to the coagulation factor Protein S

False Positive antiviral test results.

The high readings “Hepatitis A G/M” and “Parvovirus B19 IgG Antibody” relate to antiviral testing, and the high results reflect baseline positive antibody readings that are not supported by nucleic acid testing. These spuriously positive results are sometimes

seen with primary immunodeficiency patients who receive frequent infusions of Immune Globulin products.

Subject (b) (6) had a positive anti-hepatitis C antibody test after the first infusion, but was negative a screening and at all subsequent time points (infusions 4, 7, 10, 13, and end-of-study). This appears to be a false positive because of the subsequent negative readings, and because no other subject who was transfused with this product lot became positive.

6.1.12.7 Dropouts and/or Discontinuations

Subject (b) (6) (on a 4-week infusion cycle) a 64-year old white male non-Hispanic or Latino, was discontinued after experiencing a SAE of post-operative wound infection, as stated in 6.1.12.4.

Subject (b) (6), a 12 year of white male non-Hispanic or Latino on a 4-week infusion cycle, experienced a NSAE of "difficulty breathing" during the second infusion; blood pressure and heart rate were unchanged. The infustion was stopped after receiving 3 mL of RI-002, and the subject was discontinued from study ADMA-003.

Subject (b) (6) was withdrawn by the sponsor after the second infusion, with no additional details given. This subject had low protein S levels at screening and at the first and second infusions (4.8, 4.8, 5.35 grams per deciliter, normal range 6.4-8.3 g/dL).

6.1.13 Study Summary and Conclusions

The results of Study ADMA-003 demonstrate that ASCENIV is safe and effective for routine prophylaxis in adults and adolescents diagnosed as having primary immunodeficiency.

10. Conclusions

ASCENIV is safe and effect for use as routine prophylaxis in adults and adolescents with the diagnosis of primary immunodeficiency.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with primary immunodeficiency have low plasma levels of immunoglobulin, leading to an increased rate of serious bacterial infections.	• Replacement of plasma immunoglobulin has shown to be beneficial for patients with primary immunodeficiency.
Unmet Medical Need	• There are several licensed Immune Globulin (human) products.	• There are several licensed Immune Globulin (human) products, so there is no unmet medical need.
Clinical Benefit	• The results for one open-label multicenter study (ADMA-003) in 59 adult and adolescent subjects was submitted.	• There were no serious bacterial infections in any of the 59 enrolled subjects over the 12 months study period.
Risk	• One product lot 3-FIN-1500 demonstrated particle formation after 6 months storage. An examination of adverse events after infusions of ASCENIV stored more than 6 months showed an increase rate in several body system categories compare to adverse event rates after infusions of ASCENIV store less than 6 months. • Class-specific risks for Immune Globulin products include the following: - Thrombosis - Hypersensitivity reactions - Acute renal failure - Hyperproteinemia - Aseptic meningitis - Hemolysis - Transfusion-related acute lung injury - Transmissible infectious agents - Laboratory test interference	• Particle formation has been seen in BIVIGAM manufactured by the same facility and by (b) (4) process; this led to recall of product lots, but has not resulted in license revocation. The increase rate of adverse events is for adverse events that are typically reported of Immune Globulin products. Therefore, the risk associated with particle formation is primarily a risk for the product manufacturer. • Class-specific risks for Immune Globulin products are well-known.
Risk Management	• The applicant proposes routine pharmacovigilance to monitor product risks. • The CMC reviewer are requesting additional information on manufacturing procedures.	• Routine pharmacovigilance is acceptable for this product.

11.2 Risk-Benefit Summary and Assessment

Routine pharmacovigillance is acceptable to monitor the clinical risks associated with the use of ASCENIV.

11.3 Discussion of Regulatory Options

The regulatory options are as follows:

- Full approval of STN125590
- Approval of STN125590 with labeling changes
- Issuance of a Complete Response letter

11.4 Recommendations on Regulatory Actions

This reviewer recommends approval of STN125590 with labeling changes. The CMC reviewers are recommending a CR letter requesting additional information on the manufacturing process.

11.5 Labeling Review and Recommendations

Labeling review is pending the additional information that will be submitted in response to the CR letter.

11.6 Recommendations on Postmarketing Actions

There are no recommendations for additional clinical data, other than the data that will be submitted for the approved Pediatric Study Plan for pediatric subject 2 years of age and above.

Appendix 1. Diagnostic Criteria for Serious Infection Types

Note: Items in bold are considered essential diagnostic features.

Infection: Bacteremia/sepsis[a]

- *Symptoms:* chills, rigors
- *Physical findings:* fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure <90 mm Hg or a reduction of >40 mm Hg from baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oligouria, cutaneous vasodilation/vasoconstriction
- *Laboratory tests*: **positive blood cultureb**, leukocytosis (white blood cell (WBC) count > 12,000/mm3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis

Infection: Bacterial Meningitis

- *Symptoms*: headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures
- *Physical findings*: Kernig's sign, Brudzinski's sign, meningococcal rash, fever of >38 °C oral or >39°C rectal
- *Laboratory tests:* **positive cerebrospinal fluid (CSF) Gram stain and/or cultureand/or positive CSF bacterial antigen assay,** positive blood culturec, CSF leukocytosis with neutrophil predominance, decrease in CSF glucose

Infection: Osteomyelitis/Septic Arthritis

- *Symptoms*: pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (local inflammatory symptoms/signs may be lacking in adults.)

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[a] Two of the following should be present to make the diagnosis of sepsis in adults: temperature >38°C oral/ > 39°C rectal or <36°C oral or < 37°C rectal; heart rate >90 beats/min; respiratory rate >20 breaths/min, or PaCO2 <32 mm Hg; WBC count >12,000/mm 3, <4,000/mm 3, or >10% immature (band) forms (Levy *et al*., 2001). For pediatric subjects, we recommend you employ the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis (Pediatric Crit Care Med, 2005).

[b] Indwelling catheter- or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IGIV replacement therapy. For subjects without indwelling catheters or vascular access devices, a single blood culture positive for a pathogenic organism will meet the diagnostic criteria for bacteremia. (Multiple blood cultures are typically obtained in cases of suspected bacteremia/sepsis, as per standard medical practice, and the finding of a single positive culture should prompt additional confirmatory cultures). Subjects meeting criteria for positive blood culture but without 2 or more of the sepsis criteria listed above will be classified as having bacteremia. Blood culture samples and reports should indicate the method of culture collection, i.e. dedicated venipuncture, central line, peripheral line.

[c] A blood culture positive for growth of *Streptococcus pneumoniae*, *Neisseria meningitides*, or*Haemophilus influenzae*, in combination with CSF leukocytosis and/or decrease in CSF glucose,can serve to confirm the diagnosis of acute bacterial meningitis (FDA – Acute BacterialMeningitis, 1998).

- *Physical findings*: evidence of soft tissue infection adjacent to the involved bone/joint, drainage from sinus tract from involved bone, fever of >38°C oral or >39°C rectal
- *Laboratory tests*: positive blood culture, positive probe to bone, positive bone aspirate culture, positive bone biopsy culture, positive bone histopathology, positive joint fluid Gram stain and culture

Imaging studies: **positive X-ray, nuclear medicine bone scan, magnetic resonance imaging (MRI) scan, or computed tomography (CT) scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra**

Infection: Bacterial Pneumonia[d]

- *Symptoms*: productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias
- *Physical findings*: rales; pulmonary consolidation as reflected by: dullness on percussion, bronchial breath sounds, egophony; fever >38°C oral or > 39°C rectal, or <36°C, hypothermia (temperature < 36°C oral or < 37°C rectal)
- *Laboratory tests*: leukocytosis, differential WBC count of >10% band neutrophils, leukopenia, hypoxemia (PaO2 < 60 mm Hg on room air), positive blood culture, Gram stain and culture of deep expectorated sputum[e], positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with bronchoalveolar lavage (BAL) or protected brush sampling *Imaging studies*: **Pulmonary infiltrate with consolidation on chest X-Ray (CXR)** (new in comparison with baseline CXR)

Infection: Visceral Abscess

- *Symptoms:* abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present)
- *Physical findings:* intermittent fevers (temperature >38 ° C oral or >39°C rectal), abdominal tenderness, palpable mass, hepatomegaly, jaundice

[d] For the diagnosis of pneumonia in adults, commonly at least 2 of the listed symptoms and/or signs should be present in conjunction with at least one laboratory and one imaging studies diagnostic element. However, for the purposes of counting serious infection episodes in a clinical trial of IGIV, the finding of a new pulmonary infiltrate with consolidation on CXR is considered sufficient. To establish the diagnosis of bacterial pneumonia for pediatric patients, most of the same diagnostic criteria listed may be used, with the following exceptions: Because pediatric patients may not produce a sputum specimen for culture, blood cultures or serology may be substituted to identify the etiologic bacterial pathogen. In infants age 3 to 24 months, who tend to have a higher baseline temperature, fever is defined as a rectal temperature >38.3°C (101°F). In children >2 years, fever is more commonly defined as a rectal temperature >38°C (100.4°F). In pediatric patients, elevations of WBC counts >15,000/mm 3 are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count <5000/mm 3 may be observed, usually associated with severe infection (FDA - Community Acquired Pneumonia, 1998).

[e] We recommend a deep expectorated sputum gram stain to demonstrate the presence of microorganisms on examination of 10-20 oil immersion microscopic fields and <10 squamous epithelial cells and >25 polymorphonuclear leukocytes at 10X low power magnification to determine suitability of sputum culture (FDA – Community Acquired Pneumonia, 1998).

- *Laboratory tests:* **positive Gram stain and/or culture from the infected site, with isolation of an appropriate pathogen,** positive blood culture, leukocytosis with accompanying left shift, differential WBC count of >10% immature (band) neutrophils, elevated serum amylase concentration (pancreatic abscess), elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess
- *Imaging studies:* **typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan**

Appendix 2. October 7, 2014, pre-BLA meeting minutes CRMTS #9487

Meeting Summary

Meeting ID #:	CRMTS #9487
Application type and number:	IND 15308
Product name:	RI-002 Immune Globulin Intravenous (Human)
Sponsor:	ADMA Biologics, Inc.
Meeting type:	Type B
Meeting category:	Pre-BLA
Meeting date & time:	October 7, 2014, 1:30 PM – 2:30 PM
Meeting format:	Face-to-face
Meeting Chair/Leader:	Howard Chazin, MD, MBA
Meeting Recorder:	Nannette Cagungun, MS, PD, RAC
Preliminary Responses sent	October 1, 2014

FDA Participants:
Qiao Bobo, PhD, OCBQ, Division of Manufacturing and Product Quality
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Howard Chazin, MD, MBA, OBRR, Division of Hematology Clinical Review
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Christopher Sese

ADMA Biologics, Inc. Attendees:
Diane P. Myers, Regulatory Consultant, Malvern Consulting Group, Inc. (MCG)
Gerri Henwood, Development Consultant, MCG
Randall Mack, Development Consultant, MCG
Adam Grossman, President & CEO, ADMA
Lucy DeMario, PhD, Senior Director, Quality, ADMA
Janice Smith, Vice President, Quality Operations, Biotest Pharmaceuticals
James Mond, MD, PhD, Chief Scientific Officer, Chief Medical Officer, ADMA

(b) (4), Statistical Consultant

Jordan Orange, MD, PhD, Professor of Pediatrics, Chief, Department of Immunology, Allergy and Rheumatology, Baylor College of Medicine
Peter Patriarca, MD, Consultant, Biologics Consulting Group

Background and Objectives:
ADMA Biologics, Inc. submitted a meeting request on July 17, 2014, to seek Agency input on the planned BLA submission and to ensure that the data collected are sufficient to support approval for the proposed indication. The pre-meeting materials were submitted on September 4, 2014.

FDA provided its proposed responses to ADMA's questions on October 1, 2014. After reviewing the proposed responses, ADMA notified FDA on October 2, 2014, of its decision to limit the meeting to discuss only question numbers 1, 2, 6, 8a, 8b, and Additional FDA Comments 2 and 8.

Question from the Sponsor:

Clinical:

Sponsor Question 1:
The revised study ADMA-003 SAP (Version 1.0, Draft) was submitted to the Agency in March 2013 (Serial Submission # 0005) addressing feedback provided by the Agency via facsimile on 26 December 2012 (letter dated 21 December 2012), and is provided in Appendix 1 of this document.

a. Does the Agency agree with the planned analysis identified in the SAP?

b. Study database to support the analysis and CSR will be submitted when the BLA is filed. The database is formatted in SDTM and ADaM format. Does the Agency agree that the format for the database is acceptable?

FDA Response to Question 1:

a. The SAP is acceptable with the following comments:
   i. Please specify how you will handle potential over-dispersion or excessive zeros for the Poisson model used for the primary efficacy endpoint analysis.
   ii. Please revisit how you plan to calculate the number of days between infusions. The current formula will yield a higher number of study days when summed across all infusion cycles as compared to the total number of days on study.
   iii. Your efficacy and safety analyses must include separate analyses of adults (age > 16 years) and pediatric subjects (age 0-12 years). Please also report the results of efficacy and safety analyses for adolescents (ages 12-16).

iv. Please perform and report efficacy and safety analyses by sex and race regardless of the size of subgroups.

v. Please analyze and report the mean number of temporally associated adverse events reported per infusion as defined in item 7b below under Additional FDA Comments/Questions.

Please submit a revised SAP to the IND reflecting the above changes.

b. Yes.

Additional discussion:
ADMA expressed concern that there might be some confusion regarding the SAP and the definition of days of follow-up calculation. ADMA explained the exposure time as dose 1 to last dose (dose 12) and the follow-up time as dose 1 to last dose plus 30 days (13 months total). The denominator for total days on study includes the follow-up time after the last dose.

FDA asked ADMA to specify in the SAP that the follow-up time includes the 30 days after the last infusion.

FDA will accept 12 months of data, but FDA's primary concern regarding treatment duration is to ensure that there is no seasonality influence on occurrence of infections while on treatment.

Sponsor Question 2:
A total of 31 subjects have been enrolled in the pharmacokinetic portion of Study ADMA-003, including 4 pediatric subjects. Preliminary IgG and specific antibody data are provided in Section 10.1.1.3. Does the Agency agree there are adequate numbers of subjects enrolled in the pharmacokinetic portion of the study to support a BLA filing?

FDA Response to Question 2:
Yes, the data may support an indication in adults and adolescents; however, we cannot provide a definitive answer without knowing the number of subjects for which an adequate number of results from blood sampling for PK determinations is available.

The PK study in four pediatric subjects is not adequate because the study does not cover the age range from 2 to 12 years. The subjects included in your PK study are only adolescents. See also "Additional FDA Questions/Comments" item 1.

Additional discussion:
Please see Additional Discussion section under FDA Response to Question 8.

Sponsor Question 3:

A summary of the results from the ongoing viral transmission testing is provided in Section 10.1.1.2.3, as well as a proposal for ongoing monitoring and reporting. Does the Agency agree that the proposal of ongoing monitoring and reporting is acceptable?

FDA Response to Question 3:
Your proposal for submitting the final viral safety data on 25 subjects with the day 120 safety update is acceptable. Plans for ongoing monitoring and reporting of suspected/ potential viral transmissions following licensure, need to be detailed under the pharmacovigilance plan section of the BLA.

Additional discussion:
This question was not discussed during this meeting.

CMC:

Sponsor Question 4:
A proposal for cross referencing Biotest's BIVIGAM® BLA (125389 and all its amendments and supplements) is provided in Section 10.2.2 for the reports listed, provided that any updates or differences for the RI-002 process will be included in ADMA's BLA submission.

Does the Agency agree that the proposal is acceptable?

FDA Response to Question 4:
Your BLA should be a stand-alone submission and should not cross-reference another company's BLA.

It is the responsibility of the license holder to submit information required for the BLA as per CTD required sections, and FDA related guidance documents. Please refer to the "Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma or Serum-Derived Products (February 1999)" when preparing the BLA in the CTD format.

BLA holders are responsible for the content and changes of the content of the BLA per 21 CFR 601.12. Please note, the product owner's "quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company" per 21 CFR 211.22(a). Please refer to the Guidance for Industry: Contract Manufacturing Arrangements for Drugs - Quality Agreements (May 2013) and Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed Biologics (November 2008) for additional information.

Additional discussion:
This question was not discussed during this meeting.

Sponsor Question 5:
A proposal to support expiration dating of three years is provided in Section 10.2.3. Does the Agency agree that the proposal is acceptable?

FDA Response to Question 5:
We do not have enough information in the pre-meeting package to answer this question at this time. Additionally, one of the stability lots, Lot 3-FIN-1500, failed Appearance due to the presence of (b) (4) starting at the 9 month timepoint. Please submit, in the BLA, information on the investigation into this failure. The determination of expiry dating will be addressed during the review of the BLA.

Additional discussion:
This question was not discussed during this meeting.

Sponsor Question 6:
A proposal for visual inspection specifications for stability is provided in Section 10.2.4. Does the Agency agree that the proposal is acceptable?

FDA Response to Question 6:
FDA does not agree with your proposed specification and does not accept your assertion that (b) (4) particulates are typically found in Immune Globulin Intravenous (Human). The determination of acceptability of specifications and stability programs are issues that will be addressed during the review of the BLA.

Additional discussion:
ADMA plans to continue use of commercially-made (b) (4) filters. They do not expect lots will have particulates on release except in isolated cases. Assuming everything is fine, ADMA proposes to submit a Biological Product Deviation Report (BPDR) if the affected lot is in the market.

FDA pointed out that there is no licensed IGIV product that has a specification for particulates. FDA does not encourage the use of (b) (4) filters or rolling back an FDA standard that has been in place for a long time. The use of filters does not necessarily mean that no particulates will go through, or [re]form after filtration. Particulates are tied to a number of adverse events. Allowing a specification for the presence of particulates is slim unless it can be supported with appropriate justification. ADMA should perform additional analysis for sub-visible particles and have a better understanding of how these are forming. Additionally, ADMA should look at aggregates and polymer levels using different analytical tools. Stability should be the best case scenario, so finding particles on stability does not provide much assurance that particles are not in the product lots out on the market.

FDA directed ADMA to materials in the public domain, i.e., FDA website, for lot recalls and Warning Letters, which may provide some information of interest.

ADMA referred to challenges in visual inspections as there may be occasional disagreements between inspectors.

FDA remarked that visual inspection is not an exact science. The USP standard is not applicable to this type of product. There are more modern analytical tools that can be used at the sub-visible level. The presence of particulates is not a typical problem for most of FDA IGIV products and represents that something else may be going on, e.g., problems with manufacturing or formulation.

Two contract vendors provide Source Plasma: ADMA BioCenters and Biotest Pharmaceuticals Corporation. The product is prepared from a plasma pool size of (b) (4) . The sponsor does not plan a large scale production and anticipates approximately (b) (4) lots per year will be manufactured. Donors are being screened for RSV in addition to other viruses.

FDA indicated lots must be ready by the time of BLA submission.

To ensure adequate time and resources are available, FDA asked to be notified well in advance of the BLA submission.

ADMA agreed to contact the Agency once the last subject gets close to the end of the dosing study.

Sponsor Question 7:

ADMA anticipates filing a paper BLA utilizing the Common Technical Document (CTD) format. Does the Agency agree that this approach is acceptable? Specifically,

a. The ADMA paper BLA will contain significant cross references to the Biotest electronic BLA for BIVIGAM®. Does the Agency have any concerns with the planned interface with the Biotest BLA?

b. The ADMA BLA will contain the report for one clinical trial (ADMA-003). In addition, the required CMC documentation will be provided (See Appendix 2 for Draft Table of Contents). Is the proposed content of the BLA acceptable to the Agency?

FDA Response to Question 7:

a. No. As noted previously, the BLA should be a stand-alone submission. We encourage you to submit an electronic rather than a paper BLA. The FDA Electronic Secure Gateway (ESG) allows the secure transmission of regulatory submissions and is our preferred method of transmission. For questions related to providing electronic submissions, please contact CBER's

electronic submission coordinator at esubprep@fda.hhs.gov. You may also refer to Guidance for Industry: Providing Regulatory Submissions in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)."

b. The proposed content of the BLA is not acceptable (please see response above). Your BLA should include a pharmacovigilance plan as well as a request for a proposed proprietary name review. Please perform adequate quality control to assure that your BLA submission is complete and accurate [see 21 CFR 601.2(a)].

Additional discussion:
This question was not discussed during this meeting.

Sponsor Question 8:
A summary of the subjects enrolled in Study ADMA-003 below the age of 17 years old is provided in Section 10.1.1.1. The proposed Draft Pediatric Plan is summarized in Section 10.1.2, and provided in full in Appendix 3. Does the Agency agree that the pediatric plan will be sufficient to meet the requirements under PREA? Specifically,

a. Does the Agency agree the five subjects enrolled in Study ADMA-003 from the 12-16 year old group meets the requirement for studying this pediatric age strata?

b. Does the Agency agree that the proposed protocol design with optional pharmacokinetic participation outlined in Section 9.2 of the Pediatric Plan will be sufficient to provide adequate data to satisfy the requirements under PREA?

FDA Response to Question 8:

a. Yes, provided review of the submitted data does not raise additional questions, data for the five subjects in the age range of 12-16 years old are acceptable.

b. No. The Agency does not agree with your optional pharmacokinetic pediatric plan. A pharmacokinetic study is needed in children over the age range of 2-12 years (stratified into two age groups: 2-6 years and >6 years to <12 years with at least 5 subjects in each age group). Please modify the planned pediatric trial to specify a minimum number of pediatric subjects in each pediatric age stratum for which you will obtain PK measurements in addition to safety and efficacy information. Please see additional comments pertaining to your planned pediatric trial under "Additional FDA Questions/Comments."

Additional discussion:
ADMA discussed challenges in recruiting pediatric subjects with PI in this age bracket for PK sampling particularly in pediatric patients with common variable

immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA). According to guidelines, the diagnosis of CVID should not be made before age 3 years. The mean age of diagnosis of XLA is 2 ½ years of age with no family history. It is even younger for those with family history. It is necessary to distinguish transient hypogammaglobulinemia from primary humoral immunodeficiency. One out of twenty children will have low IgG using a confidence interval approach to define normal levels, and some of these will have poor vaccine responses, but most of these on follow-up do not prove to have primary humoral immunodeficiency.

It would be difficult for these children to have additional blood drawn for PK during hospitalization. In addition, some parents would not want to enroll their child in the study as a result of a PK blood sampling requirement.

Existing data indicate practitioners do not dose differently for children in this age group compared to adults.

FDA stated that the PK of IGIV may be substantially different in 2-5 year old children and recognized the problem with the collection of blood samples in this age group. Since it is difficult to take multiple blood samples in this age group, a sparse sampling approach may be used by spreading blood collection over 21 or 28 days. On sample size, the FDA stated that at least five subjects for PK measurements will be needed in each pediatric age group and that ADMA's sampling timepoint scheme should be submitted to the IND. FDA is not setting a timeframe for submission of the additional pediatric PK data. The sponsor may select a timeframe that it considers realistic.

Sponsor Question 9:
Does the Agency have any comments, suggestions or recommendations regarding any aspect of the development of RI-002 that are not addressed in the preceding questions?

FDA Response to Question 9:
Please see "Additional FDA Questions/Comments" below.

Additional discussion:
This question was not discussed during this meeting.

Additional FDA Questions/Comments:

1. Your proposed indication, "treatment of Primary Humoral Immunodeficiency (PI)" does not specify the age group(s) for which the product would be indicated. When submitting the BLA, please use appropriate language in the INDICATIONS AND USAGE section of the draft package insert to specify the age groups (e.g., adults, adolescents, etc.) for which the product would be indicated, based on adequate efficacy and safety data for subjects in those age ranges.

2. Please revise the proposed phase 4 pediatric trial protocol to require a minimum number of subjects in each of the two pediatric age stratum to be studied who will undergo PK sampling for total IgG. A minimum of five subjects in each of the age stratum is recommended for PK sampling.

   Additional Discussion:
   Please see Additional Discussion section under FDA Response to Question 8.

3. PK sampling for pathogen-specific antibodies is optional.

4. Sampling for IgG subclasses is optional.

5. Obtaining safety and efficacy data in the planned pediatric trial beyond 4 months of dosing is optional.

6. In your proposed phase 4 pediatric trial, inclusion criterion five states in part that "subjects must have been receiving IGIV at a dose that has not been changed by > 50% of the mean dose on a mg/kg basis for at least 3 months prior to study entry…" Please note that by using this criterion, a subject could have been titrated upward from 200 mg/dL to 600 mg/dL during the 3 months prior to trial entry and yet would meet this criterion, as the 200 mg/kg and 600 mg/kg doses are not > 50% different from the mean dose of 400 mg/dL during that period. Please consider using a more stringent criterion to define "steady" dose of prior IGIV therapy.

7. Please add the following safety endpoints to your proposed phase 4 pediatric trial:

   a. The mean number of temporally-associated adverse events per infusion (i.e., (a)/(b), where (a) represents the total number of AEs that begin during or within 72 hours of the end of a test product infusion, and (b) represents the total number of test product infusions).

   b. The total number and incidence of adverse reactions plus suspected adverse reactions combined. Adverse reactions and suspected adverse reactions would be defined as adverse events meeting any of the following criteria:

      i. The onset of the adverse event (AE) is during or within 72 hours following the end of the infusion of test product.

      ii. The AE is judged as possibly, probably, or definitely related to administration of the test agent by the investigator OR by the sponsor.

iii. The causality assessment of the AE by the investigator is indeterminate or missing.

8. Please submit as soon as possible an initial pediatric study plan (iPSP) to the IND with the words "Initial Pediatric Study Plan" prominently displayed at the top of the cover letter. This iPSP may contain the revised phase 4 pediatric trial protocol.

   Please note that the pediatric trial should be ongoing at the time of BLA submission.

   Please include a revised protocol for your proposed pediatric trial in children to include a statistical analysis plan. The latter should plan to combine PK data from pediatric subjects in the same pediatric age strata already studied in trial ADMA-003. Safety and efficacy analyses should be submitted separately for the proposed study, as well as combined with data from pediatric subjects of the same age strata from trial ADMA-003 in Integrated Analyses of Pediatric Safety and Efficacy. Please also include calendar milestone dates for the final agreed-upon protocol submission, completion of the pediatric trial, and for submission of the final study report. Please note that your proposed pediatric study will constitute a postmarketing requirement [see section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)].

   Additional Discussion:
   ADMA plans to submit a draft pediatric plan for the 3-5 year, >5-12 year, and >12-16 year age brackets. The protocol for the new subjects will be included. The sampling time point will be the same as that in the protocol that they are using. During the meeting, ADMA requested that the additional study not be required to be underway when they submit the BLA (target date March 2015) but to promptly conduct it after BLA approval. ADMA noted their limited resources relative to other companies. They further asked whether combining available data from the first trial with what they will obtain is acceptable. FDA indicated it would provide further guidance regarding the company's request in a post-meeting note accompanying the meeting minutes.

   FDA asked that an initial Pediatric Study Plan (iPSP) be submitted to the IND for review after which the Agency will provide feedback as well as suggestions.

Decisions made and/or agreements reached:

Action items:

1. ADMA will submit a pediatric plan for the 6-11 and 12-16 age brackets and will submit the schema for sparse sampling in the 2-6 age bracket.

Post-Meeting Note:

In terms of the pediatric study being initiated before the BLA is submitted, ADMA may request a deferral for the pediatric study in order to be able to initiate the study after the filing of the BLA.