BLA Clinical and Clinical Pharmacology Review Memorandum

Application Type	Efficacy Supplement-BLA
STN	125590/190
CBER Received Date	June 30, 2025
PDUFA Goal Date	April 30, 2025
Division / Office	DCEGM/OCE
Priority Review (Yes/No)	No
Reviewer Name(s) Clinical Clinical Pharmacology	 Brighid Imperiale, DO (signed in absentia) Yang Chang, PhD, PharmD
Review Completion Date / Stamped Date	April 29, 2026
Supervisory Concurrence Clinical Pharmacology Team Lead Clinical Branch Chief (Acting), GMB1 Director, DCEGM	 Xiaofei Wang, PhD Shelby Elenburg, MD Patroula Smpokou, MD
Applicant	ADMA Biologics, Inc.
Established Name	(Immune Globulin Intravenous, Human-slra, 10% Liquid)
Trade Name	ASCENIV™
Pharmacologic Class	Immune Globulin (liquid) 10%
Formulation(s), including Adjuvants, etc.	245 ± 45 mM glycine, 120 ± 20 mM sodium chloride, 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	300-800 mg/kg every 21 or 28 days
Indication(s) and Intended Population(s)	Primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AR	adverse reaction
AUC(0-t)	area under the concentration-time curve to last sampling time
AUC(0-tau)	area under the concentration-time curve over the dosing interval
BLA	biologics license application
CL	(statistics) confidence limit
CL	(PK) clearance
Cmax	maximum serum concentration
Cmin	minimum serum concentration
FDA	Food and Drug Administration
IG	immune globulin
IgG	immunoglobulin G
IGIV	immune globulin intravenous
IMP	investigational medicinal product
IND	investigational new drug application
iPSP	initial pediatric study plan
λ_z	elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
PeRC	Pediatric Review Committee
PI	primary humoral immunodeficiency
PID	primary immunodeficiencies
PIDD	primary immunodeficiency disease (used only by Applicant in study title)
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SBI	serious bacterial infection
SOC	system organ class

STN	submission tracking number
$T_{1/2}$	elimination half-life
TAAE	temporally associated adverse event
TEAE	treatment-emergent adverse event
Tmax	time of maximum serum concentration
Vz	Volume of distribution

1. EXECUTIVE SUMMARY

On June 30, 2025, ADMA Biologics submitted STN125590/190, an efficacy supplement for ASCENIV, to license its liquid 10% immune globulin solution for intravenous (IGIV) infusion in pediatric patients ≥2 years of age with primary humoral immunodeficiency (PI). The efficacy supplement contains the reports of Study ADMA-004 in children, intended to fulfill the Pediatric Research Equity Act Post-Marketing Requirement (PREA PMR) and a proposal for revised pediatric labeling.

ASCENIV was first licensed for replacement therapy for primary humoral immunodeficiency disease (PI) in patients 12 years and older in 2019. In accordance with the provisions of section 505B of the Food Drug and Cosmetic Act [21 U.S.C. 355c, also referred to as the Pediatric Research Equity Act (PREA)], the approval of ASCENIV included a post-marketing requirement (PMR) to complete a pediatric study in PI subjects aged ≥ 2 to < 12 years of age. In this biologics licensing application (BLA) efficacy supplement 125590/190, the Applicant (ADMA Biologics, Inc.) seeks to expand labeling of ASCENIV to patients 2 years of age and older with PI.

In this supplement, the Applicant submitted data from Study ADMA-004, a prospective, open-label, single arm, multicenter Phase 4 study wherein sixteen pediatric subjects 2 to 11 years of age with PI were administered ASCENIV (the investigational medicinal product, IMP) every 3 to 4 weeks for 5-6 months. ADMA-004 planned to enroll 6 subjects aged 2-6 years and 6 subjects aged 7-11 years, for a total of 12 pediatric subjects per the PREA PMR but was able to enroll a total of 16 subjects, 14 of whom completed treatment.

The primary efficacy endpoint was incidence of acute serious bacterial infections (SBIs) as defined in accordance with FDA's Guidance for industry, "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency (June 2008)," which will be referred to as the FDA IGIV Guidance throughout the review memo. No acute SBIs occurred during the study period, thereby meeting the pre-defined success criterion of less than one SBI per patient-year as described in the FDA IGIV Guidance.

All pediatric subjects with pharmacokinetic (PK) data had consistent immunoglobulin G (IgG) trough levels throughout Study ADMA-004. Within each subject, trough IgG concentrations were reasonably constant across all visits regardless of age and frequency of dosing, suggesting that an apparent steady-state was maintained. Based on the limited data, the clearance appears to be comparable across all age groups and similar to that of adults.

Additional efficacy data from children is from the pivotal study ADMA-003 that supported the original approval of ASCENIV. This study enrolled 6 pediatric patients <12 years of age (two patients 3-5 years of age, four patients 7-11 years of age). Of note, 5 pediatric patients were enrolled in the pivotal study, aged 12-16 years, which was used for original approval in adolescents 12 years of age and older. None of the children had acute SBIs during the 12-month study period, meeting the pre-defined success criterion of <1 SBI per patient- year.

The totality of pediatric clinical and clinical pharmacology data from ADMA-004 and ADMA-003 support the indication for children who are at least 2 years of age. In conclusion, the cumulative pediatric findings in ADMA-004 and ADMA-003 provide substantial evidence of efficacy of ASCENIV for pediatric patients who are 2 years of age and older. The Applicant has provided substantial evidence of effectiveness from a single adequate and well controlled trial, ADMA-004 with supportive evidence from Study ADMA-003 and meets the statutory requirements for approval.

Fourteen of the 16 subjects in ADMA-004 completed the study as per protocol, whereas 2 subjects discontinued early due to adverse events (AEs). There were no deaths. The safety profile of ASCENIV in pediatric subjects 2 years and older is consistent with other IGIV products and the safety profile of ASCENIV in adults. The proportion of infusions temporally associated with an adverse event was below the upper one-sided 95 percent confidence limit of 40 percent, as outlined in the FDA IGIV Guidance. Routine pharmacovigilance is recommended.

Based on the review of the data submitted, the Division determined that the PREA post-marketing requirement was fulfilled. The clinical and clinical pharmacology data demonstrate efficacy of the proposed dose range. The benefit/risk is favorable in the pediatric population studied. It is recommended that the indication for PI be expanded to pediatric patients 2 years of age and older. The Pediatric Review Committee (PeRC) agreed with the Division's determination to expand labeling to the pediatric population.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

ADMA-004 population was predominantly white (12 subjects, 75.0%) and non-Hispanic (13 subjects, 81.3%) and included 7 subjects (43.8%) aged 2 to 6 years, and 9 subjects (56.3%) aged 7 to 11 years. The overall age range was between 2 and 11 years (mean 7.1 years), with the majority (11, 69%) of the enrolled subjects being male. Table 1 shows the details of Study ADMA-004 demographics.

Table 1. Demographics for ADMA-004

Category Statistic/Response	3-Week Regimen (N=3)	4-Week Regimen (N=13)	Total (N=16)
Age (years)	--	--	--
Mean (SD)	10.3 (1.15)	6.4 (3.23)	7.1 (3.32)
Median	11.0	6.0	8.0
Min, max	9, 11	2, 11	2, 11
2 to 6 years, n (%)	0	7 (53.8)	7 (43.8)
7 to <12 years, n (%)	3 (100.0)	6 (46.2)	9 (56.3)
Sex, n (%)	--	--	--
Male	1 (33.3)	10 (76.9)	11 (68.8)
Female	2 (66.7)	3 (23.1)	5 (31.3)
Race, n (%)	--	--	--
White	3 (100.0)	9 (69.2)	12 (75.0)
Black or African American	0	3 (23.1)	3 (18.8)
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	1 (12.5)	1 (6.3)
Ethnicity, n (%)	--	--	--
Hispanic/Latino/Spanish origin	0	3 (23.1)	3 (18.8)
Not Hispanic/Latino/Spanish origin	3 (100.0)	10 (76.9)	13 (81.3)
Weight (kg)			
Mean (SD)	41.0 (8.9)	25.4 (9.9)	28.3 (11.3)
Median	37.40	25.80	30.25
Min, max	34.5, 51.2	11.4, 37.5	11.4, 51.2

Source: Adapted from sBLA 125590/190 Clinical Study Report, Table 11-3
Percentages are calculated using N as the denominator.
Abbreviations: kg=kilogram, max=maximum, min=minimum, SD=standard deviation

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	Infectious data throughout BLA represents patient- and clinician-reported outcomes
☐	Observer-reported outcome	
☒	Clinician-reported outcome	Infectious data throughout BLA represents patient- and clinician-reported outcomes
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☒	Other: (please specify)	Data from original approval under BLA 125590/0

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Primary immunodeficiencies (PIDs) are a large heterogenous group of disorders resulting from inborn errors of immunity. They are characterized by absent or poor function in one or more components of the immune system. Consequently, affected subjects are unable to mount an immune response to microorganisms and may experience recurrent protozoal, bacterial, fungal, and viral infections. The estimated overall prevalence of PIDs in the United States is approximately 1 in 1,200 live births; an exception is IgA deficiency, which occurs in approximately 1 in 200 to 1 in 500 persons.

PIDs are broadly classified based on the component of the immune system that is primarily disrupted. Disorders of the adaptive immune system include B-cell (humoral) immune deficiencies (also referred to as antibody deficiencies), T-cell (cellular) immune deficiencies, and combined (B-cell and T-cell) immunodeficiencies. Primary humoral immunodeficiency (PI) is a humoral form of PID that is characterized by impaired B-cell immunity, and thus, impaired ability to produce specific antibodies in response to pathogenic microorganisms. PI diseases include, but are not limited to, X-linked agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, severe combined immunodeficiency, and congenital agammaglobulinemia. Subjects with PI present with recurrent, often severe bacterial and viral infections affecting the respiratory tract, gastrointestinal system, skin, and other organs.

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

Replacement therapy, comprised of polyclonal human normal immune globulin (IG) infusions, is standard treatment for PI. IG is manufactured through fractionation of plasma pooled from many plasmapheresis donors and contains immune antibodies. IG restores serum IgG to protective levels and provides patients with specific antibodies to prevent or minimize the frequency or severity of severe bacterial and viral infections. For many patients, therapy is expected to be lifelong and increases life expectancy.

Additional infection prevention includes infection avoidance measures, vaccination, and prophylactic antibiotics. Treatment of infections often requires broad antimicrobial coverage and prolonged treatment courses. Bone marrow transplantation is a treatment option for some forms of PI (such as Severe Combined Immunodeficiency) but is limited by availability of appropriate donors and is associated with multiple risks including graft versus host disease, rejection of the graft, complications of conditioning agents, and death.

2.3 Safety and Efficacy of Pharmacologically Related Products

The FDA IGIV Guidance states that a statistical demonstration of an SBI rate per person-year of less than 1.0 is adequate to provide substantial evidence of effectiveness to support licensure.

There are currently 16 licensed (Human) immune globulin intravenous (IGIV) products in the United States: Alyglo (GC Biopharma), Asceniv (ADMA Biologics, Inc.), Bivigam

(Biotest Pharmaceuticals Corporation), Carimune (CSL Behring AG), Flebogamma DIF 5% and 10% (Instituto Grifols), Gammagard Liquid and Gammagard S/D (Baxter HealthCare Corp), Gammagard Liquid ERC (Takeda Pharmaceuticals), Gammaked (Kedrion Biopharma), Gammaplex 5% & 10% (Bio Products Laboratory), Octagam and Panzyga (Octapharma Pharmazeutika Produktionsges), Privigen (CSL Behring AG), Yimmugo (Biotest AG), and Qivigy (Kedrion SpA). All are indicated as replacement therapy in subjects with PI.

The safety profile for immunoglobulins as a class is well established. The incidence of adverse reactions (ARs) reported in clinical studies supporting licensure varies according to the product, route of administration, and maximum infusion rate. Severe hypersensitivity reactions may occur with IGIV products. Common ARs for intravenously administered immunoglobulins typically include headache, fatigue, nausea, diarrhea, vomiting, and/or pyrexia. IGIV (Human) as a drug class carries an obligatory boxed warning for thrombosis, renal dysfunction, and acute renal failure. Other rare risks associated with the use of IGIV include transmission of infectious agents (e.g., viruses), hemolysis, aseptic meningitis, transfusion-associated lung injury, hyperproteinemia, and increased viscosity.

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

ASCENIV™ (Immune Globulin Intravenous, Human - slra, 10% Liquid), manufactured by ADMA Biologics was approved by the U.S. FDA in 2019, for the treatment of PI in adults and adolescents (12 to 17 years of age). The recommended dose is between 300 and 800 mg/kg body weight administered every 3-4 weeks, with the dose adjusted over time to achieve the desired trough IgG levels and clinical response. The initial infusion rate is 0.5 mg/kg/min (0.005 ml/kg/min) for the first 15 minutes, with the maintenance infusion rate increased every 15 minutes (if tolerated) up to a maximum rate of 8 mg/kg/min (0.08 ml/kg/min) (ASCENIV™ United States Prescribing Information [USPI]. 2024).

The initial approval of ASCENIV was based on efficacy, safety, and PK findings from a pivotal, open-label, single-arm, multicenter, non-randomized trial (Study ADMA-003) that included 59 subjects, of which 11 were pediatric subjects. The 11 pediatric subjects included 6 children less than 12 years (4 were 6-11 years of age, 2 were 2 to 5 years of age) and 5 adolescents age 12-16 years. Study treatment was administered every 3 to 4 weeks, with 19 subjects with a 3-week cycle and 40 subjects with a 4-week cycle, at doses ranging from 284 to 1008 mg/kg/infusion for approximately 12 months, to include 17 or 13 doses respectively.

The primary efficacy analysis included 59 subjects (adult and pediatric subjects) in the intent-to-treat population. During the 12-month study period, zero serious acute bacterial infections occurred, thus, the mean event rate of serious, acute, bacterial infections per year was 0.0 (with an upper 1-sided 99% confidence interval of <1.0 per subject year, which met the study's primary efficacy endpoint).

Thirty-nine percent (39%) of subjects had days off work, school or daycare due to an infection. Of the infections reported, 1 resulted in hospitalization as a post-op local wound infection from elective surgery. The incidence and severity of infections in adolescents were similar to those in adult subjects.

The most common ARs were headache, sinusitis, diarrhea, gastroenteritis viral, nasopharyngitis, upper respiratory tract infection, bronchitis, nausea and acute sinusitis.

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

ASCENIV was approved in the United States in 2019 for treatment of PI in adults and adolescents (12 to 17 years of age). At the time of approval, a PMR was established under the Pediatric Research Equity Act to conduct a Phase IV study to evaluate the safety and pharmacokinetics of ASCENIV in subjects aged 2 to 11 years with PI. The study, known as ADMA 004 and titled, "An Open Label, Multicenter Study to Evaluate the Pharmacokinetics, Efficacy and Safety of ASCENIV (IGIV) in Pediatric Subjects with Primary Immunodeficiency Diseases (PIDD)" was submitted to FDA on June 30, 2025. The original PREA PMR completion was planned for 2019. The PREA PMR completion date was subsequently extended to 2026 because of delays involving study participants, sites, and/or management, recruitment challenges due to COVID-19 pandemic, staffing challenges, and delay in ensuring laboratory compliance with required PK and antibody testing. The first subject was screened March 09, 2023, and the last subject completed October 17, 2024.

The PREA PMR study was to include evaluation of PK, safety, tolerability and efficacy in 12 subjects in each of the following pediatric categories: ages ≥ 2 years to <6 years and ≥ 6 years to <12 years, as described in the agreed iPSP.

This efficacy supplement to satisfy the PREA PMR was submitted June 30, 2025.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

There were no concerns with Good Clinical Practice or Submission Integrity. Biomedical Monitoring Inspections of two clinical investigator study sites that participated in ADMA-004 did not reveal substantive issues that impacted the data submitted in this post-approval efficacy supplement.

3.3 Financial Disclosures

Reviewer's Comment: *Per Form 3454, the sponsor certifies that the sponsor has not entered into any financial arrangements with the listed clinical investigators and that each listed clinical investigator did not disclose any such interests.*

Covered clinical study (name): ADMA-004
Was a list of clinical investigators provided? Yes

Dr. Isaac Melamed (IMMUNOe International Research) Dr. Kelli Williams (Medical University of South Carolina) Dr. Jolan Walter (University of South Florida) Dr. Melissa Elder (University of Florida) Dr. Jennifer Heimall (Children's Hospital of Philadelphia
Total number of investigators identified: 5
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: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☒ No (Request details from applicant) N/A Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☒ No (Request information from applicant) N/A
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) N/A

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

ASCENIV is a currently marketed product. No new chemistry, manufacturing, and controls information was provided in this supplement.

4.2 Assay Validation

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical information was provided in this supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

IG replacement therapy restores serum IgG to protective levels and provides patients with specific antibodies to prevent or minimize the occurrence or severity of severe bacterial and viral infections.

4.4.2 Human Pharmacodynamics

Not applicable.

4.4.3 Human Pharmacokinetics

In study ADMA-004, a total of 16 subjects comprised the PK analysis population, including 3 subjects in the 3-week infusion regimen group (all in the 7 to 11 years age group) and 13 subjects in the 4-week infusion regimen group (7 subjects in the 2 to 6 years and 6 subjects in the 7 to 11 years age group). However, due to early discontinuations and end-of-infusion sampling errors, only 9 subjects in the PK Per Protocol Population 2 provided reliable PK parameter estimates. The individual serum concentrations for total IgG grouped by different dosing intervals at the 6th infusion (4-week regimen) or 7th infusion (3-week regimen) demonstrated that doses were individualized based on subject weight and trough IgG maintenance requirements. For subjects aged 7-11 years, only 2 of the subjects had apparent log-linear decay in serum concentrations sufficient for reliable estimation of λz and t½ values. The total IgG PK parameters of individual subjects are summarized in Table 2.

Trough total IgG concentrations represent the most critical pharmacokinetic parameter for PI patients as they determine the protective antibody levels maintained between infusions. All 14 subjects with Total IgG data available prior to their last infusion maintained trough total IgG levels above the critical 500 mg/dL threshold throughout the study period. Individual trough IgG concentrations were reasonably constant across all visits regardless of age and frequency of dosing, demonstrating that apparent steady-state was maintained throughout the treatment period. For subjects aged 2-6 years, trough levels ranged from 650-1228 mg/dL at pre-infusion 1 and 593-1283 mg/dL at the pre-last infusion, while subjects aged 7-11 years had trough levels ranging from 758-1271 mg/dL at pre-infusion 1 and 730-1294 mg/dL at the pre-last infusion.

IgG subclass concentrations (IgG1, IgG2, IgG3, IgG4) were maintained consistently between the first and last infusions across both age groups, with no apparent differences in subclass distribution before and after treatment (see Table 3).

In study ADMA-004, specific antibodies including anti-pneumococcal capsular polysaccharide, anti-Haemophilus influenzae type B, and anti-RSV neutralizing antibodies were measured prior to the first infusion and prior to the last infusion. The data show that these specific antibody levels were maintained throughout the treatment period, demonstrating that ASCENIV provides functionally relevant antibodies against key pathogens in the pediatric population.

Table 2: Individual Subject Total IgG Pharmacokinetic Parameters at the Final Infusion, PK Population

Regimen	Age Group [years]	Subject ID	Infusion	Dose (mg/kg)	AUC (c-t) (h*mg/dL)	AUC (c-tau) (h*mg/dL)	Total CL ((mL/h)/kg)	Cmin (mg/dL)	Cmax (mg/dL)	Tmax (h)	λz (/h)	T ½ (h)	Vz (mL/kg)
3-week	7-11	(b) (6)	7	651	737344	737344	0.08829	1585	2144	4.18	0.00088	783.57	99.81
3-week	7-11	(b) (6)	3 [1]	579.2	-	-	-	-	-	-	-	-	-
3-week	7-11	(b) (6)	7	387.6	419118	419118	0.09248	908	1476	1.60	-	-	-
4-week	2-6	(b) (6)	6	531.0	-	-	-	912	1449	2.25	-	-	-
4-week	2-6	(b) (6)	6	540.0	-	-	-	874	1474	2.10	-	-	-
4-week	2-6	(b) (6)	6	576.0	-	-	-	394	994	341.2	-	-	-
4-week	2-6	(b) (6)	6	394.0	-	-	-	1080	1199	0	-	-	-
4-week	2-6	(b) (6)	2 [2]	183.0	-	-	-	-	-	-	-	-	-
4-week	2-6	(b) (6)	6	680.0	-	-	-	881	1661	3.67	-	-	-
4-week	2-6	(b) (6)	6	468.0	-	-	-	1117	1787	4.02	-	-	-
4-week	7-11	(b) (6)	6	896.1	1049628	1049628	0.08537	1375	2957	3.50	-	-	-
4-week	7-11	(b) (6)	6	929.4	1055248	1055248	0.08807	1400	3205	3.77	0.00057	1208.14	153.51
4-week	7-11	(b) (6)	6	430.0	834552	-	-	1055	1850	26.65	-	-	-
4-week	7-11	(b) (6)	6	536.0	1133069	1133069	0.04731	1112	2006	5.28	-	-	-
4-week	7-11	(b) (6)	6	685.0	928413	-	-	2264	2297	6.00	-	-	-
4-week	7-11	(b) (6)	6	542.0	-	-	-	771	1678	5.62	-	-	-

Source: Adapted from ADMA-004 Clinical Study Report, Table 11-11 (page 84)
[1] Subject (b) (6) received a total of 3 IMP infusions before discontinuing from the study.
[2] Subject (b) (6) received a total of 2 IMP infusions before discontinuing from the study.

Table 3: Individual Subject Trough Serum Concentrations of Total IgG and IgG Subclasses (mg/dL), PK Population

Regimen	Age Group [years]	Subject ID	Last Dose (mg/kg)	Total IgG, Pre-INF 1	Total IgG, Pre-INF 6 or 7	IgG1, Pre-INF 1	IgG1, Pre-INF 6 or 7	IgG2, Pre-INF 1	IgG2, Pre-INF 6 or 7	IgG3, Pre-INF 1	IgG3, Pre-INF 6 or 7	IgG4, Pre-INF 1	IgG4, Pre-INF 6 or 7
3-week	7-11	(b) (6)	651	1255	1294	665	747	461	423	53	63	69.7	79.0
3-week	7-11	(b) (6)	579.2	931	-	551	-	375	-	38	-	8.9	-
3-week	7-11	(b) (6)	387.6	758	730	453	398	267	269	31	36	22.6	19.3
4-week	2-6	(b) (6)	531.0	805	727	473	390	296	248	37	42	26.7	19.9
4-week	2-6	(b) (6)	540.0	882	694	532	423	286	219	38	28	20.6	13.0
4-week	2-6	(b) (6)	576.0	652	768	298	390	262	330	25	30	14.6	7.9
4-week	2-6	(b) (6)	394.0	1228	1283	741	757	319	351	76	76	53.7	58.2
4-week	2-6	(b) (6)	183.0	1072	-	604	-	348	-	97	-	12.1	-
4-week	2-6	(b) (6)	680.0	650	593	321	351	284	259	7	14	17.0	7.0
4-week	2-6	(b) (6)	468.0	814	920	475	564	235	262	22	38	31.4	30.0
4-week	7-11	(b) (6)	896.1	1123	1255	674	773	402	411	39	43	29.5	30.8
4-week	7-11	(b) (6)	929.4	1034	1187	625	750	357	395	45	52	22.6	24.4
4-week	7-11	(b) (6)	430.0	887	930	429	462	384	389	33	37	54.5	42.8
4-week	7-11	(b) (6)	536.0	1175	1066	638	572	417	394	51	49	29.1	19.1
4-week	7-11	(b) (6)	685.0	1271	983	740	553	409	355	59	54	26.0	16.4
4-week	7-11	(b) (6)	542.0	804	739	405	381	320	287	59	54	20.5	12.3

Source: Adapted from ADMA-004 Clinical Study Report, Table 11-12 (page 86)

[1] Subject (b) (6) received a total of 3 IMP infusions before discontinuing from the study.
[2] Subject (b) (6) received a total of 2 IMP infusions before discontinuing from the study.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported by the submitted data. Please refer to the statistical review memo for further details.

4.6 Pharmacovigilance

ASCENIV has been approved in the United States for treatment of PI in adults and adolescents 12 years and up since 2019. The available safety data do not substantiate the need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related post-marketing requirement or commitment (PMR/PMC) study, and routine pharmacovigilance is appropriate.

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

5.1 Review Strategy

Data from one clinical trial, Study ADMA-004, was submitted to support approval of ASCENIV for patients ≥ 2 to <12 years with PI. This clinical and clinical pharmacology review memo provides a review of the safety, efficacy, and PK data from Study ADMA-004. However, because the previous pivotal study, included six pediatric subjects less than 12 years of age, the review team assessed data from these subjects and from Study ADMA-004 for a comprehensive evaluation of the safety and efficacy of BIGIVAM in pediatric PI patients.

The clinical review was conducted by Brighid Imperiale and the clinical pharmacology review by Yang Chang. Dr. Imperiale left FDA prior to completion and signing of the memo, so relevant revisions were completed by the acting clinical branch chief, Shelby Elenburg and review signed in absentia for Dr. Imperiale.

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

- Module 1
  - 1.2 Cover Letters
  - 1.3 Administrative Information
    - 1.3.4 Financial Certification and Disclosure
  - 1.9 Pediatric Administrative Information
    - 1.9.4 Proposed Pediatric Study Request and Amendments
  - 1.11 Information Note Covered Under Modules 2 to 5
    - 1.11.3 Clinical Information Amendment
  - 1.14 Labeling
    - 1.14.1 Draft Labeling

- Module 2
  - 2.7 Clinical Summary
    - 2.7.6 Synopses of Individual Studies
- Module 5
  - 5.2 Tabular Listing of all Clinical Studies
  - 5.3 Clinical Study Reports
    - 5.3.5 Reports of Efficacy and Safety Studies
- BLA 125590/0 Clinical Review Memo for information regarding previous pivotal study, Study ADMA-003, and the original approval

5.3 Table of Studies/Clinical Trials

Table 4: Studies/Clinical Trials Reviewed for the BLA Efficacy Supplement

Type of Study	Study Identifier	Subject Ages	Number of Subjects	Study Duration	Planned Dose	Serious Bacterial Infections
Phase 3, Efficacy, PK, Safety; Multi-center, open-label	ADMA-003 (pivotal study)	≥6 years	N=59 (48 adult and 11 pediatric)	12 months	300-800 mg/kg every 3-4 weeks	0
Phase 4, Efficacy, PK, Safety;4 Multi-center, open-label	ADMA-004 (PREA PMR study)	≥2 to ≤16 years	N=16 (all pediatric)	5 months	300-800 mg/kg every 3-4 weeks	0

Source: Clinical Reviewer

Abbreviations: PK=pharmacokinetics, PREA=Pediatric Research Equity Act, PMR: postmarketing requirement

Reviewer's Comments: *ADMA-004 data were submitted and fully analyzed under this efficacy supplement. Study ADMA-003 was the pivotal study that led to ASCENIV's initial approval in 2019. Study ADMA-003 data were fully analyzed under STN BLA 125590/0. ADMA-003 study is included in this clinical review memo because the study included 6 pediatric subjects >2 to ≤12 years. The efficacy and PK data from Study ADMA-003 alongside the efficacy and PK data from Study ADMA-004 provided substantial evidence of effectiveness for ASCENIV in treatment of PI in pediatric subjects who are at least 2 years old. For more details regarding Study ADMA-003, please refer to Section 2.4 Previous Human Experience With the Product (Including Foreign Experience) or STN BLA 125590/0 Clinical Review Memo. The details and analysis of Study AMDA-004 safety and efficacy data can be found in Section 6.1 Trial #1 of this clinical review memo.*

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee Meeting was held.

5.4.2 External Consults/Collaborations

No external consults or collaborations.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

This is a Phase IV, multicenter, open-label study of ASCENIV administered as an intravenous infusion of ASCENIV (IGIV) 300-800 mg/kg every 21 or 28 days to evaluate safety, pharmacokinetics and efficacy in approximately 12 pediatric subjects 2-11 years of age with primary humoral immunodeficiency (PI).

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective was to evaluate the safety of SCENIV in subjects 2 to 16 years with PI. The secondary objective is to evaluate the PK profile and efficacy of ASCENIV in subjects aged 2 to 16 years with PI. This study was conducted to fulfill a PREA PMR as agreed upon during the initial approval of ASCENIV in 2019.

6.1.2 Design Overview

Study ADMA-004 was a prospective, open-label, single-arm study with a treatment and follow-up duration of 5 months.

> ***Reviewer's comment:*** *Based on the FDA IGIV Guidance, in evaluating the efficacy of an IGIV product, studies should "measure the rate of serious bacterial infections during regularly repeated administration of the investigational IGIV product in adult and pediatric subjects for 12 months (to avoid seasonal biases)." The study duration of 5-months in Study ADMA-004 is not consistent with the FDA IGIV Guidance to determine the incidence of serious bacterial infection. However, due to difficulties in conducting pediatric studies with IGIV products given the widely available number of approved IGIV products, it is reasonable to look at the totality of clinical and clinical pharmacology data in determining whether data that is less than 12 months is acceptable. In this case, we believe that the data are sufficient, given the strength of the results and that treatment of patients in the study spanned the various seasons. Please refer to Section 6.1.11 Efficacy Analyses for further details regarding the efficacy analyses of Study ADMA-004.*

6.1.3 Population

Subjects were eligible for study inclusion if they met all the following inclusion criteria:

- Are male or female ≥ 2 to <12 years at time of signing Informed Consent/Assent by subject or legal guardian
- Have confirmed and documented diagnosis of PI including hypogammaglobulinemia or agammaglobulinemia
- Have received IGIV therapy maintained at a steady dose (±25 percent of the mean dose on a mg/kg basis) for at least 3 months prior to study entry and have maintained a trough IgG level of at least 500 mg/dL prior to receiving ASCENIV

Subjects were excluded from study participation if they met any of the following exclusion criteria:

- Known intolerance to immunoglobulins or any excipient in ASCENIV
- History of hemolysis while undoing treatment with IGIV therapy
- History of severe anaphylactic or anaphylactoid reaction to blood or any blood-derived product
- Selective IgA deficiency or known antibodies to IgA
- Medical condition known to cause secondary immune deficiency
- Acute or chronic Hepatitis B or C, or HIV infection; active viral or bacterial infection or symptoms/signs consistent with such an infection at screen
- Significant T-cell or granulocyte deficiency in number or function
- History of acute renal failure or significant renal impairment
- Abnormal liver function defined as ALT or AST ≥ 2.5 times the upper limit of normal
- Anemia at screening
- Uncompensated, hemodynamically significant, congenital or other heart disease
- Severe chronic lung disease
- History of DVT< thrombotic or thrombo-embolic event, or increased risk for thrombotic event
- Uncontrollable arterial hypertension
- Ongoing failure to thrive
- History of alcohol or substance abuse
- An infusion port, catheter or other foreign body present
- BMI ≥ 40
- Current daily use of corticosteroids (> 15mg/kg/day of prednisone equivalent), immunosuppressive and immunomodulatory drugs were prohibited
- Prior and/or current treatment of any of the following was exclusionary:
    - RSV-specific products within 3 months of screening
    - Hyperimmune or specialty high titer immunoglobulin product within 30 days of screening
    - An investigational product within 3 week or 5 half-lives of first infusion of ASCENIV
    - Chronic anti-coagulation therapy
    - Subjects planned or scheduled to undergo surgery during the course of study participation
    - Antibiotic treatment for a prior infection that was still ongoing at time of screening

6.1.4 Study Treatments or Agents Mandated by the Protocol

ASCENIV is a liquid IGIV that contains approximately 100 mg/mL of human IgG and no reducing stabilizers or preservative. The test product was supplied in single-use vials of 50 mL (5000 mg). The following Lot Numbers of ASCENIV were used during the study: 229156, 230661 and 261820. The investigational medicinal product was manufactured by ADMA Biologics and labelled and distributed to sites by (b) (4) . It was stored at a temperature between 2 to 8°C (36 to 46°F).

All subjects were required to have received steady doses of an IGIV product for at least 3 months and maintained a trough IgG level of at least 500 mg/dL prior to study enrollment. After enrollment into the study, the subjects were treated with the same IGIV dose (300 to 800 mg/kg) and regimen (every 3 or 4 weeks) as their previous IGIV therapy prior to study enrollment. Upon completion of the study treatment, subjects underwent a follow-up visit within 3 weeks (for those on the 3-week regimen) or within 4 weeks (for those on the 4-week regimen). This was a single-arm study, so no control product was administered to any study subjects.

Dose adjustments were permitted during the study to maintain trough total IgG concentrations at >500 mg/dL; however, dose increases above 800 mg/kg required approval by ADMA Biologics Medical Director.

Use of daily corticosteroids (>15 mg/kg/day of prednisone equivalent), immunosuppressants, or immunomodulators were prohibited. Intermittent use of corticosteroids during the study was allowed if medically necessary and approved by the ADMA Medical Director. The use of pre-medications was allowed if medically necessary. If subjects required premedication (e.g., Tylenol, Benadryl, etc.) for recurrent reactions to immune globulins, they were allowed to continue those medications for this study.

> ***Reviewer's comments:*** *The ASCENIV doses and dosing intervals used in the study are consistent with the approved doses of ASCENIV for treatment of PI. Dose adjustment criteria, prohibition of daily corticosteroids, and allowance of pre-medications with Tylenol and Benadryl are appropriate.*

6.1.5 Directions for Use

Not applicable.

6.1.6 Sites and Centers

Table 5 below lists the five principal investigators and investigative sites with active recruitment of subjects during ADMA-004.

Table 5: List of Principal Investigators and Investigative Sites with Active Recruitment

Site ID	Investigator	Location	Number of Subjects Screened/ Enrolled[1]	Number of Subjects Treated
01	Dr. Isaac Melamed	IMMUNOe International Research Centennial, CO 80112	7	5
02	Dr. Kelli Williams	Medical University of South Carolina Charleston, SC 29425	3	2
04	Dr. Jolan Walter	University of South Florida Tampa, FL 33701	5	5
05	Dr. Melissa Elder	University of Florida Gainesville, FL 32610	5	3
06	Dr. Jennifer Heimall	Children's Hospital of Philadelphia Philadelphia, PA 19104	3	1
--	Total	--	23 [1]	16

Source: Adapted from sBLA 125590/190; Clinical Study Report, Table 6-2

Note: One additional site was activated, but did not screen/enroll or treat any subjects in Study ADMA-004: Site 03 (University of Utah Primary Children 's Hospital, Salt Lake City, UT; Principal Investigator Dr. Ahmad Rayes). A further site obtained initial /RB approval, but was not activated (Site 07, Texas Children's Hospital, Houston, TX; Principal Investigator Dr. Sarah Nicholas).

1. In this study, all subjects who had given informed consent/assent to participate in the study were considered “enrolled”; these subjects constitute the “All Subjects Enrolled Set.”

6.1.7 Surveillance/Monitoring

Study visits for monitoring of safety and efficacy occurred during each infusion (six infusions for 3-week regimen cohort and seven infusions for 4-week regimen cohort) and 3 to 4 weeks after the last infusion. Assessments included adverse events (AE) and concomitant medication collection, physical exam, weight, vital signs, and IgG level, hematology, chemistry, and urinalysis testing. Infection assessments for efficacy analyses were conducted as part of AE evaluations.

6.1.8 Endpoints and Criteria for Study Success

Prespecified safety endpoints included the following:

- Incidence of temporally associated adverse events (defined as AEs occurring during or within 1 hour, 24 hours, or 72 hours of completion of an infusion)
- Mean number of temporally associated AEs per infusion
- Number and proportion of infusions with one or more temporarily associated AEs
- Incidence of SAEs and related SAEs
- Incidence of treatment-emergent adverse events (TEAEs) and related TEAEs
- Total number and incidence of adverse reactions (including suspected adverse reactions)
- Incidence of infusion site reactions
- Change in vital signs before and after administration of study drug
- Changes in hematology, chemistry and urinalysis parameters

Prespecified PK endpoints include the following:

- Trough levels of Total IgG prior to each administration and IgG subclasses 1 to 4 prior to the sixth and seventh administration
- End of infusion level of Total IgG
- Total IgG PK parameters after the sixth and seventh infusion including maximum serum concentration (C_{max}), time to C_{max} (T_{max}), minimum serum concentration (C_{min}), elimination rate constant (ƛZ), elimination half-life ($t_{1/2}$), area under the curve (AUC), total serum clearance and volume of distribution (Vz)
- Levels of specific antibody (anti-pneumococcal capsular polysaccharide, anti-haemophilus influenzae type B, and anti-RSV neutralizing antibody)

Prespecified clinical efficacy endpoints included the following:

- Primary efficacy endpoint:
  - Incidence of acute serious bacterial infections, including bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis
- Secondary efficacy endpoints:
  - Incidence of infections (serious or nonserious)
  - Time to first infection (serious and nonserious)
  - Time to resolution of infections (in days)
  - Number of days of antibiotics treatments (for treatment or prophylaxis)

Reviewer's comments: *Study endpoints were not modified during or after completion of the study. Safety, PK, and efficacy endpoints are consistent with FDA IGIV Guidance. Serious bacterial infection (i.e., bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) definitions were also consistent with the FDA IGIV Guidance.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to the statistical review memo.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Definition of analysis populations:

- Safety Analysis Set: all subjects who signed informed consent and received at least one dose of study drug. This was the primary population for the safety analyses.
- Modified Intent-to-Treat (mITT) Population: defined as all subjects in the Safety Population who had at least one post-treatment follow-up visit. This was the primary population for efficacy analyses.
- PK Population: defined as all treated subjects with PK blood samples sufficient to estimate at least one PK parameter. This was the supportive population for the PK analyses.
  - Of note, the Study ADMA-004 Pharmacokinetic Analysis Plan defined the PK analysis population as all subjects who received at least one infusion of the study drug and who had at least one PK sample drawn
- PK Per Protocol Population: defined as all subjects in the PK Population who completed all required PK samplings according to their age at enrollment. This was the primary population for the PK analyses.

A total of 23 subjects were screened and enrolled, and 16 subjects received at least one dose of ASCENIV. These 16 subjects constituted the Safety set and the mITT set. There were 3 subjects enrolled in the 3-week infusion regimen and 13 subjects enrolled in the 4-week infusion regimen. Table 6 shows the population enrolled in the study.

Table 6: Population Enrolled for Study ADMA-004

Population Sets	3-Week Infusion Regimen, n	4-Week Infusion Regimen, n	Total
Screened	-	-	23
Enrolled	3	13	16[1]
mITT set	3	13	16
Safety set	3	13	16
PK Population	3	13	16
PK Per Protocol Population [2]	2	12	14
PK Per Protocol Population [3]	2	7	9

Source: Adapted from sBLA 125590/190, Clinical Study Report, Table 11-1

1. Seven subjects were screen failures

Abbreviation: mITT=modified intent-to-treat; PK = pharmacokinetic

[1] Includes all subjects who received at least one infusion of the study drug and who had at least one PK sample drawn.
[2] Includes all subjects in the PK Population who completed all required PK samplings (including at steady-state) according to their age at enrollment. Two subjects who discontinued the study early (Subject (b) (6) in the 3-week regimen, and Subject (b) (6) in the 4-week regimen cohort) were excluded from the PK Per Protocol Population.
[3] Includes all subjects in the PK Population who completed all required PK samplings (including at steady-state) according to their age at enrollment, with no major protocol deviation. Apart from the 2 early discontinuations (Subjects (b) (6) and (b) (6)), 5 subjects in the 4-week infusion regimen cohort ((b) (6) , (b) (6) , (b) (6) , (b) (6) , and (b) (6)), and were excluded from the PK Per Protocol Population due to a major deviation.

6.1.10.1.1 Demographics

The study population was predominantly white (12 subjects, 75 percent) and non-Hispanic (13 subjects, 81.3 percent), and included 7 subjects (43.8 percent) aged to 2 to 6 years, 9 subjects (56.3 percent) aged 7 to 11 years. The overall age range was between 2 to 11 years (mean of 7.1 years), and majority of the enrolled subjects were males. Table 1 shows the study population's demographics.

> ***Reviewer's Comments:*** *Study ADMA-004 planned to enroll 12 subjects total, 6 subjects in each age group: 2 to <6 years, 6 to <12 years, as described in the agreed iPSP. They were able to enroll 16 subjects total, 7 subjects 2 to <6 years, 9 subjects 7 to <12 years.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

PI Diagnosis

The most common PI diagnoses were hypogammaglobulinemia (8 subjects, 50 percent), followed by common variable immunodeficiency (4 subjects, 25 percent), combined immunodeficiency (2 subjects, 12.5 percent), Bruton's agammaglobulinemia and selective polysaccharide antibody deficiency (2 subjects, 12.5 percent each). The mean disease duration since first PI diagnosis was approximately 2.7 years (range from 0.2 to 8.4 years).

All subjects had been receiving IGIV infusions at regular 3- or 4-week intervals with stable doses for at least 3 months prior to study enrollment. Overall, the most commonly prescribed prior IGIV product was Gammagard 10% (7 subjects, 43.8% [all in the 4-week infusion regimen cohort]), followed by BIGIVam 10% (5 subjects, 31 .3% [3 in the 3-week, and 2 in the 4-week infusion regimen cohorts]), and Gamunex-C 10% (4 subjects, 25.0% [all in the 4-week infusion regimen cohort]). The last IGIV doses prior to the first IMP administration ranged from 15 g to 30 g (~424 mg/kg to ~660 mg/kg) in the 3-week infusion cohort, and between 5 g to 25 g (~450 mg/kg and ~568 mg/kg [among subjects with doses in mg/kg available]) in the 4-week infusion regimen cohort.

Trough lgG levels measured prior to the first IMP infusion (i.e., during the most recent IGIV therapy) were above 500 mg/dl in all enrolled subjects. Overall, there were no consistent differences between the 3-week and 4-week infusion regimens in the screening and baseline (pre-infusion 1) trough lgG levels.

Table 7: Disease Characteristics at Baseline, Safety/mITT/PK Population Set

Category Statistic/Response	3-Week Regimen (N=3)	4-Week Regimen (N=13)	Total (N=16)
Years since PI diagnosis (years)[1]	--	--	--
Mean (SD)	4.13 (4.115)	2.31 (1.904)	2.65 (2.387)
Median	3.76	1.70	1.96
Min, max	0.2,8.4	0.4, 5.5	0.2, 8.4
IgG trough level (mg/dL) at screening	--	--	--
Mean (SD)	917.3 (89.03)	944.1 (202.98)	939.1 (184.75)
Median	960.0	944.0	952.0
Min, max	815, 977	561, 1152	561, 1152
IgG trough level (mg/dL) at pre-infusion 1	--	--	--
Mean (SD)	981.3 (252.29)	953.6 (210.33)	958.8 (209.77)
Median	931.0	887.0	909.0
Min, max	758, 1255	650, 1271	650, 1271

Source: Adapted from sBLA 125590/190, Clinical Study Report, Table 11-4.

1. Years since PI Diagnosis = (date of informed consent – PI diagnosis date + 1)/365.25

Abbreviations: IgG=immunoglobin G, kg=kilogram, max=maximum, Min=minimum, PI=primary humoral immunodeficiency, SD=standard deviation

Reviewer's comment: *The most common PIs included in the study represent the most common forms of PI within the general population.*

Medical History

All subjects had a history of at least one prior medical condition apart from PI. The most commonly reported (frequency ≥50 percent) prior to medical conditions/disorders by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) were infections and infestations (13 subjects, 81.3 percent), followed by respiratory thoracic and mediastinal disorders (12 subjects, 75 percent), surgical and medical procedures (12 subjects, 75 percent), and psychiatric disorders (10 subjects, 62.5%).

The most commonly reported (frequency ≥ 20 percent) prior medical conditions/disorders by MedDRA Preferred Terms (PT) were asthma, ear tube insertion, rhinitis allergic (6 subjects, 37.5% each), ear infection, tonsillectomy, upper respiratory tract infection (5 subjects, 31.3 percent each), nausea, and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (4 subjects, 25 percent each).

Reviewer's comments: *The most common medical conditions affecting subjects in the study represent common medical conditions that may affect the general population with PI.*

Prior and Concomitant Medications

Apart from prior IGIV Infusions, the most commonly used (frequency ≥ 10%) prior medications by class were analgesics and antipyretics (4 subjects, 25 percent), antihistamines for systemic use (3 subjects, 18.8 percent) and other beta-lactam antibacterials (2 subjects, 12.5 percent). The most commonly used (frequency ≥ 10%) prior medications by preferred term were paracetamol (4 subjects, 25 percent) and cetirizine hydrochloride (2 subjects, 12.5%).

The most commonly used (frequency ≥50%) *concomitant* medications by class were antihistamines for systemic use (15 subjects, 93.8%), other analgesics and antipyretics (11 subjects, 68.8%), inhalant adrenergics, and non-steroidal anti-inflammatory and antirheumatic products (8 subjects, 50.0% each). The most commonly used (frequency ≥20%) *concomitant* medications by preferred term were paracetamol (11 subjects, 68.8%), followed by ibuprofen (8 subjects, 50.0%), diphenhydramine hydrochloride, salbutamol (7 subjects, 43.8% each), ondansetron (6 subjects, 37.5%), cetirizine, cetirizine hydrochloride (5 subjects, 31.3% each), cholecalciferol, diphenhydramine, and famotidine (4 subjects, 25.0% each). Nearly all treated subjects (15 subjects, 93.8%) received premedication / medication to prevent infusion AEs prior to at least one IMP infusion.

> ***Reviewer's comments:*** *The most common concomitant medications used by subjects in the study represent common concomitant medications that may be used in the general population with PID.*

6.1.10.1.3 Subject Disposition

A total of 23 subjects were screened, 7 subjects failed screening (including 4 subjects who were rescreened and enrolled, and 16 subjects received at least one dose of IMP. 3 subjects received IMP according to the 3-week infusion regimen and 13 subjects received IMP according to the 4-week infusion regimen. Fourteen of the 16 subjects completed the study as per protocol, whereas 2 subjects discontinued early due to adverse events.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was incidence of SBIs in the mITT set (n=16). No acute SBIs occurred during the study observation period (mean 157 days). The descriptive primary efficacy results are provided in Table 8.

Table 8: Incidence of Acute Serious Bacterial Infections, mITT Set

Category Statistic/Response	3-Week Regimen (N=3)	4-Week Regimen (N=13)	Total (N=16)
Number of ASBI episodes (per person-years)[1]	--	--	--
Mean (SD)	0 (0)	0 (0)	0 (0)
Median	0	0	0
Min, max	0, 0	0, 0	0, 0
Length of observation (days)			
Mean (SD)	129 (44.17)	163.3 (31.67)	156.9 (35.41)
Median	154	172	169
Min, max	78, 155	59, 181	59, 181

Source: Adapted from sBLA 125590/190, Clinical Study Report, Table 11-6

[1] The rate of ASBI episodes per person-year was calculated for each person as 365n/d, where n is the number of episodes and d is the length of observation in days. The length of observation is the time from first infusion until ASBI onset, death, or date of last study visit.

[2] Percentages based on the total number of episodes

Abbreviations: SBI=serious bacterial infection, max=maximum, min=minimum, mITT=modified intent-to-treat, NA=not applicable, SD=standard deviation

Reviewer's comments: *The FDA IGIV Guidance considers the demonstration of SBI rate per person-year less than 1.0 as adequate to provide substantial evidence of effectiveness and that the rate of SBI is measured during regularly repeated administration of the IGIV product for 12 months to avoid seasonal bias. The SBI rate in ADMA 004 was 0 per person over a 5-month study period. Evaluation of the treatment months showed the seasons in which the subjects were treated and observed during the study were evenly distributed between seasons. Six subjects enrolled in the months of January to June and six subjects enrolled from July to December. In addition, PK data demonstrated that clearance of ASCENIV was similar across all pediatric age groups and between pediatric and adult subjects. Consistent IgG trough levels were maintained throughout the study for both 3-week and 4-week regimens. Furthermore, results from the previous pivotal study, ADMA-003, which included some children, showed no SBIs occurred during the 12-month study period. The cumulative data from ADMA-004 and ADMA-003 provide substantial evidence of effectiveness of ASCENIV for pediatric patients who are at least 2 years old.*

6.1.11.2 Analyses of Secondary Endpoints

Number of Infections of Any Kind (Serious or Nonserious)

A total of 17 infections (bacterial and viral combined) occurred in 10 subjects (62.5%) in the mITT population. Of these, 2 infections occurred in 2 subjects (66.7%) in the 3-week infusion schedule cohort, and 15 infections occurred in 8 subjects (61.5%) in the 4-week infusion schedule cohort.

Number of Nonserious Infections

All 17 infections were non-serious. No serious infections were reported during the study. The mean number of infections (and of non-serious infections) per subject was 0.7 in the

3-week infusion schedule cohort, 1.2 in the 4-week infusion schedule cohort, and 1.1 overall.

Time to First Infection of Any Kind

The mean time to first infection per subject was 77.3 days in the 3-week infusion schedule cohort, 34.2 days in the 4-week infusion schedule cohort, and 42.3 days overall.

Duration of Infections

The mean time to resolution of infections per subject was 83.7 days in the 3-week infusion schedule cohort, 62.3 days in the 4-week infusion schedule cohort, and 66.3 days overall.

Number of Days of Antibiotic Treatment for Infections

Seven of the 16 subjects (43.8%) received antibiotics for the treatment of infections during the study, including 1 subject (33.3%) in the 3-week infusion schedule cohort, and 6 subjects (46.2%) in the 4-week infusion schedule cohort. The cumulative total duration of antibiotic treatment was 6 days in the 3-week infusion schedule cohort, 69 days (mean 11.5 days per subject taking an antibiotic) in the 4-week infusion schedule cohort, and 75 days (mean 10.7 days per subject taking an antibiotic) overall. Antibiotic treatment for treatment emergent infections was mostly taken orally, with the exception of a single IV dose of ceftriaxone sodium 750 mg administered to Subject (b) (6) for the treatment of otitis media.

Number of Days of Hospitalization and Prolonged Hospitalizations Due to Infection

There were no hospitalizations due to infection during the study.

Number of Episodes of Fever ≥38°C (≥100.4°F) (Per Subject and Overall)

Treatment-emergent pyrexia occurred in 3 subjects (18.8%), all receiving study treatment according to the 4-week infusion schedule. All 3 events were assessed as not related to the study treatment, and none resulted in a dose change. Two were mild and one moderate.

- One event was reported as low-grade fever, started 30 days after the subject's first IMP infusion, resolved with treatment by the following day, and was assessed as mild in severity.
- Second event was reported as low-grade fever, started 15 days after the subject's first IMP infusion, resolved with treatment within 4 days, and was assessed as mild in severity.
- Third event started 15 days after the subject's fourth IMP infusion, resolved without treatment by the following day, and was assessed as moderate in severity.

The detailed secondary efficacy results can be found in Table 9.

Table 9: Summary of Other Secondary Efficacy Endpoints, mITT Set

Category Statistic/Response	3-Week Regimen (N=3)	4-Week Regimen (N=13)	Total (N=16)
Total number of infections (serious and nonserious) on study	2	15	17
Total number of infections (serious and nonserious) per subject	--	--	--
Mean (SD)	0.7 (0.58)	1.2 (1.21)	1.1 (1.12)
Median	1.0	1.0	1.0
Min, max	0, 1	0, 4	0, 4
Total number of serious infections on study	0	0	0
Total number of nonserious infections on study	2	15	17
Total number of nonserious infections per subject	--	--	--
Mean (SD)	0.7 (0.58)	1.2 (1.21)	1.1 (1.12)
Median	1.0	1.0	1.0
Min, max	0, 1	0, 4	0, 4
Time to first infection per subject (days) [1]	--	--	--
Mean (SD)	77.3 (75.11)	34.2 (43.93)	42.3 (50.97)
Median	82.0	14.0	24.5
Min, max	0, 150	0, 148	0, 150
Time to resolution of infection (days) [2]	--	--	--
Mean (SD)	83.7 (79.83)	62.3 (71.24)	66.3 (70.60)
Median	92.0	23.0	51.0
Min, max	0, 159	0, 170	0, 170

Source: Adapted from sBLA 125590/190, Clinical Study Report, Table 11-7

[1] Time to first infection (in days) was calculated as follows: the [earliest infection AE start date] minus the [date of the first infusion] +1 day. Subjects experiencing no infection were censored as their last date on study.

[2] Time to resolution of infections (in days) was calculated for each individual infection as follows: [end date of the latest infection AE] minus the [date of the first infusion] +1 day. Subjects experiencing no infection were censored as their latest date on study.

Abbreviations: Max=maximum; MedDRA=Medical Dictionary for Regulatory Activities; Min=minimum; SD=standard deviation; TEAE=treatment-emergent adverse event

Percentages are calculated using N as the denominator.

Infections were identified based on MedDRA coding of AEs to System Organ Class 'Infections and infestations'.

Reviewer's comments: *The above findings are similar to other U.S.-licensed IGIV products in pediatric patients with PI and ASCENIV in adults with PI.*

6.1.11.3 Subpopulation Analyses

Subpopulation analysis was not performed because there were no acute SBI events that occurred during the study.

6.1.11.4 Dropouts and/or Discontinuations

Two of the 16 subjects (12.5%; one subject in each infusion regimen cohort) discontinued from the study due to a treatment emergent adverse event (TEAE).

- One subject was an 11-year-old female receiving study treatment according to the 3-week infusion schedule, experienced 3 TEAEs (nausea, fatigue, and headache) occurring within 24 hours after her second IMP infusion that led to

discontinuation from the study. Of note, the subject also experienced nausea and procedural headache requiring dosing interruption during her first IMP infusion. The 3 events leading to discontinuation required no treatment, resolved within the same day, and were assessed as moderate in severity and possibly related to the study treatment.

- The second subject was a 2-year-old female receiving study treatment according to the 4-week infusion schedule, experienced a TEAE of hypersensitivity (reported as acute allergic reaction) during her second study drug infusion that led to discontinuation from the study. The event resolved within the same day with treatment given, and was assessed as moderate in severity, serious (based on its medical importance) and probably related to the study drug.

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety population consisted of all subjects who received any amount of ASCENIV (N=16). Adverse events were obtained by the investigator.

6.1.12.2 Overview of Adverse Events

Most subjects (14 of 16, 87.5%) experienced at least one TEAE during the study: in the 3-week infusion regimen cohort, 3 subjects (100%) experienced 7 TEAEs, and in the 4-week infusion regimen cohort, 11 subjects (84.6%) experienced 49 TEAEs, for a total of 56 TEAEs (reference Table 10).

Overall, 6 subjects (37.5%) experienced a total of 13 TEAEs assessed by the investigator as at least possibly related to the study drug. In the 3-week infusion regimen cohort, 1 subject (33.3%) experienced 5 TEAEs assessed as related to the IMP (average of 1.7 related TEAEs per subject enrolled in this cohort), and in the 4-week infusion regimen cohort, 5 subjects (38.5%) experienced 8 TEAEs assessed as related to the study drug (average of 0.6 related TEAEs per subject enrolled in this cohort).

Refer to Table 11 for summary of TEAEs.

Two subjects had SAEs. One of the 16 subjects (6.3%) experienced a treatment-emergent SAE in the 4-week infusion regimen cohort. This was a hypersensitivity reaction, reported as acute allergic reaction in a 2-year old female during her second IMP infusion. She did not require hospitalization and resolved within the same day. This led to discontinuation from the study and was moderate in intensity. The second unrelated-SAE was intussusception in a 3-year-old female 19 days prior to her first IMP infusion. The event required hospitalization, resolved within 6 days and was assessed as severe and not related to the study treatment. No SAE occurred in the 3-week infusion regimen cohort. Please refer to Section 6.1.12.4 or further details.

Two of the 16 subjects (12.5%; one in each infusion regimen cohort) discontinued from the study due to a TEAE. TEAEs were predominantly mild in intensity (44 of 56 events, 78.6%); the remaining 12 TEAEs were moderate in intensity, whereas no subjects experienced severe TEAEs; refer to Table 10for details. No TEAEs led to death.

Table 10: Summary of Adverse Events, Safety Population

Category	3- Week Regimen (N=3); Subjects n (%)	3- Week Regimen Total Events	4- Week Regimen (N=13); Subjects n (%)	4- Week Regimen Total Events	Total (N=16); Subjects n (%)	All Regimens Total Events
Subjects with any AE	3 (100.0)	8	11 (84.6)	54	14 (87.5)	62
Subjects with any TEAE[1]	3 (100.0)	7	11 (84.6)	49	14 (87.5)	56
Product-related	1 (33.3)	5	5 (38.5)	8	6 (37.5)	13
Subjects with any SAE	0	0	2 (15.4)	2	2 (12.5)	2
Treatment-emergent SAE	0	0	1 (7.7)	1	1 (6.3)	1
Subjects who discontinued due to AE	1 (33.3)	3	1 (7.7)	1	2 (12.5)	4
Subjects with AE leading to death	0	0	0	0	0	0
TEAEs by severity	--	--	--	--	--	--
Severe	0	0	0	0	0	0
Moderate	1 (33.3)	3	3 (23.1)	7	4 (25.0)	12
Mild	3 (100.0)	7	11 (84.6)	42	13 (81.3)	44
Subjects with TAAE within 1 hour of infusion[2]	1 (33.3)	2	5 (38.5)	9	6 (37.5)	11
Subjects with TAAE within 24 hours of infusion[2]	1 (33.3)	5	5 (38.5)	11	6 (37.5)	16
Subjects with TAAE within 72 hours of infusion[2]	1 (33.3)	5	6 (46.2)	14	7 (43.8)	19
Subjects with adverse infusion reaction[3]	1 (33.3)	2	5 (38.5)	7	6 (37.5)	9
Subjects with adverse infusion reaction[3]	1 (33.3)	2	5 (38.5)	7	6 (37.5)	9
Subjects with related adverse infusion reaction[3]	1 (33.3)	5	5 (38.5)	8	6 (37.5)	13
Subjects with infusion site reaction[4]	0	0	0	0	0	0

Abbreviations: AE=adverse event; SAE=serious adverse event; TAAE=temporally associated adverse event; TEAE=treatment-emergent adverse event

Notes:

- Adverse events were coded using MedDRA, Version 24.0
- [1] TEAE: defined as an AE that started on or after the first IMP infusion
- [2] TAAE: defined as an AE with onset between the start of an infusion until 1 hour, 24 hours, or 72 hours after the end of the infusion
- [3] As marked in the electronic Case Report Form
- [4] Defined as TEAEs occurring at the site of the study drug infusion

Source: Created with ELSA and reviewer revised, Adapted from Clinical Study Report

Overview of Adverse Events by Age Group

Age Group 1 (2 to 6 years; N=7):

All 7 subjects aged 2 to 6 years received study treatment according to the 4-week infusion schedule. All 7 subjects experienced at least one TEAE, for a total of 33 TEAEs (4.7 TEAEs per subject) in this age group. Of these, 3 subjects (42.9%) experienced 5

TEAEs assessed by the investigator as at least possibly related to the study treatment. The majority of the TEAEs (31 of 33 events, 93.9%) were assessed as mild in intensity; the remaining 2 TEAEs were assessed as moderate in intensity. Two of the 7 subjects (28.6%) aged 2 to 6 years experienced one SAE each; none resulted in death. One of the 7 subjects (14.3%) discontinued from the study due to a TEAE.

The most common TEAEs by MedDRA SOC (frequency ≥30 percent) for subjects aged 2 to 6 years were Infections and infestations (6 subjects [85.7%], 12 events), followed by Respiratory, thoracic and mediastinal disorders (4 subjects [57.1 %], 6 events), Gastrointestinal disorders (3 subjects [42.9%], 4 events), and Injury, poisoning and procedural complications (3 subjects [42.9%], 4 events). Common TEAEs (occurring in ~20% of subjects in Age Group 1) included: COVID-19, epistaxis, headache, otitis media, and sinusitis (2 subjects [28.6%], 2 events for each).

Age Group 2 (7 to 11 years; N=9):

Of the 9 subjects aged 7 to 11 years enrolled in the study, 3 subjects received study treatment according to the 3-week infusion schedule, and 6 subjects received study treatment according to the 4-week infusion schedule.

All 3 subjects aged 7 to 11 years receiving study treatment according to the 3-week infusion schedule, and 4 of the 6 subjects (66.7%) receiving study treatment according to the 4-week infusion schedule experienced at least one TEAE, for a total of 23 TEAEs (2.6 TEAEs per subject) in this age group. Of these, 3 of the 9 subjects (33.3%) experienced 8 TEAEs assessed by the investigator as at least possibly related to the study treatment. The majority of the TEAEs (13 of 23 events, 56.5%) were assessed as mild in intensity; the remaining 10 TEAEs (experienced by 2 subjects, 22.2%) were assessed as moderate in intensity. No SAEs occurred in this age group. One of the 9 subjects (11.1 %) discontinued from the study due to 3 TEAEs.

The most common TEAEs by MedDRA SOC (frequency ~30%) for subjects aged 7 to 11 years were General disorders and administration site conditions and Infections and infestations (4 subjects [44.4%], 5 events each), followed by Gastrointestinal disorders (3 subjects [33.3%], 4 events), and Nervous system disorders (3 subjects [33.3%], 3 events each). Common TEAEs (occurring in ~20% of subjects in Age Group 2) included: headache (3 subjects [33.3%], 3 events), nausea (2 subjects [22.2%], 3 events), nasopharyngitis, and pyrexia (2 subjects [22.2%], 2 events for each).

TEAEs by Body System

The most common TEAEs by MedDRA SOC (frequency ≥30% in the overall Safety Population) were:

- Infections and infestations, with 10 subjects (62.5% of the Safety Population) reporting 17 events;
- Gastrointestinal disorders, with 6 subjects (37.5%) reporting 8 events;
- Respiratory, thoracic and mediastinal disorders, with 5 subjects (31.3%) reporting 8 events;

- General disorders and administration site conditions, with 5 subjects (31.3%) reporting 6 events;
- Injury, poisoning and procedural complications, with 5 subjects (31.3%) reporting 6 events;
- Nervous system disorders, with 5 subjects (31.3%) reporting 5 events.

Table 11: Common Adverse Events, by MedDRA System Organ Class and Preferred Term, Safety Population

System Organ Class/Preferred Term	3-Week Regimen (N=3) Total Events	3-Week Regimen (N=3) Subjects (n) (%)	4-Week Regimen (N=13) Total Events	4-Week Regimen (N=13) Subjects (n) (%)	All Regimens (N=16) Total Events	Total (N=16) Subjects (n) (%)
Subjects with at least one TEAE	7	3 (100)	46	11 (84.6)	56	14 (87.5)
Infections and infestations	2	2 (66.7)	15	8 (61.5)	17	10 (62.5)
COVID-19	0	0 (0)	2	2 (15.4)	2	2 (12.5)
Nasopharyngitis	1	1 (33.3)	1	1 (7.7)	2	2 (12.5)
Otitis media	0	0 (0)	2	2 (15.4)	2	2 (12.5)
Sinusitis	0	0 (0)	2	2 (15.4)	2	2 (12.5)
Gastrointestinal disorders	2	1 (33.3)	6	5 (38.5)	8	6 (37.5)
Nausea	2	1 (33.3)	2	2 (15.4)	4	3 (18.8)
Vomiting	0	0 (0)	2	2 (15.4)	2	2 (12.5)
Respiratory, thoracic, and mediastinal disorders	0	0 (0)	8	5 (38.5)	8	5 (31.3)
Cough	0	0 (0)	2	2 (15.4)	2	2 (12.5)
Epistaxis	0	0 (0)	2	2 (15.4)	2	2 (12.5)
Nasal Congestion	0	0 (0)	2	2 (15.4)	2	2 (12.5)
General disorders/ administration site conditions	1	1 (33.3)	5	4 (30.8)	6	5 (31.3)
Pyrexia	0	0 (0)	3	3 (23.1)	3	3 (18.8)

System Organ Class/Preferred Term	3-Week Regimen (N=3) Total Events	3-Week Regimen (N=3) Subjects (n) (%)	4-Week Regimen (N=13) Total Events	4-Week Regimen (N=13) Subjects (n) (%)	All Regimens (N=16) Total Events	Total (N=16) Subjects (n) (%)
Injury, poisoning and procedural complications	1	1 (33.3)	5	4 (30.8)	6	5 (31.3)
Procedural headaches	1	1 (33.3)	1	1 (7.7)	2	2 (12.5)
Skin abrasions	0	0 (0)	2	2 (15.4)	2	2 (12.5)
Nervous system disorders	1	1 (33.3)	4	4 (30.8)	5	5 (31.3)
Headache	1	1 (33.3)	4	4 (30.8)	5	5 (31.3)
Immune system disorders	0	0 (0)	2	2 (15.4)	2	2 (12.5)
Musculoskeletal and connective tissue disorders	0	0 (0)	2	1 (7.7)	2	1 (6.3)
Blood and lymphatic system disorders	0	0 (0)	1	1 (7.7)	1	1 (6.3)
Eye disorders	0	0 (0)	1	1 (7.7)	1	1 (6.3)

Source: Adapted from sBLA 125590/190, Clinical Study Report, Table 12-4

Abbreviations: TEAE=treatment-emergent adverse event

Adverse events were coded using MedDRA, Version 24.0. All events are included events columns.

System Organ Class and Preferred Term were sorted by incidences in the overall Safety Population. A subject was only counted once within each Preferred Term and System Organ Class.

• All SOCs with at least one event are listed in this table; Preferred Terms are listed if the event occurred in ;,:10% of subjects in the Safety Population.

Reviewer's Comments: *The most common TEAEs are common symptoms and conditions that occur in children irrespective of IGIV therapy. For the purposes of this review, similar items were not combined for the TEAE table.*

Seven subjects (43.8%) experienced a total of 19 temporally associated AEs (TAAEs; defined as AEs occurring within 72 hours after a study drug infusion) during the study. In the 3-week infusion regimen cohort, 1 of the 3 subjects (33.3%) experienced a total of 5 TAAEs, of which 2 events occurred during or within 1 hour following an infusion, and all 5 occurred during or within 24 hours after an infusion. In the 4-week infusion regimen cohort, 6 subjects (46.2%) experienced a total of 14 TAAEs; of these, 5 subjects (38.5%) experienced 11 TAAEs occurring within 24 hours following an infusion, of which 9 TAAEs occurred during or within 1 hour following an infusion. A total of 6 subjects (37.5%) reported a related adverse infusion reaction. No infusion site reactions occurred during the study; refer to Table 10 for details.

Four subjects (57.1 %) aged 2 to 6 years experienced a total of 11 TAAEs (. Of these, 3 subjects (42.9%) experienced 8 TAAEs occurring within 24 hours following an infusion, including 6 events occurring during or within 1 hour after an infusion. Three of the 7 subjects (42.9%) aged 2 to 6 years reported 5 related adverse infusion reactions, whereas no infusion site reactions occurred in this age group.

Three of the 9 subjects (33.3%) aged 7 to 11 years experienced a total of 8 T AAEs within 72 hours after a study drug infusion. All 8 TAAEs occurred within 24 hours following an infusion, including 2 events occurring during or within 1 hour after an infusion. Three of the 9 subjects (33.3%) aged 7 to 11 years reported 8 related adverse infusion reactions, whereas no infusion site reactions occurred in this age group.

Table 12 shows the adverse reactions (ARs) that occurred within 72 hours after the end of an ASCENIV infusion. For the purposes of this review, all TAAEs are considered as ARs. Table 13 shows the details regarding the infusions temporally associated with adverse events.

Table 12: Adverse Reactions Within 72 Hours After the End of an ASCENIV Infusion

Adverse Reaction (AR)	Subjects Reporting AR (N=16) n (%)	Number of Infusions (N=91) With AR n (%)
Hypersensitivity	1 (6)	1 (1)
Diarrhea	1 (6)	1 (1)
Epistaxis	1 (6)	1 (1)
Headache*	4 (25)	5 (5)
Fatigue	1 (6)	1 (1)
Nausea	3 (19)	4 (4)
Chest pain	1 (6)	1 (1)
Otitis*	2 (13)	2 (2)
Viral rash	1 (6)	1 (1)
Vomiting	1 (6)	1 (1)

Source: Clinical reviewer from analysis of safety database

Abbreviation: AR=adverse reaction

*Includes similar combined terms

Reviewer's comments: *ADMA Biologics initially coded "procedural headache," "headache," "headaches," "headache during infusion," "infusion-related headache" and "increase recurrent chronic headache" separately. However, all terms describe the same symptoms of headache during or shortly after infusion, and therefore should be coded as "headache." FDA and ADMA Biologics re-coded these terms as headache. Additionally, ADMA Biologics initially coded "increase recurrent chronic nausea," "nausea," "nausea during infusion" separately. However, all terms describe the same symptoms of nausea and therefore should be coded as "nausea." FDA and ADMA Biologics re-coded these terms as nausea. Similarly, otitis externa and otitis media were combined under the term "otitis." The above table was included in the label for clarity.*

Table 13: Infusions Temporally Associated with Adverse Events, Safety Set

Category Statistic/Response	3-Week Regimen (N=3)	4-Week Regimen (N=13)	Total (N=16)
Study[1]	--	--	--
Total infusions	17	74	91
Total infusions with ≥1 TAAE	2	9	11
Proportion of infusions with ≥1 TAAE, m/n (%)	2/17 (11.8)	9/74 (12.2)	11/91 (12.1)
Proportion of subjects with ≥1 TAAE, m/n (%)	1/3 (33.3)	6/13 (46.2)	7/16 (43.8)

Category Statistic/Response	3-Week Regimen (N=3)	4-Week Regimen (N=13)	Total (N=16)
Per subject Aged 2 to 6 years[2]	--	--	--
N	0	7	7
Mean (SD)	0	21.4(23)	21.4 (23)
Median	0	16.7	16.7
Min, max	0, 0	0, 50	0, 50
Upper one-sided 95% CL of mean	0, 0	0.2, 42.7	0.2, 42.7
Per subject Aged 7 to 11 years[2]	--	--	--
N	3	6	9
Mean (SD)	22.2 (38.5)	5.6 (8.6)	11.1 (22)
Median	0	0	0
Min, max	0, 66.7	0, 16.7	0, 66.7
Upper one-sided 95% CL of mean	-73.4, 117.8	-3.5, 14.6	-5.8, 28.1

Source: Adapted from sBLA 125590/190, Clinical Study Report, Table 12-6.

1. The calculation is the percentage of infusions with ≥1 TAAE is calculated as m/n, where m is the number of infusions with ~1 TAAE, and n is the number of infusions.

2. The calculation is the percentage of infusions with ≥1 TAAE for each subject, then calculating the mean of these percentages, with a 95% (one-sided) confidence limit for the mean.

Abbreviations: CL=confidence limit, max=maximum, min=minimum, SD=standard deviation, TAAE=temporally associated adverse event (defined as adverse events occurring during or within 1 hour, 24 hours, or 72 hours following an infusion of the study drug)

Reviewer's comments: *The upper one-sided 95 percent CI of the probability that an infusion was associated with an AE was below the threshold of 40 percent as outlined in the FDA IGIV Guidance.*

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

One subject experienced a single SAE of acute allergic reaction during the study. The event occurred in a 2-year-old female during the second IMP infusion. The infusion was stopped due to developed of an acute allergic reaction, described as hives, increased blood pressure and agitation for which she received Benadryl, cetirizine and IM epinephrine. Following treatment, the hives resolved, blood pressure normalized and the subject appeared comfortable. The subject was monitoring for 3 hours after epinephrine treatment and discharged home the same day. The SAE was assessed to be probably related to the study treatment.

Reviewer's comments: *This SAE is probably related to the study treatment as hypersensitivity is a known class effect for immunoglobulin products.*

6.1.12.5 Adverse Events of Special Interest

No adverse events of special interest (AESIs) were pre-identified as such for this study. However, the study protocol identified two AE categories as potentially significant safety observations requiring that subject enrollment be halted until a safety review committee could evaluate all relevant safety data and provide their recommendations regarding continued recruitment. These included thrombotic events experienced by ≥1 treated

subject and clinically significant hemolysis experienced by ≥ 1 treated subject. No thrombotic events and no events suggestive of hemolysis occurred during the study.

6.1.12.6 Clinical Test Results

There were no consistent changes from baseline to last infusion in hematological parameters. For leukocytes, including neutrophils, minor increases in mean counts were observed; however, values remained below the age-specific upper normal limits and were not considered clinically relevant.

6.1.12.7 Dropouts and/or Discontinuations

Two subjects discontinued the study early due to adverse events. One subject received the 3-week regimen and discontinued after 3 infusions and another subject received the 4 week regimen and discontinued after 2 infusions.

6.1.13 Study Summary and Conclusions

ADMA-004 was a prospective, open-label, single arm, multicenter study wherein 16 pediatric subjects 2 to 11 years of age with PI were administered ASCENIV every 3-4 weeks at the same dose and regimen as their previous IGIV therapy prior to study enrollment. The subjects were followed over a mean period of approximately 5 months. The primary efficacy endpoint was incidence of acute SBIs as defined in accordance with FDA IGIV Guidance, <1.0 SBIs per person-year.

ADMA-004 planned to enroll 12 subjects, 6 subjects in each age group: 2 to 6 years 7-11 years, as described in the iPSP. A total of 16 subjects were included in the analysis set.

No acute SBIs occurred during the mean 5-month study period, and subjects were observed over an even distribution of seasons. The study was thus successful on its primary endpoint and provided substantial evidence of effectiveness.

The efficacy of ASCENIV in the pediatric PI population was further supported by PK assessments for all pediatric age groups. IgG trough levels remained consistent and throughout ADMA-004. Based on the limited data, the clearance appears to be comparable across all age groups and similar to that of adults.

14 of the 16 treated subjects completed all planned infusions and there were no deaths. 2 of the 16 subjects discontinued from the study due to a TEAE. The safety profile of ASCENIV in pediatric subjects 2 years of age and older is consistent with other IGIV products and the safety profile of ASCENIV in adults. The proportion of infusions temporally associated with an adverse event was below the upper one-sided 95 percent confidence limit of 40 percent, as outlined in the FDA IGIV Guidance.

7. INTEGRATED OVERVIEW OF EFFICACY

Not applicable as the primary basis for review of this application was the single adequate and well controlled trial submitted for the pediatric population labeling expansion.

8. INTEGRATED OVERVIEW OF SAFETY

No new safety signals were identified in this clinical trial and safety data in children were consistent with previously submitted data. As such, an integrated safety evaluation was not done.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No new human reproduction or pregnancy data was submitted in this efficacy supplement.

9.1.2 Use During Lactation

No new human data on use during lactation was submitted in this efficacy supplement.

9.1.3 Pediatric Use and PREA Considerations

The pediatric study, ADMA-004, was conducted to fulfill PREA requirements and PMR as agreed upon during the initial approval of ASCENIV in 2019.This study fulfills the PREA PMR. The Applicant has received a partial waiver for pediatric studies in patients 0 to less than 2 years old because such studies are impossible and highly impracticable due to the rarity of PI in this age group. The application was presented to PeRC who agreed with the Division in extending labeling to pediatric patients 2 years and older with PI.

9.1.4 Immunocompromised Patients

Not applicable as subjects have immunodeficiency.

9.1.5 Geriatric Use

Not applicable as this supplement is for approval in pediatric subjects.

10. CONCLUSIONS

The cumulative pediatric evidence from ADMA-004 and previous pivotal study, ADMA-003, provides substantial evidence of effectiveness of ASCENIV for pediatric patients who are 2 years of age and older. The safety profile of ASCENIV is consistent with the IGIV class of products and is similar between children and adults.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Primary Immunodeficiency (PI) represents a heterogeneous group of disorders resulting from inherited defects of the immune system. • Patients with PI are at increased risk for recurrent, severe infections	• PI diseases are serious, chronic conditions associated with considerable morbidity and mortality. • IG replacement therapy (administered either intravenously or subcutaneously) has been shown to reduce the incidence of serious infections through provision of passive immunity and prolong life span.
Unmet Medical Need	• Numerous marketed IG products (both intravenous and subcutaneous forms) have demonstrated efficacy with serious bacterial infection rates less than 1.0 per subject-year.	• Currently, there is not an unmet medical need. • However, given potential for supply chain disruptions and shortages, there is a public health benefit for having additional immunoglobulin replacement products on the market.
Clinical Benefit	• One pediatric study, ADMA-004, was submitted to support the safety and efficacy of ASCENIV as replacement therapy in PI in a pediatric population and to fulfill the PREA PMR. Additional supportive pediatric data from the original registrational study (ADMA-003) was supportive. • No SBI occurred in 16 children (age 2 to 11 years) during a mean observation period of approximately 5 months in ADMA-004. The product was already approved for adolescents 12 years and older with the original approval. • All pediatric subjects had consistent IgG trough levels throughout the study. Drug clearance was similar between pediatric age groups, and between adult and pediatric PI subjects.	• The product is effective at preventing acute SBIs in children 2 to 16 years of age based on clinical and clinical pharmacology data.
Risk	• Most common adverse reactions in children with PI included fatigue, headache, nausea, and rash. • Adverse reactions in children were similar to those observed in adults and in other immunoglobulin products. • There were no deaths reported in children in the clinical studies.	• The safety profile of ASCENIV in pediatric subjects 2 years to 16 years is consistent with other IgG products and the safety profile of ASCENIV in adults.
Risk Management	• IGIV products carry an obligate boxed warning for thrombosis and renal dysfunction due to known class effects. • Warnings and Precautions for this class of products include hypersensitivity, aseptic meningitis, hemolytic anemia, TRALI, and transmissible infectious agents.	• Labeling and routine pharmacovigilance are appropriate. • Patients should be monitored for signs and symptoms of thrombosis, renal dysfunction, hypersensitivity, aseptic meningitis, hemolytic anemia, TRALI and transmissible infectious agents.

Table 14: Risk-Benefit Considerations

Abbreviations: IG=immune globulin, IGIV=immune globulin intravenous, PI=primary humoral immunodeficiency, SBI=serious bacterial infection, TRALI=transfusion-related acute lung injury

11.2 Risk-Benefit Summary and Assessment

Data submitted to this BLA supplement establish a benefit in pediatric patients 2 years of age and older with PI. The risks associated with ASCENIV for the treatment of PI are minimal, similar to those observed in adults and across IGIV products, and are outweighed by the benefits. Compared indirectly to other IGIV products, the safety profile appears similar. The overall benefit-risk profile is favorable.

11.3 Discussion of Regulatory Options

The regulatory options for this application are approval for the entire pediatric population 2 years of age and older with PI, approval for a subset of the pediatric population with PI, or a complete response letter. The clinical and clinical pharmacology review teams support approval for the entire pediatric population 2 years of age and older with PI.

11.4 Recommendations on Regulatory Actions

The Applicant has provided substantial evidence of effectiveness and an adequate assessment of safety for the proposed pediatric population based on a single adequate and well controlled trial with confirmatory evidence from a previously conducted clinical trial. The clinical and clinical pharmacology review teams recommend that ASCENIV be approved for pediatric patients 2 years of age and older with PI.

11.5 Labeling Review and Recommendations

The Applicant satisfactorily addressed the labeling revisions requested by FDA prior to the action date and the final agreed-upon label was reviewed and cleared by the Advertising and Promotional Labeling Branch. The clinical team finds the final agreed-upon labeling with all revisions acceptable.

11.6 Recommendations on Postmarketing Actions

No postmarketing studies or REMS are recommended. Routine surveillance appropriate for the product class is recommended.