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Division / Office	DCEGM/OCE/OTP
Committee Chair	Brighid Imperiale, MD
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Priority Review	No
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Applicant	ADMA Biologics
Established Name	Immune Globulin Intravenous, Human-slra, 10% Liquid
(Proposed) Trade Name	ASCENIV
Pharmacologic Class	Immune Globulin
Dosage Form(s) and Route(s) of Administration	A liquid solution containing 10% IgG (100 mg/mL) for Intravenous infusion
Dosing Regimen	300-800 mg/kg every 3-4 weeks
Indication(s) and Intended Population(s)	Indicated for the treatment of primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. The purpose of this supplement is to expand the age range in the indication from ≥12 to ≥2 years of age.

Table of Contents

Glossary 3

1. Executive Summary 3

2. Clinical and Regulatory Background 4

2.1 Disease or Health-Related Condition(s) Studied 4
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) 4
2.4 Previous Human Experience with the Product (Including Foreign Experience) 4
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 5

3. Submission Quality and Good Clinical Practices 5

3.1 Submission Quality and Completeness 5

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

5.1 Review Strategy 5
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review 5
5.3 Table of Studies/Clinical Trials 5

6. Discussion of Individual Studies/Clinical Trials 6

6.1 Trial #1 ADMA-004 6
6.1.1 Objectives (Primary, Secondary, etc) 6
6.1.2 Design Overview 6
6.1.3 Population 6
6.1.4 Study Treatments or Agents Mandated by the Protocol 7
6.1.6 Sites and Centers 7
6.1.8 Endpoints and Criteria for Study Success 7
6.1.9 Statistical Considerations & Statistical Analysis Plan 7
6.1.10 Study Population and Disposition 9
6.1.11 Efficacy Analyses 12
6.1.12 Safety Analyses 13

10. Conclusions 13

10.1 Statistical Issues and Collective Evidence 13
10.2 Conclusions and Recommendations 14

GLOSSARY

AE	Adverse Events
AESI	Adverse Events of Special Interest
CSR	Clinical Study Report
CVID	common variable immunodeficiency
FDA	Food and Drug Administration
IgG	Immunoglobulin G
IGIV	Intravenous Immunoglobulin
IgM	Immunoglobulin M
mITT	Modified Intent-to-Treat
NIH	National Institutes of Health
PI	primary humoral immunodeficiency
PIDD	Primary Immunodeficiency Diseases
PMR	Post-Marketing Requirement
SAE	Serious Adverse Events
SBI	serious bacterial infection
sBLA	supplemental Biologics License Application
SQ	subcutaneous
TAAEs	temporally associated adverse events
TEAEs	Treatment Emergent Adverse events

1. Executive Summary

ASCENIV (Intravenous Immunoglobulin, IGIV) was approved by the Food and Drug Administration (FDA) on April 1, 2019, for the treatment of Primary Immunodeficiency Diseases (PIDD) in patients 12 years and older. The purpose of this supplemental Biologics License Application (sBLA) is to request the Agency's approval for the administration of ASCENIV in children 2 to 11 years of age based on the findings included in the final report of a pediatric study, ADMA-004. The study was conducted for compliance with the Post-Marketing Requirement (PMR) issued on December 31, 2019.

ADMA-004 was a phase IV, multicenter, open-label study of ASCENIV administered as an intravenous infusion at 300-800 mg/kg every 21 or 28 days in approximately 12 pediatric subjects with PIDD. The primary efficacy endpoint was the incidence of serious bacterial infection (SBI). SBIs encompass bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, or visceral abscess.

In the study, 16 pediatric subjects were enrolled, 7 subjects were ages 2 to 6 years old, and 9 subjects were ages 7 to 11 years old at time of enrollment. No acute SBIs occurred during the observation period (average of 157 days),

yielding a mean of 0.0 acute SBI episodes per person-year. No other serious infections, or hospitalizations due to infections occurred.

No deaths and no study treatment-related serious adverse events (SAEs) occurred during the study.

I conclude that ASCENIV is efficacious and safe for the intended expanded age group. I recommend approval of the indication in the expanded age group.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

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

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

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

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

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

ASCENIV was approved in US in 2019 and has been used in adults and adolescents (12 to 17 years of age) with PI.

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

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

5.1 Review Strategy

In this submission, one Phase 4 clinical study, Study ADMA-004, was provided in support of this application. Accordingly, the safety and efficacy database, consisting of data from Study ADMA-004, is reviewed in detail in this memo.

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

BLA 125590/190.0

- Module 1.14 Labeling
- Module 2.5 Clinical Overview
- Module 2.7.3 Summary of Clinical Efficacy
- Module 2.7.4 Summary of Clinical Safety
- Module 5.3.5 Clinical Study Reports (CSRs), supporting documents, data files, and programs

5.3 Table of Studies/Clinical Trials

The following clinical study, summarized in Table 1, is included in the submission.

Table 1 Summary of the clinical study in the submission

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK, Efficacy and Safety	ADMA-004	5.3.5.2	PK analysis; Long-term efficacy and safety	Open-Label, Single-arm, Multicenter	Planned 300-800 mg/kg (actual 183-929 mg/kg) every 3- or 4-weeks, IV	16	Patients with PIDD	5 months	Complete; Full

IV-Intravenous, PK-Pharmacokinetic, PIDD- Primary Immunodeficiency Diseases
Source: BLA 125590/190; 5.3.5.2 Study Reports of Uncontrolled Clinical Studies

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 ADMA-004

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective:
The primary objective of this study is to evaluate ASCENIV's pharmacokinetic profile of total IgG in pediatric subjects with PIDD.

Secondary Objectivs:
1. To evaluate the efficacy and safety of dosing with ASCENIV, including adverse events, serious adverse events, and infusion associated adverse events.
2. To evaluate trough total IgG levels at regular intervals
3. To evaluate levels of specific antibodies (anti-pneumococcal capsular polysaccharide, anti-haemophilus influenzae b, and anti-RSV neutralizing antibody)

6.1.2 Design Overview

This is a Phase 4, multicenter, open-label study of ASCENIV administered every 21 or 28 days in approximately 12 pediatric subjects with PIDD. Once registered, the subject would receive ASCENIV on Study Day 1 (required to be within 28 days of screening) and every 21 or 28 days thereafter according to their current interval of IGIV treatment.

All enrolled subjects completed pharmacokinetic sampling according to their age. Pharmacokinetic assessment was initiated after the 6th infusion for subjects on a 28 day regimen, or after the 7th infusion for subjects on a 21 day regimen.

To avoid seasonal bias in the evaluation of SBIs, enrollment was split into two 6 month increments, with six subjects enrolled in the months of January-June and six subjects enrolled from July-December. Effort was made to ensure enrollment is spread as evenly as possible over the calendar year.

6.1.3 Population

Be male or female, and ≥ 2 years and < 12 years at the time of informed consent by legal guardian and have confirmed and documented clinical diagnosis of PIDDs including but not limited to: common variable immunodeficiency, X-linked and autosomal forms of agammaglobulinemia, hyper-IgM syndrome, or antibody deficiencies.

6.1.4 Study Treatments or Agents Mandated by the Protocol

ASCENIV was given as an intravenous infusion at the same dose, or higher dose where medically appropriate, as the subject's previous IV Immunoglobulin G treatment (300-800 mg/kg) every 21 or 28 days.

6.1.6 Sites and Centers

The study was conducted in five centers located in the United States.

6.1.8 Endpoints and Criteria for Study Success

Efficacy Endpoints:

1. Incidence of serious bacterial infections meeting the FDA criteria.
2. Incidence of all kinds of infections (serious and non-serious)
3. Days on antibiotic therapy (treatment and prophylaxis)
4. Evaluate trough total IgG levels at regular intervals
5. Levels of IgG subclasses 1-4 prior to Infusions 1 and 6/7
6. Levels of specific antibodies (anti-pneumococcal capsular polysaccharide, antihaemophilus influenzae b, anti-RSV neutralizing antibody) prior to Infusions 1 and 6/7

Safety Endpoints:

1. Evaluate the safety of ASCENIV, including incidence of adverse events that occur during or within 1 hour, 24 hours and 72 hours of completion of an infusion (ie, temporally associated adverse events, TAAEs) and mean number of TAAEs per infusion
2. Incidence of SAEs and related SAEs
3. Incidence of Treatment Emergent Adverse events (TEAEs) and related TEAEs
4. Evaluate the total number and incidence of adverse reactions plus suspected adverse reactions combined
5. Incidence of infusion site reactions
6. Change in vital signs before and after administration of study drug
7. Changes in hematology, chemistry and urinalysis parameters

6.1.9 Statistical Considerations & Statistical Analysis Plan

<u>Determination of Sample Size</u>
The sample size for this study was determined without a formal power analysis. The enrollment targets for this study were determined in accordance with guidance documents provided by the FDA. The study will require treatment of 12 evaluable pediatric subjects (six aged 2-6 years and six aged 7-11 years); evaluable subjects are defined as a subject who has completed their assigned pharmacokinetic sampling schedule. Enrollment was to be split into two 6 month increments, with six subjects enrolled in the months of January-June and six subjects enrolled from July-December.

Analysis Populations

Safety Population: all subjects who have signed informed consent and received at least one dose of study drug. This was to be the primary population for the safety analysis.

Modified Intent-to-Treat (mITT): all subjects from the safety population with at least one post-treatment follow-up visit. This was to be the primary population for the efficacy analysis.

Key Efficacy Endpoint Analysis

The rate of SBIs is the key efficacy parameter. The following were to be provided:

- Summary statistics for the number of SBI episodes and acute SBI episodes per person--year:
    - The end of observation period is defined as the minimum of death date, SBI onset date, date of study follow-up visit, or last known visit if lost to follow-up. Each subject will have a time, and this will be considered as the length of observation (or length of "at-risk").
    - The cumulative length of observation will be the sum of each subject's value.
    - The per person-year is obtained by calculating the days (End of Observation date-First infusion date + 1 day), then converting years (365 days in 1 year, divide by 365).
    - The rate of occurrence will be calculated for each subject as 365n/d where n is the number of reported infections and d is the number of days on study through end of observation.

- Summary statistics will be provided for the length of observation of each subject.

Methods for Missing Data

No data imputation will be used in the analysis of this study. Missing data will be omitted from summary statistics.

Interim Analysis

There is no interim analysis planned for this study.

Subgroup analyses

Summary statistics will be produced for subgroups of subjects based on the following, whenever sufficient subjects in the subgroup exist:

- Age group
- Gender
- Race

Due to the potentially small sample size in the following proposed subgroups, subgroup analyses will be performed using descriptive statistics only.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 2 presents the numbers of subjects in different analysis sets.

Table 2 Numbers of subjects in different analysis sets

	3-Week Infusion Regimen (N=3) n (%)	4-Week Infusion Regimen (N=13) n (%)	Total (N=16) n (%)
Enrolled	3 (100)	13 (100)	16 (100)
Safety Population	3 (100)	13 (100)	16 (100)
mITT Population	3 (100)	13 (100)	16 (100)

Source: sBLA 125590/190; Clinical Study Report, Table 11-1 (p.65).

Reviewer's comment: All enrolled subjects were treated.

6.1.10.1.1 Demographics

The overall study population (N=16) 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 other subject demographic characteristics are summarized in Table 3.

Table 3 Summary of Demographic Characteristics

Category Statistic/Response	3-Week Infusion Regimen (N=3)	4-Week Infusion 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 11 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	0	3 (23 .1)	3 (18. 8)
American	0	0	0
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	1 (7.7)	1 (6.3)
Ethnicity, n (%)			
Not Hispanic/Latino/Spanish Origin	0	3 (23.1)	3 (18.8)
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	37.4	25.8	30.3
Min, Max	34.5, 51.2	11.4, 37.5	11.4, 51.2

Source: sBLA 125590/190; Clinical Study Report, Table 11-3 (p.66).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The mean disease duration since first PIDD diagnosis was approximately 2.7 years (range from 0.2 to 8.4 years). The other relevant disease characteristics at Baseline are presented in Table 4.

Table 4 Relevant Disease Characteristics at Baseline

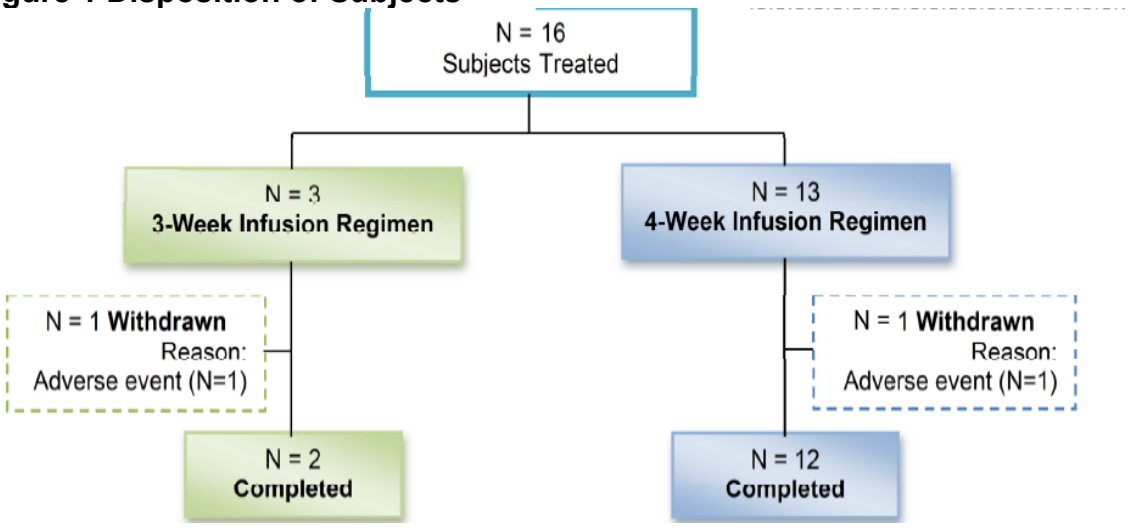
Category Statistic/Response	3-Week Infusion Regimen (N=3)	4-Week Infusion Regimen (N=13)	Total (N=16)
Years since PIDD Diagnosis (years) [1]			
Mean (SD)	4.13 (4.115)	2.31 (1.904)	2.65 (2.387)
Median	3.76	1.70	1. 96
Min, Max	0.2, 8.0	0.4, 5.5	0.2, 8.4
IgG Trough Level (mg/dL) at Screening			
Mean (SD)	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			
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

[1] Years since PIDD Diagnosis = (date of informed consent - PIDD Diagnosis date+ 1)/365.25
Source: sBLA 125590/190; Clinical Study Report, Table 11-4 (p.68).

6.1.10.1.3 Subject Disposition

Of the 23 subjects screened, 7 subjects failed screening, and 16 subjects received at least one dose of ASCENIV; 3 subjects received ASCENIV according to the 3-week infusion regimen, and 13 subjects received ASCENIV 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 (AEs). The disposition is presented in Figure 1.

Figure 1 Disposition of Subjects



Source: sBLA 125590/190; Clinical Study Report, Figure 1 (p.63).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

No acuts SBI occurred during the observation period (mean 129 days [median 154 days, range: {78, 155} days] for 3-Week Infusion Regimen, mean 164 days [median 172 days, range: {59, 181} days] for 4-Week Infusion Regimen, and mean 157 days [median 169 days, range: {59, 181} days] for the Total population); therefore, the mean number of acute SBI episodes per person-year was 0.0.

6.1.11.2 Analyses of Secondary Endpoints

No other serious infections, or hospitalizations due to infections occurred.
A total of 17 infections (all non-serious) occurred in 10 subjects in the mITT Population; 2 infections occurred in 2 subjects in the 3-week infusion schedule cohort, and 15 infections occurred in 8 subjects in the 4-week infection schedule cohort. The mean number of infections per subject was 0.7 infections/subject (2 /3) in the 3-week infusion schedule cohort, 1.2 infections/subject (15/13) in the 4-week infusion schedule cohort, and 1.1 infections/subject (17/16) overall. The mean time to first infection per subject was 77 days [median 82 days, range:{0, 150} days] in the 3-week infusion schedule cohort, 34 days [median 14 days, range:{0, 148} days] in the 4-week infusion schedule cohort, and 42 days [median 24.5 days, range:{0, 150} days] overall. The mean time to resolution of infections per subject was 84 days [median 92 days, range:{1, 159} days] in the 3-week infusion schedule cohort, 62 days [median 23 days, range:{1, 170} days] in the 4-week infusion schedule cohort, and 66 days [median 51 days, range:{1, 170} days] overall.
Overall, 7 subjects required antibiotic treatment for treatment-emergent infections during the study, for a mean duration of 11 days [median 6 days, range:{6, 26} days], and a cumulative duration of 75 days. One subject required antibiotic treatment for 6 days in the 3-week infusion schedule cohort, and 6 subjects required antibiotic treatment for a total of 69 days (mean duration of 12 days, median 8 days, range:{1, 26} days) in the 4-week infusion schedule cohort.

Reviewer Comment:
During the review, we identified an issue that can cause confusion in interpreting time-to-event endpoints. For patients not experiencing the event of interest, the applicant set the time-to-event as 0 day. Instead of using this erroneous time for patients not experiencing the event, we instead used as the duration for these patients the time from treatment to the last day of record for the patient. Below is the updated result. The median time to first infection per subject was 142 days, [range: {82, 150} days] in the 3-week infusion schedule cohort, 78 days [range: {11, 181} days] in the 4-week infusion schedule cohort, and median 112 days [range: {11, 181} days] overall. The median time to resolution of infections per subject was 142 days [range: {92, 159} days] in the 3-week infusion schedule cohort, 168 days [range: {23, 181} days] in the 4-week infusion schedule cohort, and 163 days [range: {23, 181} days] overall.

Because these results are not included in the updated label, an information request was not sent to the applicant.

6.1.11.3 Subpopulation Analyses

Given that no acute SBI events occurred during the study, no subgroup analyses were performed for this endpoint.

6.1.11.4 Dropouts and/or Discontinuations

Two subjects discontinued the study early: Subject (b) (6) (3-week regimen) after 3 infusions, and Subject (b) (6) (4-week regimen) after 2 infusions. In both cases, the reason for early termination was an adverse event.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.5 Adverse Events of Special Interest (AESI)

The majority (87.5%) of the 16 subjects experienced at least one TEAE during the study, for a total of 56 TEAEs reported during the study.

Common TEAEs included: headache (31.3%), nausea, pyrexia (18.8% each), cough, COVID-19, epistaxis, nasal congestion, nasopharyngitis, otitis media, procedural headache, sinusitis, skin abrasion, and vomiting (12.5% each).
No severe TEAEs occurred during the study, and the majority (78.6%) of the TEAEs were mild in intensity. No thrombotic events and no events suggestive of hemolysis occurred during the study.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

There is no statistical issue for this submission. The collective evidence is based on Study ADMA-004 which was a Phase IV, multicenter, open-label study of ASCENIV administered as an intravenous infusion at 300-800 mg/kg every 21 or 28 days in approximately 12 pediatric subjects with Primary PIDD. The primary efficacy endpoint was the incidence of serious bacterial infection (SBI). SBIs encompass bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, or visceral abscess.

Sixteen pediatric subjects were included in this final report, 7 subjects were ages 2 to 6 years old, and 9 subjects were ages 7 to 11 years old at time of enrollment. No acute SBIs occurred during the observation period (average 157

days), yielding a mean number of acute SBI episodes per person-year of 0.0. No other serious infections, or hospitalizations due to infections occurred.

No deaths and no study treatment-related SAEs occurred during the study.

10.2 Conclusions and Recommendations

I conclude that ASCENIV is efficacious and safe for the intended expanded age group. I recommend approval of the indication in the expanded age group.