



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

Date: 24 November 2015

From: Wambui Chege, MD
Medical Officer, Pharmacovigilance Branch

Re: STN 125590\0

Through: Jane Woo, MD
Acting Branch Chief, Pharmacovigilance Branch

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Acting Director, Division of Epidemiology

Product: RI-002 (Immune Globulin Intravenous (Human), 10% Liquid with standardized, (b) (4) [REDACTED])

Submission: Original Biologics License Application

Subject Pharmacovigilance Plan Review Memorandum

Sponsor: ADMA Biologics, Inc

ADD: 30 July 2016

1. INTRODUCTION

On 31Jul2015, ADMA Biologics, Inc. submitted an original Biologics License Application (BLA) to the Food and Drug Administration (FDA) for RI-002, Immune Globulin (Ig) Intravenous (Human), 10% Liquid with (b) (4)

The product was known in development as RI-002, and several proposed proprietary names including (b) (4) are currently under review. For purposes of clarity, this product will be referred to in this memorandum by the name used in development – RI-002.

RI-002 will be supplied as a liquid solution containing 10% IgG (100 mg/mL) for intravenous (IV) infusion. The product will be available in a single vial size of 5g in 50 mL solution. The sponsor's current proposed indication for RI-002 is for the treatment of primary humoral immunodeficiency (PI).

1.1 Safety Related Product Information

1.1.1 General Safety Concerns for IgIV Products

Review of the safety data submitted in support of this BLA will include assessment of known safety concerns for the class of IgIV products. Well described safety concerns for IgIV products include anaphylaxis (especially in IgA-deficient patients), acute renal failure, thromboembolic events, aseptic meningitis and hemolytic anemia.¹ In addition, as with other plasma-derived infusions, IgIV products carry an inherent risk of transmission of infectious pathogens. This risk is mitigated in the production of RI-002 using virus filtration and solvent/detergent treatment “known to eliminate enveloped viruses” and thus promote the manufacture of “a sterile, non-pyrogenic preparation.”²

Several recent evaluations by FDA have resulted in safety labeling changes for currently approved IgIV products. In 2012, in accordance with Section 921 of the FDA Amendments Act (FDAAA), FDA posted a potential signal for a serious risk of hemolysis with an Ig product named Privigen based on an increase in reports of hemolysis to the FDA Adverse Event Reporting System (FAERS).³ That same year FDA issued a Safety Communication for the class of Ig products, stating that a potential risk of hemolysis has been associated with the administration of human immune globulin.⁴

In 2013, FDA instituted a safety labeling change for the class of Ig products. At that time, FDA announced that analyses of recent data had strengthened the association between the use of Ig products and the risk of thrombosis, and therefore required manufacturers to add information on

¹ Orbach O, Katz U, Sherer Y, et al: Intravenous immunoglobulin: adverse effects and safe administration. *Clin Rev Allergy Immun.* 2005; 29(3): 173-84

² ADMA Biologics, Inc. Risk Management Plan [RI-002] eCTD 125590/0

³ FDA. Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) between January – March 2012. Available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm307608.htm>

⁴ FDA. FDA Safety Communication: Updated information on the risks of thrombosis and hemolysis potentially related to administration of intravenous, subcutaneous and intramuscular human immune globulin products. Available at <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm327934.htm>

thrombosis to the existing boxed warning in the labels of all IgIV.⁵ The current boxed warning on labels of IgIV also notes the risk of renal dysfunction and acute renal failure (ARF).⁶

1.1.2 Specific Safety Concerns for RI-002

1.1.2.1 (b) (4)

RI-002 is a sterile preparation of Ig obtained from pooled plasma from normal source donors

(b) (4)

However, the sponsor did not propose in the current BLA that RI-002 be used specifically for management of (b) (4), and did not provide data supporting the safety or efficacy of RI-002 for this indication. As a result, FDA requested that the sponsor, “remove any mention of (b) (4) from the Package Insert as well as from the Drug Product release specifications.”⁸ In response to FDA’s request, ADMA reports that the company has been “following a co-development strategy to pursue the utilization of RI-002 not only for PIDD, (b) (4)

¹⁰ The sponsor therefore requests that FDA permit inclusion of “supportive statements regarding (b) (4) in the labeling of RI-002.” ADMA’s request is currently under review by OBRR.

Of the FDA approved products used to treat (b) (4), RI-002 may be most similar to a (b) (4) product licensed in (b) (4) named (b) (4)

With regard to the strategy for development of RI-002, ADMA notes “the lot release specification for standardized, high titers of (b) (4) is intended to mimic or exceed the levels present in (b) (4)

A BLA

⁵ FDA. Immune Globulin Products (Human) intravenous, subcutaneous and intramuscular. Detailed View: Safety Labeling Changes Approved By FDA Center for Biologics Evaluation and Research (CBER) – June 2013. Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360566.htm>

⁶ FDA. Adverse Event Report for an Immune Globulin: FDA Investigation and Actions. Available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/InternationalActivities/UCM273193.pdf>

⁷ (b) (4)

⁸ FDA. Information Request (Response Due by Friday, January 29, 2016): Original BLA, BL 125590/0, Immune Globulin Intravenous (RI-002), ADMA Biologics, Inc. 11Jan2016 eCTD 125590/0

⁹ ADMA Biologics Inc. Cover Letter. Response to FDA Request for Changes to the Package Insert and Drug Product Specifications. 03Feb2016 eCTD 125590/0 seq 0022

(b) (4)

(b) (4)

(b) (4) was not approved by FDA due to evidence in prelicensure trials of an increased frequency and greater severity of hypersensitivity reactions compared to (b) (4)

1.1.2.2 Polysorbate 80

RI-002 bears some manufacturing similarities to a recently licensed IgIV product named Bivigam. The sponsor for RI-002, ADMA Biologics, Inc. has a contract manufacturing relationship with Biotest Pharmaceuticals (BPC), the manufacturer of Bivigam. Under the agreement, BPC is responsible for the fractionation of RI-002 and the contract allows for both “the clinical and commercial supply” of the product.¹⁵

Bivigam is a 10% liquid human IgIV.¹⁶ The original BLA for Bivigam initially received Complete Response letters from FDA due to multiple manufacturing issues including concerns regarding the amount of the excipient Polysorbate 80 (PS80) in the final product. In particular FDA’s communication to the sponsor noted that “the amount of PS80 administered in a labeled dose of Bivigam has been associated with hepatic or renal failure” and that high levels of PS80 have been associated with hypotension in animal models.¹⁷ In addition, FDA noted that although there were no clinically significant cases of hypotension or other cardiac adverse events in the prelicensure data for Bivigam, the prelicensure clinical database was too limited in size to exclude a lack of excess risk of hypotension with Bivigam compared to other IgIV treated patients.¹⁴

Bivigam was eventually approved on 19Dec2012, at which time, the package insert was crafted to state that in animal studies, IV infusions of PS80 have been linked to hypotension and increased liver enzymes. In addition, following discussions with FDA, the sponsor agreed to a postmarketing commitment (PMC) study to assess the potential risk of hypotension as well as hepatic and renal impairment following use of Bivigam.¹⁸ A recent request from the sponsor to change the study design of this PMC from a prospective, observational study to a retrospective chart review has been denied by FDA.¹⁹ As part of FDA’s evaluation of the sponsor’s request a query of FAERS was conducted to identify any reports of hypotension received following Bivigam from the time of licensure through 30Nov2015. The search identified a single FAERS report of a symptomatic hypotensive episode (FAERS # 9769337) which describes a 70 year old female with a history of hypertension. On (b) (6), about 2 hours into her Bivigam infusion, her blood pressure dropped from 120/70 to 88/51. She became disoriented, dizzy, and fatigued. Her blood pressure returned to baseline about 20 minutes after reducing the infusion rate to 100 cc/hr.¹⁶

The final formulation of RI-002 contains 0.15–0.25% PS 80,²⁰ the same amount found in the final formulation of Bivigam.¹³ Review of the clinical safety database for RI-002 will therefore include an assessment of the safety concerns specific to the excipient PS80.

(b) (4)

¹⁵ ADMA Biologics Inc. Drug Development RI-002. Available at <http://www.admabiologics.com/drug-development/ri-002>

¹⁶ Biotest Pharmaceuticals. Bivigam Immune Globulin Intravenous (Human), 10% Liquid. Package Insert. Available at <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm334601.htm>

¹⁷ FDA. Complete Response Letter regarding Original BLA for Bivigam 1Sep2011. eCTD 125389/0

¹⁸ FDA. Approval letter. Bivigam. 19Dec2012. eCTD 125389/0

¹⁹ Winiecki S. CBER/OBE Review Memo: Bivigam Hypotension PMC eCTD 125389/105

²⁰ ADMA Biologics, Inc. RI-002. Proposed package Insert. eCTD 125590/0

2. OBJECTIVES

This memorandum follows a request from the Office of Blood Research and Review (OBRR) to review the available safety-related data for RI-002 and the Pharmacovigilance Plan (PVP) proposed by the sponsor. The Risk Management Plan (RMP) submitted by the sponsor and the safety-related results from the prelicensure clinical trial ADMA-003 were also reviewed.

3. PHARMACOVIGILANCE PLAN REVIEW

3.1 Clinical Safety Database

The clinical data submitted by the sponsor in support of the licensure for RI-002 consist of a single clinical trial: ADMA-003, an open label, multicenter study to evaluate the pharmacokinetics (PK), efficacy and safety of RI-002 in subjects with PI. Safety related data from this study have been reviewed in detail and are summarized in Table 1 below.

Table 1. Summary of Clinical Trial ADMA-003

Table 1. Summary of Clinical Trial ID: NCT01662			
Study Title:	An open label, multicenter study to evaluate the PK, efficacy and safety of RI-002 in subjects with PI		
Study Design:	Phase III multicenter, open label trial		
Eligibility criteria:	Subjects 2 to 75 yo with a confirmed diagnosis of PI who have received IgIV therapy at a steady dose (\pm 50% of the mean dose for ≥ 3 months), and have maintained a trough IgG level ≥ 500 mg/dL prior to study entry.		
Study Duration:	18Feb2013 to 25Nov2014		
Study Status:	Complete. Final study report submitted.		
Objectives:	1° 2°	<ul style="list-style-type: none">○ To demonstrate reduced frequency of SBIs in subjects with PI○ To evaluate the incidence of infections, number of lost work/school days, number of physician visits, time to resolution of infections, hospitalizations, antibiotic therapy, product trough levels and PK profile	
Safety-related endpoints:	<ul style="list-style-type: none">● Incidence of AEs that occur during or within 1 hour, 24 hours and 72 hours of completion of an infusion● Incidence of infusion site reactions, study discontinuation, all-cause mortality and PI related deaths● VS and laboratory monitoring		
Study Population:		(n)	%
	Total:	59	100
	Gender: Male	28	47.5
	Female	31	52.5
	Age: ≤ 16 yo	11	18.6
	17-64yo	37	62.7
	≥ 65 yo	11	18.6
	Race: White	58	98.3
African-American	1	1.7	
Ethnicity: Non-Hispanic	56	94.9	
	Hispanic	3	5.1
Study Results:	AE monitoring	<ul style="list-style-type: none">● 2 SAEs in 2 subjects – Wound Infection and Migraine.● 2 subjects discontinued the study due to 2AEs – Wound Infection and Adverse Drug Reaction.● No TEs, ARF, hemolysis, viral transmission, aseptic meningitis or TRALI. No deaths.	
	PE	<ul style="list-style-type: none">● No clinically significant findings were noted in subjects	
	Laboratory parameters	<ul style="list-style-type: none">● Labs at end of study were generally similar to screening assessments, with no trends noted	

		<ul style="list-style-type: none"> Clinically significant results were identified, and were single occurrences or were due to an active infection
Conclusion:	No clinically significant safety issues were identified	

AE=Adverse Event, ARF=Acute Renal Failure, PE=Physical Examination, PI=Primary Immunodeficiency, PK=Pharmacokinetics, SAE=Serious AE, SBI=Serious Bacterial Infection, TE=Thrombotic Events, TRALI=Transfusion Related Acute Lung Injury, VS=Vital Signs

3.1.1 Analysis of Adverse Events in the Clinical Safety Database

3.1.1.1 Serious Adverse Events in Clinical Trial ADMA-003

Two SAEs were reported by 2 study subjects (Table 1 above). Clinical data for both study subjects were reviewed in detail and are summarized below.

Subject (b) (6) – 64yo M with PI was receiving RI-002 when he underwent left shoulder replacement surgery on (b) (6) due to a long history of rheumatologic joint disease. On (b) (6) he was admitted for the SAE of wound infection following a cat bite and underwent left shoulder revision surgery without complication. The infection resolved with antibiotics. The subject was discontinued from the study due to the AE and did not receive further doses of RI-002.

Subject (b) (6) – 43yo F with a history of migraines was receiving RI-002 for PI and experienced an SAE of migraine on (b) (6), 20 days after the previous infusion. The migraine required hospitalization for 3 days, after which the headache resolved and the subject went on to receive further dosing with RI-002.

3.1.1.2 Study Discontinuations due to Adverse Events in Clinical Trial ADMA-003

Two subjects discontinued the study ADMA-003 due to 2 AEs (Table 1 above). Of the 2 study subjects who discontinued the study, 1 patient – subject (b) (6), experienced a SAE and has previously been described in section 3.1.1 above. Clinical data for the second study subject have also been reviewed and are summarized below.

Subject (b) (6) – 12yo M received a second dose of RI-002 on (b) (6). The dose was discontinued after 3 minutes because the patient experienced flushing and “difficulty breathing” with no change in blood pressure, respiratory rate, or heart rate, after receiving the study infusion at a rate faster than prescribed in the protocol. The incident was recorded as a protocol deviation and the subject was discontinued from the study due to the AE on (b) (6).

3.1.1.3 Adverse Events of Interest – Acute Renal Failure, Transaminitis, and Hypotension

Given the manufacturing similarities between RI-002 and Bivigam, and the ongoing PMC evaluating Bivigam AEs of interest, the clinical safety database was evaluated for the same AEs – acute renal failure (ARF), elevated liver function tests (LFTs) and hypotension.

A search of the line listing of All AEs in the clinical safety database for Preferred Terms (PTs) consistent with the three AEs of interest identified no potential cases of ARF, increased LFTs or hypotension.²¹ A search of line listings of the Observed Change in Biochemistry Tests from Baseline identified a single potential case of ARF (b) (6), defined by this reviewer as both an increase in serum creatinine (Cr) and a decrease in estimated glomerular filtration rate (eGFR) compared with baseline, resulting in values outside of the normal range. Pertinent details of this case are summarized in Table 2 below and appear to represent mild acute on chronic renal failure.

²¹ ADMA Biologics, Inc. Protocol ADMA-003 Clinical Study Report. Listing 16.2.14.1, All Adverse Events, Safety Analysis Set eCTD 125590/0

Table 2. Potential Case of Acute Renal Failure in Clinical Trial ADMA-003

Study Subject	Visit	Abnormal Lab Value (unit)	Normal Range	Result	Baseline	Change Relative to Baseline
(b) (6)	Infusion 10	Cr (umol/L)	26.5 - 61.9	88.4 (H)	79.6 (H)	+8.8
		eGFR (mL/min/1.73m ²)	97.5 - 135.3	60 (L)	65 (L)	-5

A search of the same line listings identified two potential cases of transaminitis (b) (6) defined by this reviewer as an increase in both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) compared with baseline, resulting in values above the upper limit of the normal.²² Pertinent details from both cases are summarized in Table 3 below.

Table 3. Potential Cases of Transaminitis in Clinical Trial ADMA-003

Study Subject	Visit	Elevated Lab Value	Normal Range (U/L)	Result (U/L)	Baseline (U/L)	Change Relative to Baseline
(b) (6)	Infusion 14	ALT	17-63	82 (H)	15 (L)	+67
		AST	15-41	196 (H)	21	+175
(b) (6)	Infusion 3	ALT	17-63	88 (H)	16 (L)	+72
		AST	15-41	50 (H)	16	+34

Review of a line listing of vital signs recorded during the study has been provided by the sponsor,²³ and is notable for multiple patients who experience a drop in blood pressure during an infusion. The case report forms (CRFs) for subjects who experienced SAEs or who discontinued the study due to AEs (sections 3.1.1.1 and 3.1.12 above) have been submitted by the sponsor. Vital signs recorded in the CRFs for these 3 subjects were also analyzed for changes consistent with hypotension, defined by this reviewer as a drop in systolic blood pressure (SBP) ≥ 20 mmHg and/or a drop in diastolic blood pressure (DBP) ≥ 10 mmHg. The study subjects described in each of the 3 case report forms were identified as potential cases of hypotension, and details are summarized in Table 4 below.

Table 4. Potential Cases of Hypotension Among Subjects Who Experienced Serious Adverse Events or Were Discontinued From Clinical Trial ADMA-003.

Events Were Discontinued From Clinical Trial ADAM 002:			
Study Subject	Visit Date	BP (mmHg)	Comment
(b) (6)	(b) (6)	123/67	p. 23: Screening
		91/49	p. 79: Visit 2, Infusion 1; 10 minutes after infusion rate increased
(b) (6)		131/89	p. 38: Screening
		110/89	p. 288:Visit 7, Infusion 5; 10 minutes after infusion rate increased
(b) (6)		133/82	p.34: Screening
		109/69	p.79: Visit 2, Infusion 1; 10 minutes after infusion rate increased

²² ADMA Biologics, Inc. Protocol ADMA-003 Clinical Study Report. Listing 16.2.8.1, Biochemistry Tests Observed Value, Change from Baseline and CS/NSC Assessment, Safety Analysis Set eCTD 125590/0

²³ ADMA Biologics, Inc. Protocol ADMA-003 Clinical Study Report. Listing 16.2.7, Vital Signs Observed Value, Change from Baseline and CS/NSC Assessment Safety Analysis Set eCTD 125590/0

3.2 Summary of Pharmacovigilance Plan

The PVP submitted by the sponsor is summarized in Table 5 below.

Table 5. Pharmacovigilance Plan for RI-002

SAFETY CONCERN	PLANNED ACTION
Identified Risks	
None	N/A
Important Potential Risks	
Thrombotic Events	Routine pharmacovigilance
Hypersensitivity	
Acute Renal Dysfunction and Acute Renal Failure	
Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia	
Aseptic Meningitis Syndrome	
Hemolysis	
Transfusion-Related Acute Lung Injury (TRALI)	
Transmissible Infectious Agents	
Monitoring Lab Tests performed to assess potential risks	
Interference with Lab Tests due to passive transfer of antibodies	
Important Missing Information	
Limited experience in Pediatric <15yo and Elderly >65yo subjects	Routine pharmacovigilance
Limited experience with ethnic minorities	
Pregnant or lactating women	
Patients with Renal or Hepatic Insufficiency	
Off-label use for conditions other than Primary Immunodeficiency (PI)	

Routine pharmacovigilance as described by the sponsor will include:

- Systems and processes that ensure that information about all suspected adverse reactions reported to the personnel of the company are collected and collated in an accessible manner.
- The preparation of reports for regulatory authorities including expedited adverse drug reaction (ADR) reports and periodic safety update reports (PSURs) which will be submitted to FDA via the electronic portal.
- Continuous monitoring of the safety profile of RI-002, including initial monthly review for signal detection and issue evaluation. After 12 months, this review will be conducted quarterly. Review at these same meetings will include evaluation of current labelling and assessment of whether modification is needed.

3.3 Proposed Postmarketing Safety Commitment Study ADMA-005

Many of the known safety concerns for the class of IgIV products have been addressed in the proposed PVP for RI-002 (Table 4 above). However, following review of the PVP, OBE/DE noted that the potential safety concerns that may result from the amount of the excipient PS80 in the final formulation of RI-002 have not fully been addressed by the sponsor. While ARF is listed in the PVP by the sponsor as a potential safety concern, the sponsor has not listed either liver dysfunction or hypotension in the PVP. In addition, there is evidence in the clinical safety database of potential cases of hepatic dysfunction (Table 2 above) and hypotension (Table 3 above) following RI-002. A request for information was therefore sent to the sponsor requesting a proposal for additional pharmacovigilance activities to address these concerns. In response to this request, ADMA has submitted study protocol ADMA-005 for a postmarketing commitment

(PMC) study to evaluate these safety concerns.²⁴ The protocol has been reviewed in detail and is summarized in Table 6 below.

Table 6. Summary of ADMA-005 Postmarketing Commitment Study Protocol

Study Title:	A Multicenter, Non-interventional, Observational, Prospective Post-Marketing Study in Subjects with Primary Immunodeficiency Diseases (PIDD) Treated with RI-002 or Other Commercial Human 10% Immune Globulin (Intravenous) (IgIV) Products
Study Design:	Phase 4, non-interventional, prospective, observational 2 arm study where subjects receive a dose of either RI-002 or another IgIV every 21 or 28 days, for a total of 8 doses per subject
Eligibility criteria:	<ul style="list-style-type: none"> • A confirmed clinical diagnosis of PIDD • On IgIV monthly therapy at a steady dose (\pm 25% of the mean dose) for at least 3 months prior to study entry
Study Duration:	2Q2019 to 2Q2021
Goal Enrollment:	Approximately 50 subjects total with 25 subjects receiving 8 doses of RI-002 and 25 subjects receiving 8 doses of another IgIV
Objectives:	<div>1°</div> <ul style="list-style-type: none"> • To assess the incidence of hypotension in subjects treated with RI-002 and other commercial (Human 10%) IgIV products under observational, standard of care conditions. <div>2°</div> <ul style="list-style-type: none"> • To evaluate hepatic and renal impairment in subjects treated with RI-002 and other commercial (Human 10%) IgIV products under observational, standard of care conditions
Safety related endpoints:	<ol style="list-style-type: none"> 1) Incidence of adverse events 2) Changes in vital signs 3) Incidence of clinically significant abnormal results in liver and renal function laboratory tests, per usual practice 4) Clinically significant findings in physical examination, per usual practice

The sponsor reports that the pivotal study ADMA-003 (Table 1) included 793 infusions and provided a 99% probability to observe at least 1 incidence of hypotension if the post infusion hypotension rate was 1% or higher. Given that no spontaneous reports of hypotension were received in the clinical safety database, the sponsor assumes that the rate of hypotension following RI-002 is less than 1%. The PMC study ADMA-005 will observe 200 infusions per treatment arm which the sponsor estimates will provide a 95% probability to observe at least 1 event of hypotension in each arm if the real hypotension rate is 1.49% or higher. For this reason the sponsor suggests that the sample size of the PMC study is adequate to meet the primary study objective to assess the incidence of hypotension in subjects receiving RI-002.

4. INTEGRATED RISK ASSESSMENT

4.1 Underrepresented Populations in the Clinical Safety Database

The clinical safety database for RI-002 is comprised of a single trial ADMA-003 with a relatively small sample size totaling 59 patients. Of the 59 patients in this trial, 63% are aged 17 to 64, 98% are white and 95% are non-Hispanic (Table 1 above). Because pediatric, elderly and ethnic minority populations are underrepresented in the clinical safety database, there is limited information regarding the use of RI-002 in these patients. In addition, pregnant and nursing women were excluded from the prelicensure study. In the proposed PVP, the sponsor recognizes

²⁴ ADMA Biologics. RI-002 PROTOCOL ADMA-005 A Multicenter, non-interventional, observation, prospective post-marketing study in subjects with primary immunodeficiency diseases (PIDD) treated with RI-002 or other commercial human 10% immune globulin (intravenous) (IGIV) eCTD 125590/0.25

that there is limited safety information for RI-002 in these populations and plans routine pharmacovigilance (Table 4 above).

4.2 Limited Long-term Safety Evaluation

The sponsor does not propose either extension of the prelicensure study or establishment of a new postmarketing study to evaluate the long-term safety of RI-002 following licensure. The rationale for this decision by the sponsor is that the product was well tolerated in the prelicensure trial “which followed subjects for up to 12 months during dosing...as well as for a 90 day follow up period post completion of the last dose.”²⁵ However, given that PI, the proposed indication, is a chronic condition which requires lifelong treatment, longer term follow up may be warranted.

4.3 Known Safety Concerns for the Class of IgIV Products

Known safety concerns for IgIV products, including hemolysis, thromboembolic events, acute renal failure, hypersensitivity reactions, aseptic meningitis and transmissible infectious pathogens (section 1.1.1 above), have been evaluated in the pre-licensure trial for RI-002. No events of hemolysis or thrombosis or other known safety concerns were identified in the clinical safety database (Table 1 above). Nonetheless, these safety concerns are recognized by ADMA as important potential risks for which the sponsor proposes routine pharmacovigilance.

Safety concerns more specific to RI-002 include the fact that the product contains a standardized amount of (b) (4). Although the sponsor does not currently seek an indication for use in the management of (b) (4) a somewhat similar product used in the past for this particular indication was eventually removed from the market due to increased morbidity and mortality in infants with congenital heart disease (section 1.1.2.1). No infant deaths were observed in the prelicensure trial of RI-002; however, since none of the study subjects were under 2 years of age,²⁵ the absence of infants precludes analysis of infant deaths and other AEs in this study. The sponsor plans to monitor the off-label use of RI-002 with routine pharmacovigilance (Table 4 above).

4.4 Potential Safety Concerns Related to Polysorbate 80

Of particular interest are the known safety concerns for Bivigam, an IgIV produced by the same manufacturer as RI-002. Due to the amount of the excipient PS80 in the final formulation of the product, a PMC to evaluate the risk of hypotension, as well as renal and hepatic failure was planned for Bivigam at the time of approval (section 1.1.2.2). The final formulation of RI-002 will include the same amount of PS80 as Bivigam. In addition, there is evidence in the clinical safety database of potential cases of hepatic dysfunction and hypotension following RI-002 (Tables 2 and 3 above).

The sponsor has submitted the ADMA-005 protocol for a PMC study to address these potential safety concerns (Table 5). The sponsor reports that the sample size is adequate to observe at least 1 event of hypotension in each arm, but does not provide similar analyses regarding the adequacy of the proposed sample size to detect ARF or hepatic dysfunction. It is therefore unclear that the study will meet the stated secondary objectives.

Of note, it may prove difficult to compare RI-002 to a treatment arm in which subjects receive an unspecified 10% human IgIV product, as opposed to a single predetermined comparator product. The inclusion of multiple products in the comparator arm may introduce a bias toward the null, because the administration of numerous other IgIV products may mask the incidence of hypotension, ARF, elevated LFTs, or some other safety outcomes of interest.

²⁵ ADMA Biologics, Inc. Protocol ADMA-003 Clinical Study Report. Table 14.1.3.1 Summary of Demographic and Baseline Characteristics mITT Analysis Set eCTD 125590/0

In addition, sensitivity analyses by product may be limited in the comparator arm as the number of subjects receiving each product may be relatively small resulting in low statistical power.

5. RECOMMENDATIONS

The sponsor's proposed PVP addresses some of the known safety concerns for the class of IgIV products such as hemolysis and thrombosis, and also addresses potential safety concerns more specific to RI-002 such as off-label use and use in underrepresented populations. While there are some limitations to the proposed PMC study to assess the potential risks associated with amount of PS80 in the final formulation of RI-002, the study may provide some useful information given the paucity of information currently available regarding the potential risks of ARF, hypotension and hepatic dysfunction. Should the product be approved, the available data do not indicate that a required postmarketing study (PMR) or a Risk Evaluation and Mitigation Strategy (REMS) is warranted at this time.