Application Type	Supplemental New Drug Application
Application Number(s)	NDA 50-684/S-096 NDA 50-750/S-043
Priority or Standard	Standard
Submit Date(s)	April 26, 2019
Received Date(s)	April 26, 2019
PDUFA Goal Date	May 26, 2020
Division/Office	DAI/OID
Review Completion Date	May 26, 2020
Established/Proper Name	Piperacillin and tazobactam
(Proposed) Trade Name	Zosyn
Pharmacologic Class	Extended Spectrum Penicillin
Applicant	Wyeth Pharmaceuticals, LLC
Dosage forms	For injection as powder for reconstitution in single dose and pharmacy bulk vials (NDA 50-684) For injection as solution in single-dose Galaxy containers (NDA 50-750)
Applicant proposed Dosing Regimen	N/A
Applicant Proposed Indication(s)/Population(s)	N/A
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	N/A
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of nosocomial pneumonia in pediatric patients 2 months of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	For pediatric patients 2 months to 9 months of age: 90 mg/kg (80 mg piperacillin/10 mg tazobactam) every 6 hours For pediatric patients older than 9 months of age: 112.5 mg/kg (100 mg piperacillin/12.5 mg tazobactam) every 6 hours

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Reviewers

Regulatory Project Manager	Naseya Minor, MPH
Clinical Reviewer	Rama Kapoor, MD
Statistical Reviewer	Daniel Rubin, PhD
Statistical Team Leader	Karen Higgins, ScD
Clinical Pharmacology Reviewer	Anthony Nicasio, PharmD
Clinical Pharmacology Team Leader	Seong Jang, PhD
Clinical and Cross-Disciplinary Team Leader	Edward Weinstein, MD, PhD
Division Director	Sumathi Nambiar, MD, MPH

Signatures See signature block in DARRTS

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Rama Kapoor, MD	OID/DAI	Sections: 1-3, 5-12	Select one: __X_ Authored ___ Approved
	Signature:			
Clinical Team Leader	Edward Weinstein, MD, PhD	OID/DAI	Sections: 1-3, 5-12	Select one: ___ Authored __X_ Approved
	Signature:			
Division Director (Clinical)	Sumathi Nambiar, MD, MPH	OID, DAI	Sections: 1 - 12	Select one: ___ Authored __X_ Approved
Statistical Reviewer	Daniel Rubin, PhD	OB/Division 4	Sections: 6	Select one: __X_ Authored ___ Approved
	Signature:			
Statistical Team Leader	Karen Higgins, ScD	OB/Division 4	Sections: 6	Select one: ___ Authored __X_ Approved

	Signature:			
	Signature:			
Clinical Pharmacology Reviewer	Anthony Nicasio, PharmD	OCP/DIDP	Sections: 4	Select one: __X_ Authored ___ Approved
	Signature:			
Clinical Pharmacology Team Leader	Seong Jang, PhD	OCP/DIDP	Sections: 4	Select one: ___ Authored __X_ Approved
	Signature:			

Glossary

AE	adverse event
AR	adverse reaction
CFR	Code of Federal Regulations
CRF	case report form
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ITT	intent to treat
mITT	modified intent to treat
NDA	new drug application
NP	nosocomial pneumonia
OPQ	Office of Pharmaceutical Quality
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
P/T	piperacillin and tazobactam
SAE	serious adverse event
SAP	statistical analysis plan
sNDA	supplemental new drug application
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Zosyn (piperacillin and tazobactam; P/T) is an intravenously administered fixed-dose combination antibacterial drug product composed of an extended-spectrum penicillin, piperacillin sodium, and a β-lactamase inhibitor, tazobactam sodium. It was initially approved for marketing in 1993 and is currently indicated for the treatment of complicated appendicits and peritonitis, skin and skin structure infections, female pelvic infections, community-acquired pneumonia, and nosocomial pneumonia (NP) in adult patients. In pediatric patients aged 2 months or older it is approved for the treatment of appendicits (complicated by rupture or abscess) and peritonitis. The objective of these supplemental NDAs (sNDAs) is to provide specific dosing recommendations for pediatric patients aged 2 months or older with NP and to review the available safety information to support the pediatric NP dosing recommendations.

Zosyn was approved for the treatment of NP in adults on May 8, 1996, with a dosing regimen of 3.375 g (3 g piperacillin, 0.375 g tazobactam) every 4 hours. Subsequently, NP dosing was revised (April 28, 2003) to 4 g/500 mg every 6 hours. No pediatric postmarketing requirements were issued because the approval occurred in the period of time after the suspension of the Pediatric Rule (October, 2002) and before PREA became law (December, 2003).

1.2. Conclusions on the Substantial Evidence of Effectiveness and Safety

The effectiveness of piperacillin/tazobactam for the treatment of NP in the pediatric population (2 months to <18 years of age) is based on extrapolation of efficacy from adequate and well-controlled studies in adult patients with NP and pharmacokinetic model-based approaches. Similar exposure in adult and pediatric populations is achieved with a dosing regimen of 90 mg/kg (80 mg piperacillin/10 mg tazobactam) every 6 hours in pediatric patients aged 2 to 9 months, and 112.5 mg/kg (100 mg piperacillin/12.5 mg tazobactam) every 6 hours in pediatric patients older than 9 months. The rationale for extrapolation of efficacy from adultsis based on the fact that the range of pathogens causing NP, the presentation and course of disease, as well as the anticipated response to antibacterial therapy are sufficiently similar in the pediatric and adult populations. A partial waiver was granted in 2008 for pediatric patients from birth to 3 months of age due to the rare occurrence and the impracticability of conducting an NP study in this age group.

The safety of piperacillin/tazobactam was evaluated in a retrospective study conducted by the Applicant with a primary objective to assess the relative rate of serious adverse events in patients treated with piperacillin/tazobactam for NP as compared to patients prescribed other antibacterial treatments for NP (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime,

cefepime, ciprofloxacin). The retrospective, case-controlled nature of the study has several important limitations. It does not have the advantage of prospective randomization to control for potential study confounders. It utilizes multiple piperacillin/tazobactam dosing regimens and multiple comparator antibacterial drugs. The serious adverse events reported in the study were prespecified; nevertheless, no significant safety signals were identified in the pediatric population in relation to any of the dosage regimens for the treatment of NP. Given that piperacillin/tazobactam has a long history of clinical use for NP in adults and pediatric patients (on and off label use, respectively), safety information from the published scientific literature was reviewed as well as postmarketing safety reports from both the Applicant and the FDA adverse event reporting system (FAERS). The totality of the data supports the overall conclusion that the safety profile of piperacillin/tazobactam in the pediatric population aged 2 months or older is similar to that of adults.

It is therefore concluded that these sNDAs provides sufficient evidence of effectiveness and safety of piperacillin/tazobactam for the treatment of NP at the recommended dosage in pediatric patients from 2 months to less than 18 years of age.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk assessment of the information provided in these sNDAs supports the approval of piperacillin/tazobactam (P/T) for the treatment of pediatric patients from 2 months to less than 18 years of age with NP. A partial waiver was granted for pediatric patients from birth to 3 months of age due to the rare occurrence and the impracticability of conducting an NP study in this age group. The development of a pediatric formulation was not necessary since piperacillin/tazobactam is administered intravenously.

Efficacy

A finding of efficacy for the treatment of NP in pediatric population (from 2 months to less than 18 years of age) is based on extrapolation of efficacy from adequate and well controlled studies in adult patients with NP and pharmacokinetic model-based analyses demonstrating similar drug exposure in adults and the pediatric population at a dose of 80 mg piperacillin/10 mg tazobactam/kg for children 2 to ≤9 months of age, and 100 mg piperacillin/12.5 mg tazobactam/kg for children >9 months (weighing up to 40 kg) administered IV every 6 hours.

Safety

The safety profile of piperacillin/tazobactam in the pediatric population with NP was evaluated in a retrospective comparative study (Study B2361001) in pediatric patients 2 months to <18 years of age. In this study, the piperacillin/tazobactam group was defined by receipt of at least one dose of piperacillin/tazobactam (80-100 mg/kg of piperacillin and 10-12.5 mg/kg tazobactam) every 6 hours, compared with patients treated with comparators (which included ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin) at a dose consistent with the respective product label for moderate to severe infections in pediatric patients. The primary study endpoint was the development of prespecified 'serious adverse events' within 40 days of treatment initiation, and all-cause mortality 30 days from the day of study drug initiation. The study included 412 pediatric patients from 7 hospitals across the US to assess safety and effectiveness of piperacillin/tazobactam in pediatric patients with NP. Of 412 patients included in the study, 407 (98.8%) patients who received treatment for NP were included in primary analysis set (PAS). Of 407 patients, 140 (34%) patients were treated with piperacillin/tazobactam, and 267 (65%) patients treated with comparators. Mean age of patients in the piperacillin/tazobactam and comparator group was 7.65 years and 6.57 years, respectively. Slightly more than half (55%) of the patients were males, and whites in both groups. Patients in the two groups were comparable with regards to the distribution of sex, race and other demographic and clinical characteristics. The proportion of infants (2 months to 9 months of age) were 21.4% (n=30) and 29.5% (n=110) in piperacillin/tazobactam and comparator group, respectively. Overall, the crude incidence rate per 100 person-days of serious adverse events was 1.27 [95% CI: 0.84-1.70] in the piperacillin/tazobactam group and

1.02 [95% CI: 0.76-1.28] in the comparator group. Further, sensitivity analysis showed no substantial difference in incidence rates per 100 person- days of all serious events in the two treatment groups for various treatment durations (i.e., at least 2 days of therapy, at least 5 days of therapy and at least 7 days of therapy).

Since the serious adverse events in Study B2361001 were prespecified, the published scientific literature and postmarketing adverse events reported to FAERS were reviewed from 1999 to present for the proposed dosing of piperacillin/tazobactam for NP. This supplemental review approach did not reveal any significant new safety signals across pediatric age groups.

The Zosyn prescribing information has been updated to include pediatric patients in the NP indication, study information was added to clinical trials experience in the adverse reactions section (6.1) and pediatric use subsection in the specific populations section (8.4). The retrospective study was not described in the clinical studies section of labeling since it was not designed to provide adequate and well-controlled efficacy information.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Nosocomial pneumonia (NP) is defined as pneumonia occurring at or beyond 48 hours after admission to hospital that was not present nor incubating at the time of admission. • The pediatric NP patient population is at risk for disease progression to respiratory failure, sepsis, and multi-organ failure and death.	• NP is often caused by pathogens with antibacterial drug resistance mechanisms such as beta-lactamases, which are associated with an increased risk of treatment failure and death.
Current Treatment Options	• There are currently limited approved treatment options for pediatric NP caused by Gram-negative bacteria.	• Drugs that are FDA-approved with Gram-negative activity for pediatric NP are cefepime, which is approved for 'severe pneumonia due to *P. aeruginosa*' in pediatric patients aged 2 months to 16 years; imipenem, approved for 'Lower respiratory tract infections' in pediatric patients from birth to <18 years; and ceftazidime for 'Lower respiratory tract

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		infections including those caused by *P. aeruginosa'*.
Benefit	• Antibacterial drugs approved for adult NP (HABP/VABP), including piperacillin/tazobactam, have been used off-label by the prescribers for the treatment of pediatric NP without labeled dosing recommendations. There is risk of treatment failure due to under-dosing, and conversely, increased risk of drug-related toxicities due to over-dosing. Therefore,there is a need of safe and effective dosing recommendations for pediatric NP. • Efficacy in the pediatric population is based on extrapolation of efficacy from adults and population pharmacokinetic (PK) modeling and simulations.	• Recommended pediatric dosing for NP is based upon extrapolation of efficacy from adults to pediatric patients with population pharmacokinetic (PK) modeling and simulations.
Risk and Risk Management	• Safety information to support the recommended dosing in pediatric patients aged 2 months or older is provided by a retrospective comparative study of pediatric patients receiving antibacterial drug for NP at multiple pediatric hospitals across the US, by evaluating serious events in patients treated with piperacillin/tazobactam compared to patients treated with other NP appropriate antibacterial drugs (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, ciprofloxacin). • Key safety concerns for piperacillin/tazobactam include hypersensitivity reactions, severe cutaneous adverse reactions, hematologic adverse reactions, seizures, and *C. difficile* associated diarrhea (CDAD), all of which appear as warnings in the current product labeling. • Routine postmarket safety monitoring has not revealed additional safety signals to date.	No unexpected safety signals were identified in the pediatric NP patient population. Labeling adequately informs the benefits and risks of piperacillin/tazobactam use. Postmarketing risk management activity should include standard postmarketing reporting of adverse drug experiences in pediatric population with NP.

1.4. Patient Experience Data

Patient experience data were not submitted as part of this application.

2 Therapeutic Context

2.1. Analysis of Condition

Nosocomial pneumonia (NP) is defined as pneumonia occurring at or beyond 48 hours after admission to hospital that was not present nor incubating at the time of admission.[1] Ventilator associated bacterial pneumonia (VABP) is a type of NP that develops in mechanically ventilated patients later than 48 hours after intubation. Overall, NP accounts for 10 to 15% of all nosocomial infections in children,[2] with mortality ranging from 20 to 70% depending on the organism and underlying illness.[3] Risk factors for NP in children are similar to those in adult patients and include intubation, prolonged hospitalization, underlying illnesses, immunosuppression, or recent antimicrobial therapy.

Children in pediatric intensive care units (PICUs) have a higher incidence of NP than those in general wards.[4] Neonatal NP encompasses only infections that are truly hospital-acquired during neonatal period and, therefore, excludes pneumonia acquired by mother-to-child transmission. Nosocomial infections in the neonatal nursery are uncommon.

A number of bacteria, viruses, and fungi cause NP in children; however, Gram-negative bacilli predominate and are associated with a mortality rate of around 50%.[2] The organisms cultured from lower respiratory tract specimens from neonates, infants, and children that are presumed to cause NP are similar to those cultured from specimens from adults. *E. coli, K. pneumoniae* and *P. aeruginosa* are the most common gram-negative isolates, comprising up to 73% of all isolates.[4] Other Gram-negative bacilli implicated in NP include *Acinetobacter*, *Serratia*, and *Proteus species*. The type and antimicrobial resistance of pathogens causing NP depends on the local prevalence and susceptibility patterns, which differ according to specific regions,

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[1] Craven DE, Steger KA. Hospital-acquired pneumonia: perspectives for the healthcare epidemiologist. Infect Control Hosp Epidemiol 1997; 88 (11): 783-95
[2] Jacobs RF. Nosocomial pneumonia in children. Infection 1991; 19 (2): 64-72
[3] Stein F, Trevino R. Nosocomial infections in the pediatric intensive care unit. Paediatr Clin North Am 1994; 41 (6): 1245-57
[4] Tullu MS, Deshmukh CT, Baveja SM. Bacterial nosocomial pneumonia in paediatric intensive care unit. J Postgrad Med 2000; 46 (1): 18-22

institutions, and units. *S. aureus*, including methicillin- resistant strains, has been documented to be the most common gram-positive isolate.

2.2. Analysis of Current Treatment Options

Early initiation of appropriate empiric therapy is essential to reduce morbidity and mortality from NP. Empiric therapy should cover the likely causative pathogens. General principles for empiric treatment of NP include the use of antibacterial drugs directed against the common nosocomial pathogens, and modification once a specific organism is identified. In general, for children in an ICU or immunosuppressed patients, empiric therapy should provide Gram-negative coverage against *P. aeruginosa* as this is a common cause of NP and associated with a high mortality. Anti-pseudomonal coverage is also effective against most other aerobic Gram-negative pathogens responsible for NP.

Drugs that are FDA-approved with Gram-negative activity are cefepime, which is approved for 'severe pneumonia due to *P. aeruginosa*' in pediatric patients aged 2 months to 16 years; imipenem, approved for 'Lower respiratory tract infections' in pediatric patients from birth to <18 years; and ceftazidime for 'Lower respiratory tract infections including those caused by *P. aeruginosa'.*

3 Regulatory Background

Nosocomial Pneumonia (NP)

Zosyn (piperacillin/tazobactam) was approved for the indication of treatment of NP on May 8, 1996, for adults in the United States at a dose of 3.375 g (3 g piperacillin, 0.375 g tazobactam) given every 4 hours at a total daily dose of 18 g piperacillin and 2.25 g tazobactam. On April 28, 2003, a revised dose of piperacillin/tazobactam (4 g/500 mg) given every 6 hours, at a total daily dose of 16 g of piperacillin and 2 g of tazobactam was approved for adult patients with NP (NDA 50-684/S-033).

3.1. Pediatric Regulatory History

A summary of regulatory history relevant to these sNDAs is summarized in the Table 1 below.

Table 1 Regulatory History

Year	Description of Events
1993	Original approval of Zosyn in the United States on October 22, 1993 for adults with moderate to severe infections caused by piperacillin-resistant, piperacillin/tazobactam-susceptible, β-lactamase producing strains of the microorganisms in the following conditions: • Intraabdominal infections (Appendicitis complicated by rupture or abscess and peritonitis) • Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections • Postpartum endometritis or pelvic inflammatory disease • Community-acquired pneumonia (moderate severity only)
1996	Zosyn approved for adults for the treatment of nosocomial pneumonia on May 8, 1996, at a dose of 3.375 g (3 g piperacillin, 0.375 g tazobactam) given every 4 hours, a total daily dose of 18 g piperacillin and 2.25 g tazobactam. No pediatric studies were required at the time of approval in 1996.
2003	On April 28, 2003, a revised dose of piperacillin/tazobactam (4 g/500 mg) given every 6 hours, at a total daily dose of 16 g of piperacillin and 2 g of tazobactam was approved for adult patients with NP. No pediatric post-marketing requirements were issued because the approval occurred in the period of time after the suspension of the Pediatric Rule (October, 2002) and before PREA became law (December, 2003). The sponsor was asked to submit a pediatric plan and conduct the appropriate pediatric studies to provide information on the safe and effective use of Zosyn in the relevant pediatric populations.
2005	On June 21, 2005, [redacted] (b) (6) PREA triggered study in pediatric patients for the treatment of NP.
2006	In July 27, 2006, Zosyn was approved for the pediatric indication of treatment of appendicits (complicated by rupture or abscess) and peritonitis in children from 2 months to less than 18 years of age.
2008	On January 25, 2008, [redacted] (b) (6), a partial waiver was granted for pediatric patients from birth to 3 months of age for the treatment of NP.
2009	On October 21, 2009, sponsor submitted a request for Special Protocol Assessment (SPA) for the retrospective clinical study protocol entitled, "*Safety and Effectiveness of Piperacillin/Tazobactam (Zosyn) in the Treatment of Pediatric Hospital Acquired Pneumonia: A Retrospective Cohort Study*". On December 4, 2009, a 'No Agreement Letter' was issued.
2011	A Type A meeting was scheduled for December 19, 2011 to discuss study requirements. Preliminary comments were provided and the meeting was cancelled.
2012	A second meeting was requested, to discuss the December 15, 2011 comments; this was held as a teleconference on March 26, 2012. The record of the meeting is dated April 12, 2012.
2014	A study protocol, amended was submitted December 18, 2014.
2015	A December 11, 2015 submission states that the study started March 2, 2015 with an end date of September 28, 2017.

Source: FDA Clinical Reviewer; DARRTS

4 Clinical Pharmacology

4.1. Executive Summary

No new clinical pharmacology studies were submitted in this application for the proposed dosing regimen. The proposed dosing regimen for pediatric nosocomial pneumonia were evaluated based on the information and data submitted in the original approved pediatric efficacy supplement for complicated appendicitis and peritonitis (NDA50684/S-046). The Office of Clinical Pharmacology (OCP) review team on July 16, 2009 accepted the proposed piperacillin/tazobactam dose regimens for pediatric patients with nosocomial pneumonia. The modeling and simulation data based on available pharmacokinetic demonstrated comparable systemic concentration-time profiles above minimum inhibitory concentration (MIC) to the adult dosing regimen for nosocomial pneumonia. Please refer to OCP 2009 review by Dr. Pravin Jadhav for additional information.

4.2. Summary of Clinical Pharmacology Assessment

There are no original clinical pharmacology studies conducted to assess the pharmacokinetics of piperacillin/tazobactam in pediatric patients with nosocomial pneumonia. The pediatric dosing regimens for nosocomial pneumonia of 80/10 mg/kg (2 to ≤9 months old) and 100/12.5 mg/kg (>9 months old, weighing up 40 kg) every six hours infused over 30 minutes were deemed acceptable by the OCP (Pharmacometric reviewer, Dr. Pravin Jadhav) in July 16, 2009.

Briefly, pharmacokinetic noncompartmental analyses from piperacillin/tazobactam prescribing information and OCP review (Clinical Pharmacology reviewer, Dr. Jeffrey Tworzyanski) datedJuly 26, 2006 of NDA50684/S-046 were used to compare pharmacokinetic parameters of pediatrics (2-5 months and 6 to 23 months) at 50/6.25 mg/kg and 100/12.5 mg/kg to the adult dose of 4.5 g. At doses of 100/12.5 mg/kg, the mean [CV%] Cmax and AUC for pediatrics 6 to 23 month old were both comparable to the adult Cmax and AUC at ~15% increase (344 [35] vs. 298 [34] µg/mL and 373 [42] vs. 322 [40] µg·h/mL). In pediatrics 2-5 months at 100/12.5 mg/kg, the Cmax and AUC were ~30% higher (382 [43] vs. 298 [34] µg/mL) and 67% higher (539 [63] vs. 322 [40] µg·h/mL).

Next, population pharmacokinetics modeling were used to perform simulations of steady-state piperacillin concentration-time profiles for 3 dosing regimens (80/10, 100/12.5, and 120/15 mg/kg) over 30 min infusions. Based on the systemic concentration-time simulations of the pediatric doses, dose regimens of 80/10 mg/kg and 100/12.5 mg/kg achieved comparable time above MIC as adults receiving 4.5 g every 6 hours over a 30-minute infusion. Thus, the pediatric dosing regimens for the ≤9 month of age and >9 months of age were considered acceptable at 80/10 mg/kg every 6 hours over a 30 minute infusion and 100/12.5 mg/kg every 6 hours over a 30 minute infusion, respectively.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The submission included a single clinical study, Study B2361001, which is briefly summarized in the table below (Table 2) and will be described in more detail in Section 6.

Table 2 Table of Clinical Study

Protocol number	Primary objective	Treatment groups and sample sizes in the Primary Analysis Set	Design
B2361001	To estimate the risk of serious events, including mortality, among pediatric patients with hospital-acquired pneumonia in the United States treated with piperacillin/tazobactam compared with other appropriate antibacterial drugs	Piperacillin/tazobactam: n = 140 patients Comparator group: n = 267 patients	Retrospective cohort study of patients aged 2 months to <18 years. Hospital-acquired pneumonia patients from 2003-2016 were identified from the Pediatric Health Information Systems database. Diagnoses and outcome assessments were performed through blinded chart reviews.

Source: B2361001 Final Study Report.

5.2. Review Strategy

Efficacy for nosocomial pneumonia in pediatric patients is extrapolated from efficacy in adults. Therefore, this review was mainly conducted to focus on the safety of piperacillin/tazobactam in pediatrics.

Patient-level datasets were not initially submitted with these sNDAs, but were provided following a request to the applicant. Other materials reviewed included the protocol and statistical analysis plan.

The statistical reviewer was mainly responsible for assessing the information on efficacy while the clinical reviewer was mainly responsible for assessing safety. However, because this was a non-randomized study, the statistical reviewer additionally provided assessments on regression adjustments for potential confounders that were used for both efficacy and safety analyses.

6 Statistical and Clinical Evaluation

6.1. Review of Relevant Individual Trials Used to Support Efficacy

6.1.1. Study Plan for Study B2361001

Study Design

Study B2361001 was a retrospective cohort study of pediatric patients who received piperacillin/tazobactam (will be referred as P/T hereon) or comparator antibacterial drugs for the treatment of nosocomial pneumonia. Patients were initially identified from the Pediatric Health Information system (PHIS), which is an administrative database for pediatric hospitals in the United States.

Patients were identified in two steps. In Step I, the PHIS database was screened for patients based on the following criteria:

- Hospital admission between January 1, 2003 and June 30, 2016
- Aged between 2 months and <18 years at the time of hospital admission
- Presence of at least one ICD-9 discharge code consistent with bacterial pneumonia
- Received at least one dose of piperacillin/tazobactam or a comparator antibacterial drug appropriate for hospital-acquired pneumonia during the hospitalization

Patients were excluded during this initial database screening for any of the following reasons:

- Received an antibacterial drug consistent with the treatment of community-acquired pneumonia during the first two days of hospitalization
- Had a diagnosis of cystic fibrosis
- Were treated with two NP antibacterial drugs simultaneously within one day
- Received piperacillin/tazobactam or comparator antibacterial drugs for other infection(s) during the admission or before the NP diagnosis
- Had missing pharmacy data in the PHIS

In Step II of patient identification, the medical chart was reviewed for each potential case to confirm that inclusion/exclusion criteria in Step I were met.

The following data were collected from medical charts in the pre-diagnosis and post-diagnosis period, when available, for patients diagnosed with hospital-acquired pneumonia:

- Date of birth
- Date of diagnosis
- Sex
- Race
- Ethnicity

- Pre-existing medical conditions as reported in admission notes by medical system (e.g., central nervous system, cardiovascular, respiratory, renal, hepatic, gastrointestinal, hematological)
- Presence of co-infectious processes at time of diagnosis
- The floor or hospital unit prior to NP diagnosis (e.g., oncology, pediatric intensive care unit, neonatal intensive care unit, cardiac intensive care unit)
- Laboratory results (e.g., complete blood count, metabolic panels, liver function tests)
- Imaging results (e.g., chest radiography)
- Dosage and duration of use (i.e., #of days) for P/T and comparator antibacterial drugs administered during the study period.
- Comprehensive list and duration of use of all other enteral, intravenous, and inhaled medications
- Admission and discharge dates from ICUs
- Use of mechanical ventilator, including start and stop dates
- Endotracheal intubation, including start and stop dates
- Tracheostomy, including start and stop dates
- Results from respiratory or sputum cultures taken within 24 hours of NP diagnosis
- Vital status at end of 30-days (if unknown, the National Death Index was to be queried)
- Date of death
- Clinical impression of the patient (pertinent to treatment effectiveness) at 14 days by the physician of record
- Discharge location at the end of the study period (up to 40 days from NP diagnosis/treatment initiation)

Although the PHIS database contained information on patient identification, demographics, dates of admission and discharge, and codes for diagnoses/procedures/discharges, the database did not contain information on daily physical exams, medication, and daily physician impressions or patient management. Therefore, hospitals were invited to participate and provide such information upon Institutional Review Board approval. For participating sites, chart reviews were performed by trained data abstractors and research personnel. The data abstractors produced structured case report forms. For recording serious events the study physicians were blinded to antibacterial treatment when reviewing abstracted data.

The Full Analysis Set (FAS) was defined as any patient who received antibacterial drugs at any dose for the treatment of NP. The P/T group was comprised of patients who received this drug as the first antibacterial treatment for NP. The comparator group was comprised of patients who received other antibacterials appropriate for NP including ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin. The carbapenem group was defined as the subset of the comparator group that received a carbapenem as the first antibacterial for NP.

The Primary Analysis Set (PAS) was comprised of patients from the FAS whose first dose of an

antibacterial drug for treatment of NP was appropriate for the disease (hospital acquired or nosocomial pneumonia). For the P/T group this was defined by receipt of at least one dose of 80-100 mg/kg of piperacillin and 10-12.5 mg/kg tazobactam every 6 hours; and for comparator drugs this was defined by doses consistent with the respective product labels indicated for moderate to severe infections in pediatric patients. As will be discussed in the next subsection, almost all patients in the FAS were included in the PAS, and thus this review focuses on the PAS.

The index date for each patient (i.e., Day 1) was the date of NP treatment initation. The follow-up time for a patient outcome measured person-time at risk, and was defined separately for the analysis of mortality outcomes and other outcomes. For all-cause mortality the follow-up time was censored at 30 days. For other outcomes the follow-up time was censored by death, discharge from the hospital, or 40 days from treatment initiation.

Study Endpoints

The primary endpoint in this study was the safety endpoint of "serious events" within 40 days of treatment initiation for NP. Serious events were defined as follows in the italicized text from statistical analysis plan. Worsening of pre-existing conditions was to be counted as a serious event if it met any of these criteria. For each patient the primary endpoint was the number of serious events, but multiple episodes of a specific type of serious event were only counted once.

A serious event is defined as any untoward medical occurrence in patients taking P/T or comparator NP appropriate antibacterials that results in death, is life-threatening, requires prolongation of hospitalization, or results in persistent or significant disability/incapacity.

The following serious events in pediatric NP patients treated with P/T or comparator NP appropriate antibacterials (irrespective of 'causal' relationship to therapy) have been reported in clinical studies and post-marking data, and therefore will be specifically focused upon:

- *Central nervous system (CNS)/neurologic: seizure*
- *Gastrointestinal: cholestatic jaundice, hepatoxicity, hepatitis*
- *Hematologic: hemolytic anemia, thrombocytosis, agranulocytosis, pancytopenia*
- *Immune: anaphylactic/anaphylactoid reactions (including shock)*
- *Infection: sepsis, super-infectious, C. difficile infection*
- *Skin and appendages: erythema multiforme, Stevens-Johnson Syndrome*
- *Renal: interstitial nephritis, renal failure*

In addition to serious events, the statistical analysis plan specified that all-cause mortality would be analyzed through 30 days after initiation of treatment. Vital status was captured both by reviewing medical charts and querying the National Death Index (NDI) for matching patient records.

A secondary endpoint in this study was effectiveness of antibacterial therapy. Each patient was classified as "clinically improved" or "clinically did not improve." This endpoint was assessed in

two steps. First, a clinical research nurse would review daily progress notes of the treating physician through up to 14 days after NP treatment initiation to consider whether the physician considered the patient to be clinically improved or not improved, and record one of these two outcomes. Second, a study physician blinded to antibacterial use would review abstracted data (including a data abstractor's assessment of physician notes and other data such as x-rays or laboratory results) to make a final classification of each patient as having clinically improved or not having clinically improved.

Statistical Analysis Plan

The planned sample size in this study was 150 patients in the P/T group and 300 patients in the comparator group. The sample size was chosen based on anticipated width of confidence intervals for comparing event rates, and this study was not based on powering for formal statistical hypothesis testing. Because this was a non-randomized study, adjustment for confounding was needed when attempting to estimate causal effects of P/T. The statistical analysis plan (SAP) specified that a Poisson regression model would be fit to examine serious events. The model was to have an offset for person-time at risk and use a robust variance estimate. Results were to be presented by treatment group for the total number of events, cumulative person-time at risk, the model adjusted event rate per 1,000 person years with the corresponding 95% confidence interval, and the model adjusted incidence rate ratio with corresponding 95% confidence interval.

Reviewer's Comment: The SAP did not provide complete details regarding which covariates would be used for regression modeling. Instead the analysis plan was somewhat noncommittal in that Section 7.3 in SAP stated "Variables that could be associated with the outcome will be evaluated for inclusion in the final analytic models as covariates. Example covariates include: age, gender; co-morbid conditions at the time of NP diagnosis; acuity of illness at the start of NP therapy (e.g., presence in the ICU, need for mechanical ventilation etc.); study center."
The SAP also stated that a negative binomial regression model would be fit for sensitivity analysis, and would use similar model terms as the Poisson regression. This model allows for regression of count outcomes with overdispersion or underdispersion (i.e., different conditional means and variances).

All-cause mortality was to be descriptively compared between treatment groups without regression adjustments.

For the secondary objective of examining efficacy, logistic regression was to be used to control for confounding because the outcome was binary ("clinically improved" or "clinically did not improve"). According to the statistical analysis plan, the model terms were to be the same as used in the Poisson regression analysis of serious events. The statistical analysis plan further stated that a model adjusted odds ratio and associated 95% confidence interval would be reported for the association between piperacillin/tazobactam and the clinical improvement outcome.

Reviewer's Comment: The Study Report departed from the SAP in several respects. One post-hoc analysis change from the applicant was that the Poisson, negative binomial, and logistic regression models described above were fit with inverse probability of treatment weights (i.e., inverse propensity score weights). The applicant stated that weighting was a preferable way of adjusting for a large number of potential confounders than including all of them in a multivariate regression model.

Propensity scores were constructed using a logistic regression of treatment group on the following baseline covariates: age, race/ethnicity, hospitalized within 30-days prior to NP admission, cardiovascular comorbid condition, respiratory comorbid condition, other congential or metabolic defect, required a tracheostomy or endotracheal intubation prior to NP admission, leukopenia, anemia, high creatinine, number of days in the ICU prior to admission, other bacterial co-infection at the time of NP diagnosis, at least one positive respiratory or sputum culture within 24 hours of NP admission, vecuronium use, vancomycin use, and aminoglycoside use. Once propensity scores were formed based on these covariates, the sponsor fit the previously described Poisson, negative binomial, and logistic regression models with inverse weighting by the propensity scores. In each case three sets of models were fit: (i) an unadjusted regression of the outcome on treatment with no weighting; (ii) a regression of the outcome on treatment with inverse propensity score weighting; (iii) a regression of the outcome on treatment and study site with inverse propensity score weighting.

The Study Report additionally presented post-hoc results from random effect models that included study site as a random effect. This was done due to the extreme imbalance between treatment groups in some participating hospitals.

The SAP stated that missing data were not to be imputed. The applicant stated that the only deviation from this in Study Report was that 9 patients had their number of Intensive Care Unit (ICU) days imputed using means from the entire sample so that they were not dropped from regression models.

In the Study Report the applicant described a new measure called the E-value that attempted to quantify the degree of unmeasured confounding that would need to exist to move point estimates for measured rate ratios to values of 1 (the null value representing no association between the treatment and outcome) and 1.25 (which the applicant called an arbitrary value of positive association between the treatment and outcome). This measure does not appear to have been previously discussed in the statistical literature and its properties are not well characterized.

After the Study Report was submitted the applicant notified the Agency that a single patient in the P/T had the treatment group misclassified and should have been in the comparator group. Summaries in this review are based on the corrected treatment group labels except where otherwise noted.

General comments on the statistical analysis will be summarized in Section 6.3 of this review.

Protocol Amendments

The study protocol was amended 4 times. The first amendment incorporated FDA feedback and primarily dealt with inclusion/exclusion criteria and sample size. The main changes to the second amendment were updated case report forms based on lessons from a pilot study. The third and fourth amendments were implemented to increase enrollment by expanding the study period and allowing local site staff to abstract data at additional study sites.

6.1.2. Study Results for Study B2361001

Compliance with Good Clinical Practices

This retrospective study did not raise any concerns with good clinical practice standards. Informed consent was not required for this study because data were used from existing medical charts, which were de-identified. Institutional review boards approved the protocol and amendments at each participating study site.

Patient Disposition

The flowcharts below display Step I and Step II of patient screening. Of the almost 300,000 patients initially identified from the Pediatric Health Information System database, approximately 1,900 had medical charts reviewed in Step II. A total of 407 patients were included in the Primary Analysis based on the previously described inclusion and exclusion criteria. Of these 407 patients in the Primary Analysis Set, there were 141 patients in the P/T group and 266 patients in the comparator group. The sample size in the Primary Analysis Set was slightly less than the sample size of 150 P/T patients and 300 comparator patients that had been specified in the statistical analysis plan.

Reviewer's Comment: Of note, only 5 patients (all in the comparator group) were excluded from the Full Analysis Set superset of the Primary Analysis Set. Recall that the Full Analysis Set was based on receipt of antibacterial drugs at any dose rather than dosing considered appropriate for hospital-acquired pneumonia. Because such a limited number of patients were excluded, only the Primary Analysis Set rather than the Full Analysis Set will be emphasized in this review.

Figure 1: Step I of Pediatric Health Information System (PHIS) database screening to identify patients with potential nosocomial pneumonia admitted to pediatric hospitals across the United States between 2003 and 2016

Inclusions: a patient had to meet all of the following in order to be included in the initial PHIS screening cohort

- Admission to PHIS hospitals between January 1, 2003 and June 30, 2016
- Aged between 2 months and 18 years at the time of hospital admission
- Presence of any discharge ICD 9 CM code consistent with bacterial pneumonia

• Receipt of at least one dose of piperacillin/tazobactam or other hospital-acquired pneumonia appropriate antibacterials during hospitalization
↓
n = 289,185 patients identified from 43 PHIS sites
Exclusions: A patient had to not meet any of the following criteria to be included in the PHIS screening cohort • Claim for an antibacterial consistent with community acquired pneumonia • Diagnosis of cystic fibrosis • Initiation of hospital-acquired pneumonia therapy with two appropriate antibacterials simultaneously (within 1 day) • Receipt of piperacillin/tazobactam of comparator antibacterials for other infection(s) prior to the diagnosis of hospital-acquired pneumonia • Hospital was not asked or did not agree to participate in the study
↓
n = 1,899 patients remained from 7 PHIS sites
↓
Proceed to Step II to review medical charts and confirm diagnoses

Source: Source: B2361001 Final Study Report, Figure 1.

Figure 2: Step II of review of medical chart to confirm the diagnosis of hospital-acquired pneumonia in pediatric patients admitted across the United States between 2003 and 2016

n = 1,899 identified from Step 1
Was the full chart able to be located?
↓
Yes (n = 1,464 patients)
Confirm from the admission notes that bacterial pneumonia was absent at admission
↓
Yes (n = 1,223 patients)
Confirm the patient did not have cystic fibrosis on an admission note or progress note prior to the hospital-acquired pneumonia diagnosis
↓
Yes (n = 1,222 patients)
Confirm administration of at least one dose of piperacillin/tazobactam or other hospital-acquired pneumonia appropriate antibacterial within one day of pneumonia diagnosis
↓
Yes (n = 1,088 patients)
Confirm diagnosis of pneumonia at any point after the first two days of hospitalization
↓
Yes (n = 1,001 patients)

Confirm the patient was started on only one hospital-acquired pneumonia appropriate antibacterial at the same time
↓
Yes (n = 859 patients)
Confirm that the patient did not receive piperacillin/tazobactam or comparator antibacterials for other infection(s) prior to the diagnosis of hospital-acquired pneumonia
↓
Yes (n = 412 patients)
Full Analysis Set: proceed to full patient chart abstraction • n = 412 total patients • n = 140 in the piperacillin/tazobactam group • n = 272 patients in the comparator group
Exclude patients who were not treated with hospital-acquired pneumonia dosing
↓
Primary Analysis Set: • n = 407 total patients • n = 140 in the piperacillin/tazobactam group • n = 267 patients in the comparator group

Source: Source: B2361001 Final Study Report, Figure 2.

The following table (Table 3) displays antibacterial drugs used in the various treatment groups. The most common drug in the comparator group was cefepime and was given for treatment in approximately one third of patients. Ceftazidime, ticarcillin/clavulanate, and meropenem were each given to approximately one fifth of patients in the comparator group. Patients treated with meropenem comprised almost the entirety of the carbapenem subset of the comparator group.

Table 3 Antibacterial drugs for hospital-acquired pneumonia by treatment group (PAS)

	P/T Group (n = 140) n (%)	Comparator Group (n = 267) n (%)	Comparator Subset: Carbapenem Group (n = 57) n (%)
Piperacillin/tazobactam	140 (100.0)		
Cefepime		92 (34.5)	
Ceftazidime		55 (20.6)	
Ticarcillin/clavulanate		50 (18.7)	
Ciprofloxacin		13 (4.9)	
Meropenem		56 (21.0)	56 (98.2)
Imipenem		1 (0.4)	1 (1.8)

Abbreviation: P/T = piperacillin/tazobactam.

Note: Antibacterial drug assignment in this study and above table were based on the initial therapy for nosocomial pneumonia. If a patient received 2 days of P/T and then discontinued to receive meropenem, the patient would be assigned to the P/T group and all documented serious events would be counted toward this group rather than the comparator group or carbapenem subset. The table corrects for one subject in the Study Report whose treatment group was mislabeled.
Source: B2361001 Final Study Report Amendment, Summary of Changes, Table 2.1.1.

Protocol Violations/Deviations

Protocol violations were not an issue in this retrospective study because decisions regarding patient management and data recording were made before the protocol was written.

Demographic Characteristics

The table below (Table 4) displays demographic characteristics by treatment group. There were no major differences between the P/T group and comparator group in terms of age, sex, or race. However, one possible source of confounding was the extreme imbalance between treatment groups in participating study sites. For example, all 44 patients from Rady Children's Hospital in San Diego were in the comparator group while all 36 patients from Columbia University Medical Center in New York were in the P/T group. Study site differences may have confounded results if different hospitals served different populations, and if these differences were too complex to be captured by measured covariates.

Table 4 Patient demographic characteristics by treatment group (PAS)

Characteristic	P/T Group (n = 140) n (%)	Comparator Group (n = 267) n (%)	Comparator Subset: Carbapenem Group (n = 57) n (%)
Age at NP diagnosis			
Infant (2 months to <2 years)	47 (33.6)	110 (41.2)	24 (42.1)
Child (2 to <12 years)	47 (33.6)	88 (33.0)	17 (29.8)
Adolescent (12 to <16 years)	25 (17.9)	44 (16.5)	10 (17.5)
≥16 years	21 (15.0)	25 (9.4)	6 (10.5)
Sex			
Male	81 (57.9)	148 (55.4)	33 (57.9)
Female	59 (42.1)	119 (44.5)	24 (42.1)
Race			
White or Caucasian	66 (47.1)	129 (48.3)	27 (47.4)
Black or African American	41 (29.3)	92 (34.5)	22 (38.6)
Latino	8 (5.7)	5 (1.9)	1 (1.8)
Asian	2 (1.4)	4 (1.5)	2 (3.5)

Other	2 (1.4)	25 (9.4)	4 (7.0)
Unknown	21 (15.0)	12 (4.5)	1 (1.8)
Participating site			
Children's Hospital of Philadelphia	7 (5.0)	68 (25.5)	1 (1.8)
Randy Children's Hospital, San Diego, CA	0 (0.0)	44 (16.5)	13 (23.8)
Children's National Medical Center, Washington, DC	16 (11.4)	55 (20.6)	7 (12.3)
Columbia University Medical Center, New York, NY	36 (25.7)	0 (0.0)	0 (0.0)
Cincinnati Children's Hospital Medical Center	43 (30.7)	10 (3.7)	3 (5.3)
St. Louis Children's Hospital	2 (1.4)	43 (16.1)	1 (1.8)
Children's Healthcare of Atlanta	36 (25.7)	47 (17.6)	32 (56.1)

Abbreviations: P/T = piperacillin/tazobactam, NP = hospital-acquired pneumonia.
Note: The table corrects for one subject in the Study Report whose treatment group was mislabeled.
Source: B2361001 Final Study Report Amendment, Summary of Changes, Table 4.1.1.

Other Baseline Characteristics

The following table (Table 5) displays clinical data before admission for each treatment group. There were no obvious differences between the groups in terms of inpatient/outpatient status or comorbidities by body system. The P/T group had a numerically lower rate of hospitalization within the prior 30 days and a numerically lower rate of ventilator dependence than the comparator group.

Table 5 Clinical data prior to admission by treatment group (PAS)

Characteristic	P/T Group (n = 140) n (%)	Comparator Group (n = 267) n (%)	Comparator Subset: Carbapenem Group (n = 57) n (%)
Patient location prior to study institution			
Another facility/inpatient	35 (25.0)	82 (30.7)	18 (31.6)
Outpatient	101 (72.1)	182 (68.2)	38 (66.7)
Unknown	4 (2.9)	3 (1.1)	1 (1.8)
Hospitalized within last 30 days prior to this admission			
Yes	35 (25.0)	92 (34.5)	21 (36.8)
No	89 (63.6)	136 (50.9)	26 (45.6)
Unknown	16 (11.4)	39 (14.6)	10 (17.5)
Tracheostomy prior			
Yes	12 (8.6)	24 (9.0)	3 (5.3)
No	128 (91.4)	242 (90.6)	53 (93.0)
Unknown	0 (0.0)	1 (0.4)	1 (1.8)
Ventilator dependent			
Yes	17 (12.1)	48 (18.0)	11 (19.3)
No	119 (85.0)	214 (80.1)	44 (77.2)

Unknown	4 (2.9)	5 (1.9)	2 (3.5)
Comorbidity by system			
Neurologic/CNS	56 (40.0)	111 (41.6)	20 (35.1)
Cardiovascular	52 (37.1)	81 (30.3)	16 (28.1)
Respiratory	37 (26.4)	89 (33.3)	17 (29.8)
Renal	9 (6.4)	23 (8.6)	6 (10.5)
Gastrointestinal	34 (24.3)	54 (20.2)	12 (21.1)
Hematological and immunodeficiency	10 (7.1)	9 (3.4)	2 (3.5)
Metabolic disease	7 (5.0)	14 (5.2)	0 (0.0)
Other congenital or metabolic defect	31 (22.1)	50 (18.7)	8 (14.0)
Malignancy	13 (9.3)	23 (8.6)	6 (10.5)
Rheumatologic	3 (2.1)	1 (0.4)	0 (0.0)

Abbreviations: P/T = piperacillin/tazobactam, CNS = central nervous system.
Note: The table corrects for one subject in the Study Report whose treatment group was mislabeled.
Source: B2361001 Final Study Report, Table 4.1.2.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The duration of therapy in each treatment group with the initial NP antibacterial drug is summarized in the table below. Almost all patients received antibacterial therapy for NP for at least 2 days. The majority of patients received at least one week of therapy, and therapy durations appeared somewhat shorter in the P/T group than the comparator group (Table 6).

Table 6 Duration of antibacterial therapy for nosocomial pneumonia (PAS)

Therapy duration	P/T Group (n = 140) n %	Comparator Group (n = 267) n %	Comparator Subset: Carbapenem Group (n = 57) n %
At least 2 days	137 (97.9)	267 (100.0)	57 (100.0)
At least 5 days	118 (84.3)	256 (95.9)	57 (100.0)
At least 7 days	101 (72.1)	234 (87.6)	51 (89.5)

Abbreviations: P/T = piperacillin/tazobactam.
Note: The table corrects for one subject in the study report whose treatment group was mislabeled.
Source: FDA Statistical reviewer and B2361001 Final Study Report, Table 6.1.1.

The next table (Table 7) displays concomitant antibacterial drugs used from 1 day after NP diagnosis through discharge or the end of the 40-day follow-up period. Approximately one of every four patients in each treatment group received concomitant vancomycin and approximately one of every 6 patients in each treatment group received concomitant aminoglycosides. The protocol did not distinguish concomitant therapy from rescue therapy, and rescue therapy was instead presumably incorporated into the efficacy analysis of clinical improvement.

Table 7 Concomitant medications 1 day after diagnosis through discharge or the end of 40-day follow-up (PAS)

	P/T Group (n = 140) n %	Comparator Group (n = 267) n %	Comparator Subset: Carbapenem Group (n = 57) n %
Vancomycin	39 (27.9)	67 (25.1)	15 (26.3)
Vecuronium	8 (5.7)	32 (12.0)	5 (8.8)
Methotrexate	0 (0.00)	5 (1.9)	2 (3.5)
Aminoglycosides	20 (14.3)	38 (14.2)	7 (12.3)

Abbreviations: P/T = piperacillin/tazobactam.
Note: The table corrects for one subject in the study report whose treatment group was mislabeled.
Source: Statistical reviewer and B2361001 Final Study Report, Table 4.1.7.

Data Quality and Integrity

Patient level datasets were not initially included in this application, and were requested from the applicant. Datasets were then provided by the applicant in a nonstandard format. In general, it was possible to perform analyses without complex manipulations.

Efficacy Results – Primary Endpoint

There was no primary efficacy endpoint in this study because the primary objective was to assess the risk of serious adverse events.

Efficacy Results – Secondary and other relevant endpoints

The table below (Table 8) shows rates at which patients in different treatment groups were categorized as "clinically improved" at or before 14 days from the start of NP therapy. The rate of improvement was approximately 90% in both the P/T group and the comparator group. Clinical improvement occurred at a slightly less common rate of 84% in the carbapenem subset of the comparator group, but this may have reflected a sicker patient population treated with carbapenems.

Table 8 Patients categorized as "clinically improved" at or before 14 days from the start of NP therapy (PAS)

P/T Group (n = 140) n %	Comparator Group (n = 267) n %	Comparator Subset: Carbapenem Group (n = 57) n %
127/140 (90.7)	245/267 (91.8)	48/57 (84.2)

Source: Statistical reviewer and B2361001 Final Study Report, Table 7.

The subsequent table (Table 9) displays clinical improvement rates by baseline characteristics.

Across subgroups defined by age, sex, race, or duration of hospitalization prior to diagnosis, perhaps the only notable observation was a numerically lower clinical improvement rate in the P/T group than the comparator group for infants 2 months to <2 years of age (83% versus 89%). However, this difference was consistent with chance variation.

Table 9 Patients categorized as "clinically improved" at or before 14 days from the start of HAP therapy, by select patient characteristics (Primary Analysis Set)

Subgroup	P/T Group (n = 140) n %	Comparator Group (n = 267) n %	Comparator Subset: Carbapenem Group (n = 57) n %
Age at HAP diagnosis			
Infant 2 months to <2 years	39/47 (83.0)	98/110 (89.1)	18/24 (75.0)
Child 2 years to <12 years	44/47 (93.6)	83/88 (94.3)	16/17 (94.1)
Adolescent 12 years to <16 years	24/25 (96.0)	41/44 (93.2)	10/10 (100.0)
≥16 years	20/21 (95.2)	23/25 (92.0)	4/6 (66.7)
Sex			
Male	75/81 (92.6)	136/148 (91.9)	29/33 (87.9)
Female	52/59 (88.1)	109/119 (91.6)	19/24 (79.2)
Race			
White	60/66 (90.9)	119/129 (92.2)	23/27 (85.2)
Black	39/41 (95.1)	84/92 (91.3)	19/22 (86.4)
Latino	7/8 (87.5)	4/5 (80.0)	0/1 (0.0)
Asian	2/2 (100.0)	4/4 (100.0)	2/2 (100.0)
Other	2/2 (100.0)	24/25 (96.0)	4/4 (100.0)
Unknown	17/21 (81.0)	10/12 (83.3)	0/1 (0.0)
Duration of hospitalization prior to diagnosis			
2 days	13/13 (100.0)	15/15 (100.0)	0/0
3 to 6 days	62/67 (92.5)	125/133 (94.0)	27/30 (90.0)
7 to 14 days	35/38 (92.1)	67/75 (89.3)	12/15 (80.0)
15 to 30 days	9/10 (90.0)	24/27 (88.9)	6/8 (75.0)
31 to 45 days	5/7 (71.4)	6/8 (75.0)	1/2 (50.0)
46 to 60 days	1/2 (50.0)	2/3 (66.7)	1/1 (100.0)
≥61 days	2/3 (66.7)	6/6 (100.0)	1/1 (100.0)

Abbreviations: HAP = hospital-acquired pneumonia/nosocomial pneumonia
Note: Percentages refer to the rate of clinical improvement within each subgroup. The table corrects for one subject in the study report whose treatment group was mislabeled.
Source: Statistical reviewer and B2361001 Final Study Report, Table 7.

The cross-tabulation above was only able to adjust for a single potential confounder in each row. Therefore, the next table displays results of the applicant's logistic regression analysis. As previously described, clinical improvement was regressed on treatment group with inverse propensity score weights. Odds ratios in the table greater than 1 represented an association between P/T group and failure to achieve clinical improvement. The three columns display unadjusted odds ratios that ingore covariates, adjusted odds ratios from a model fit using inverse propensity score weights, and adjusted odds ratios from a model with study site as a fixed effect and inverse propensity score weights.

The first row of odds ratios in the table were based on comparing P/T to the entire control group, and these odds ratios all exceeded 1. Thus, these analyses estimated that P/T was associated with less clinical improvement than the comparator group. However, the confidence interval for each odds ratio was consistent with either positive or negative association between P/T and clinical improvement.

The next row of odds ratios in the table were based on repeating this logistic regression analysis, but instead comparing the P/T group to the carbapenem subset rather than to the entire comparator group. In these analyses all odds ratios were below 1. Hence, these analyses estimated that P/T was associated with greater clinical improvement than use of carbapenems, even when controlling for confounding factors. Like the preceding analyses, the confidence interval for each odds ratio was consistent with either positive or negative association between P/T and clinical improvement. Because patients with greater comorbidities may have been more likely to receive carbapenems, these analyses may still have been confounded in that measured covariates may not have encapsulated all underlying differences between treatment groups.

Including the study site as a fixed effect in the logistic regression models did not have a large impact on adjusted odds ratios. In general, inverse weighting by propensity scores did not lead to outliers or high leverage points when fitting regression models.

The applicant's confidence intervals for adjusted odds ratios were based on robust variance estimates, but did not take into account the noise injected due to fitting propensity scores using multivariate logistic regression. Thus, the statistical reviewer also considered inference using the nonparametric bootstrap (i.e., resampling all subjects with replacement) for the entire procedure of estimating propensity scores and then fitting weighted regressions. Bootstrap inference did not lead to qualitative interpretational differences from the applicant's reported uncertainty measures, but confidence intervals were slightly wider and less symmetric on the log scale (Table 10).

Table 10 Logistic regression analysis evaluating the global response of "clinically improved" versus "did not improve" (Primary Analysis Set)

Piperacillin/tazobactam versus comparator group

Unadjusted OR, 95% CI	Adjusted OR without site, 95% CI	Adjusted OR with site, 95% CI
OR: 1.13 CI: (0.55, 2.31)	OR: 1.45 CI: (0.65, 3.27)	OR: 1.26 CI: (0.41, 3.90)
Piperacillin/tazobactam versus carbapenem subset		
Unadjusted OR, 95% CI	Adjusted OR without site, 95% CI	Adjusted OR with site, 95% CI
OR: 0.53 CI: (0.21, 1.32)	OR: 0.58 CI: (0.22, 1.52)	OR: 0.63 CI: (0.20, 1.97)

Abbreviations: OR = odds ratio, CI = confidence interval.
Note: This is a logistic regression for determining the odds ratio for failure to improve. The table corrects for one subject in the study report whose treatment group was mislabeled.
Source: B2361001 Final Study Report, Tables 8.1.1 and 8.1.2 and Final Study Report Amendment Summary of Changes.

6.2. Review of Safety

6.2.1. Safety Review Approach

This safety review is based on a retrospective cohort study of pediatric patients aged 2 months to <18 years diagnosed with NP and receiving antibacterials for the indication of NP at multiple pediatric hospitals across the US. Pediatric patients with an indication of NP receiving P/T were included in the PT group and those receiving comparator antibacterial drugs were included in the comparator group. The date of initiation of NP treatment was considered as "index date", and follow-up time for a patient outcome, which measures the person-time at risk, was defined as the time interval from the index date until one of the following safety outcomes:

1. All serious adverse events: following completion of 40 days after the first dose of P/T or comparator antibacterials, or discharge from the hospital (or death), whichever occurs first (after which time all surviving patients were considered censored).
2. All cause mortality: following a period of 30-days after the first dose of P/T or comparator antibacterial (at which time all surviving patients were considered censored).

A serious event was defined as any untoward medical occurrence documented in a physician's progress note in patients taking P/T or comparator antibacterial drug that results in death, is life-threatening, requires prolongation of hospitalization, or results in persistent or significant disability/incapacity.

Following serious events in pediatric patients with NP treated with P/T or comparator (irrespective of 'causal' relationship to therapy) were collected:
Central nervous systems (CNS)/neurologic: seizure
Gastrointestinal: cholestatic jaundice, hepatic disorder, hepatitis
Hematologic: hemolytic anemia, thrombocytosis, agranulocytosis, pancytopenia

Immune: anaphylactic/anaphylactoid reactions (including shock)
Infection: sepsis, super-infections, *C. difficile* infection
Skin and appendages: erythema multiforme, Stevens-Johnson Syndrome
Renal: interstitial nephritis, renal failure

Reviewer's Comment: Based on the study protocol, applicant focused on serious events that have been reported in prior clinical trials and post-marketing data for P/T. Ascertainment of all-cause mortality at 30-days after initiation of NP treatment, was ascertained for all patients via review of medical charts, and for patients who stayed in hospital less than 30-days after initiation of NP treatment, PHIS database was queried for the patient's medical record to identify any subsequent hospital admissions or outpatient encounters that would confirm patient was alive 30-days or more after initiation of treatment for NP.

The trained research personnel (physicians, clinical research nurses, or research assistants), performed chart reviews and collected all untoward medical events documented in the daily progress notes of the problem list or impression section of the chart from the day of initiation of P/T or comparator through the duration of hospitalization or 40 days after the first dose of the antibacterial(s) for NP, whichever came first. The trained research personnel also collected serious event onset date, corresponding to the date of the progress note and supporting medical record documentation, when available.

Scanned copies of the physician documentation/notes that detailed the identified serious event were obtained and documented for each patient sustaining a serious event. Worsening of pre-existing conditions which was present prior to the diagnosis of NP was captured as a serious event if it met any of the criteria for a serious event described above. Subsequently, the serious events from each chart were reviewed by one of two study physicians, who were blinded to the antibacterial that each patient received for treatment of NP, to determine whether the event meets the definition of a serious adverse event, specified above. In addition, daily pertinent laboratory, radiographic and co-morbidity data were collected and reviewed by trained research personnel.

6.2.2. Limitations of the Study Safety Assessment

This retrospective cohort study investigated the risk of serious events (primary objective) as well as treatment effectiveness outcomes (secondary objective) among pediatric patients with nosocomial pneumonia by comparing P/T to comparator antibacterials (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin). There are some inherent limitations to this study due to its observational nature utilizing retrospective data which includes the possible inaccuracies and incompleteness in medical records. There was also a possibility of underestimation of incidence rate of serious events, given that only documented events that appeared in the daily progress notes and met the definition of 'serious events' were included, however, this would be expected for both treatment groups and there is no reason to

believe that documentation of serious events in medical records would occur systematically differentially between patients treated with P/T and Comparator group.

Additionally, for mortality assessment, the vital status at 30-days after initiation of treatment for HAP was not available in medical charts for patients who were discharged from the hospital prior to 30 days of initiation of treatment for NP. PHIS database were queried to identify any subsequent hospital admissions or outpatient encounters that to confirm patient's vital status 30-days or more after initiation of HAP therapy. If no medical encounter was identified then the NDI (NDI is a central computerized index of death record information compiled from local state files submitted to the National Center for Health Statistics (NCHS) by each state's vital statistics office) was queried. Information on each patient's name and date of birth or social security number was needed in order to search for a 'matching record' in the NDI. Once a patient was recognized as having an unknown vital status, the site was asked to provide the patient's complete first and last name, for which individual site's IRB approval was required. The applicant noted that all sites were not able to secure this level of IRB approval. Therefore information on date and causality of death was obtained from the the death certificate. The causes of death listed on the death certificate were reviewed by a study physician to identify any additional serious events that may not have been captured in the daily progress notes.

6.2.3. Safety Results

I. Overall Exposure

A total of 407 patients were treated for NP, of those, 140 (34.64%) patients received P/T as the first antibacterial administered for treatment of NP and were included in the P/T group, and 267 (65.35%) patients received one of the compactor antibacterials as the first antibacterial drug administered for NP and were included in the comparator group. Table 11 summarizes the safety population by treatment group in primary analysis set.

Table 11 Safety Population for hospital-acquired pneumonia by treatment group (PAS)-Study B2361001

	P/T Group (n = 140) n (%)	Comparator Group (n = 267) n (%)	Comparator Subset:Carbapenem Group (n = 57) n (%)
Piperacillin/tazobactam	140 (100.00)		
Cefepime		92 (34.5)	
Ceftazidime		55 (20.6)	
Ticarcillin/clavulanate		50 (18.7)	
Ciprofloxacin		13 (4.9)	
Meropenem		56 (21.0)	56 (98.2)
Imipenem		1 (0.4)	1 (1.8)

Source: FDA Reviewer

Exposure By Dosing Frequency among subjects in P/T group:

Protocol specified evaluation and comparison of serious adverse events among pediatric patients with NP who received at least one dose of P/T at a dose 80-100 mg/kg piperacillin/10-12.5mg/kg tazobactam every 6 hours ("HAP dosing") to those who received at least one dose of a comparator NP appropriate antibiotic at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients. Table 12 below summarizes P/T exposure by age group.

Table 12 Piperacillin/tazobactam exposure by dosing regimen and age group category

Dosing Regimen	2 to 9 months	>9 months to <18 years
	n = 30	n = 110
>70-80 mg/kg Q 6 h	n = 2	n= 24
80 to <100 mg/kg Q 6 h	n = 3	n = 7
100 mg/kg Q 6 h	n = 3	n= 9
>100 mg/kg Q 6 h	n = 2	n = 6
80-100 mg/kg Q 8 h to 12 h	n = 20	n= 64

Source: FDA Reviewer

Reviewer's Comment: Based on PK studies, half-lives of piperacillin/tazobacatam was prolonged and clearance was reduced in the youngest age group (0 to 9 months of age), as compared with the values in the older infants and children where exposures were comparable to adults. Therefore, a dosage of 80mg/10 mg/kg Q 6 hours were selected for youngest age group, whereas, 100 mg/12.5 mg/kg Q 6 hours (similar to recommended dose in adults) were chosen to treat older infants and children. In this study, 8 patients received P/T doses at or above 80 mg/kg Q 6 hours and 15 patients in 9 months and older age group received doses at or above 100 mg/kg Q 6 hours. Majority of patients in both age group category received dosing between 80-100 mg at a frequency of every 8 hours, with few received every 12 hours.

As mentioned earlier in this review, this study had several limitations, and one of which was use of range of P/T dosing regimen. Based on protocol specifications, patients in P/ T group was defined by receipt of at least one dose of 80-100 mg/kg of piperacillin and 10-12.5 mg/kg of tazobactam every 6 hours , which were supposed to be selected dosing for nosocomial pneumonia ('HAP dosing'). It is likely that some patients who received less than selected dose for particular age group might have been dose adjustments for renal impairment, however, it is not clear since majority of patients had missing baseline creatinine levels and thus rationale for wide variety of dosing is not clarified. Of those who had measurements prior to NP diagnosis, elevated levels of serum creatinine were noted in 6.38% of patients in the P/T group and 8.65% in the comparator group.

In terms of duration of exposure, the majority of patients received at least one week of therapy (101 (72.1%) and 234 (87.6%) in P/T and comparator groups, respectively (See Section 6.1.2). Durations of therapy was somewhat shorter in the P/T group than the comparator group. The

reason for this difference in treatment durations was unclear. In particular, it was not possible to determine from the information provided whether this was related to study site preferences, outcomes, or treatment switches. As this was a retrospective study the protocol did not specify what durations were allowed for either treatment group.

II. Relevant characteristics of safety population

Table 13 summarizes baseline demographic information by age group in the two treatment arms.

Table 13 Patient demographic characteristics by treatment group and age groups

Characteristic	P/T Group		Comparator Group		Comparator Subset: Carbapenem Group	
	2-9 months (n = 30) n (%)	>9 months (n = 110) n (%)	2-9 months (n = 79) n (%)	>9 months (n = 188) n (%)	2-9 months (n = 17) n (%)	>9 months (n = 40) n (%)
Age at HAP diagnosis						
	30 (100.00)	-	79 (100.00)		17 (100.00)	
>9 months to <2 years		17 (15.45)	-	31 (16.49)	-	7 (17.50)
2 to <12 years	-	47 (42.73)	-	88 (46.81)	-	17 (42.50)
12 to <16 years	-	25 (22.73)	-	44 (23.40)	-	10 (25.00)
≥16 years	-	21 (19.09)	-	25 (13.30)	-	6 (15.00)
Sex						
Male	19 (63.33)	62 (56.36)	39 (49.37)	109 (57.98)	10 (58.82)	23 (57.50)
Female	11 (36.67)	48 (43.64)	40 (50.63)	79 (42.02)	7 (41.18)	17 (42.50)
Race						
White or Caucasian	10 (33.33)	56 (50.91)	28 (35.44)	101 (53.72)	4 (23.53)	23 (57.50)
Black or African American	12 (40.00)	29 (26.36)	37 (46.84)	55 (29.26)	11 (64.71)	11 (27.50)
Latino	1 (3.33)	7 (6.36)	1 (1.27)	4 (2.13)	0 (0.00)	1 (2.50)
Asian	1 (3.33)	1 (0.91)	1 (1.27)	3 (1.60)	0 (0.00)	2 (5.00)
Other	0 (0.00)	2 (1.82)	8 (10.13)	17 (9.04)	1 (5.88)	3 (7.50)
Unknown	6 (20.00)	15 (13.64)	4 (5.06)	8 (4.26)	1 (5.88)	0 (0.00)
Participating site						
Children's Hospital of Philadelphia, Philadelphia, PA	1 (3.33)	6 (5.45)	19 (24.05)	49 (26.06)	0 (0.00)	1 (2.50)
Rady Children's Hospital, San Diego, CA	0 (0.00)	0 (0.00)	12 (15.19)	32 (17.02)	2 (11.76)	11 (27.50)
Children's National Medical Center, Washington, DC	4 (13.33)	12 (10.91)	14 (17.72)	41 (21.81)	1 (5.88)	6 (15.00)
Columbia University Medical Center, New York, NY	8 (26.67)	28 (25.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Cincinnati Children's Hospital Medical Center, Cincinnati, OH	11 (36.67)	32 (29.09)	2 (2.53)	8 (4.26)	0 (0.00)	3 (7.50)
St. Louis Children's Hospital, St. Louis, MO	0 (0.00)	2 (1.82)	14 (17.72)	29 (15.43)	0 (0.00)	1 (2.50)
Children's Healthcare of Atlanta, Atlanta, GA	6 (20.00)	30 (27.27)	18 (22.78)	29 (15.43)	14 (82.35)	18 (45.00)

Source: FDA Reviewer

Table 14 summarizes baseline clinical characteristics of safety population.

Table 14 Baseline clinical characteristics of safety population

Characteristic	P/T Group n = 140		Comparator Group n = 267	
	2-9 months n = 30 n (%)	>9 months n = 110 n (%)	2-9 months n = 79 n (%)	>9 months n = 188 n (%)
Patient location prior to study institution				
Another facility/inpatient	13 (43.33)	22 (20.00)	34 (43.04)	48 (25.53)
Outpatient	16 (53.33)	85 (77.27)	43 (54.43)	139 (73.94)
Unknown	1 (3.33)	3 (2.73)	2 (2.53)	1 (0.53)
Hospitalized within last 30 days prior to this admission				
Yes	12 (40.00)	23 (20.91)	38 (48.10)	54 (28.72)
No	14 (46.67)	75 (68.18)	30 (37.97)	106 (56.38)
Unknown	4 (13.33)	12 (10.91)	11 (13.92)	28 (14.89)
Tracheostomy prior				
Yes	0 (0.00)	12 (10.91)	6 (7.59)	18 (9.57)
No	30 (100.00)	98 (89.09)	72 (91.14)	170 (90.43)
Unknown	0 (0.00)	0 (0.00)	1 (1.27)	0 (0.00)
Ventilator dependent				
Yes	6 (20.00)	11 (10.00)	21 (26.58)	27 (14.36)
No	24 (80.00)	95 (86.36)	57 (72.15)	157 (83.51)
Unknown	0 (0.00)	4 (3.64)	1 (1.27)	4 (2.13)
Co-morbidity by system				
Neurologic/CNS	12 (40.00)	44 (40.00)	22 (27.85)	89 (47.34)
Cardiovascular	20 (66.67)	32 (29.09)	44 (55.70)	37 (19.68)
Respiratory	11 (36.67)	26 (23.64)	29 (36.71)	60 (31.91)
Renal	1 (3.33)	8 (7.27)	3 (3.80)	20 (10.64)
Gastrointestinal	9 (30.00)	25 (22.73)	18 (22.78)	36 (19.15)

Hematological and immunodeficiency	2 (6.67)	8 (7.27)	2 (2.53)	7 (3.72)
Metabolic disease	1 (3.33)	6 (5.45)	1 (1.27)	13 (6.91)
Other congenital or metabolic defect	8 (26.67)	23 (20.91)	15 (18.99)	35 (18.62)
Malignancy	0 (0.00)	13 (11.82)	1 (1.27)	22 (11.70)
Rheumatologic	0 (0.00)	3 (2.73)	1 (1.27)	0 (0.00)

Source: FDA Reviewer

Reviewer's Comment: Overall, patients in the two groups were comparable with regards to the distribution of age, sex and race. Mean age of patients in the P/T group was 7.65 years as compared to 6.57 years in the comparator group. Over half of the patients were white and males in both groups.

The majority of patients in both groups were admitted to the participating study site from outpatient setting (either clinic or ER): 72.34% in the P/T group and 68.05% in the comparator group. The most commonly reported co-morbidities were neurologic (39.72% in P/T and 41.73% in comparator), cardiovascular diseases (36.88% in P/T and 30.45% in comparator), respiratory system related (26.95% in P/T and 33.08% in cmparator), gastrointestinal diseases (24.11% in P/T and 20.30% in comparator) and congenital or metabolic defects (21.99% in P/T and 18.80% in comparator) prior to the hospital admission.

The indication for hospital admission was non-infectious illness in the majority of patients in both groups (80.85% in P/T and 75.19% in comparator groups). The median number of days in the hospital prior to NP diagnosis was comparable in both groups: 5 days in PT versus 6 days days in the comparator group. At the time of NP diagnosis, 63.12% of patients in the P/T group and 78.20% in the comparator group were in the ICU; and a comparatively, lower proportion of patients in the P/T group than the comparator group were shifted to ICU after the HAP diagnosis (14.29% versus 26.32%). However, this might not signify severity of illness based on treatment group, as choice of antibacterial drug used for NP treatment varied by site irrespective of location of treatment in the hospital or endotracheal intubation. It is likely that the use of antibacterial was dependent on the formulary and site treatment protocol and/or treating physician.

Of note, all of the patients (36/36, 100%) at the Columbia University Medical Center, and most patients (43/53, 81.13%) at the Cincinnati Children's Hospital Medical Center were treated with P/T, whereas all or most patients were treated with comparator drugs at the Rady Children's Hospital (44/44, 100%), St. Louis Children's Hospital (43/45, 95.56%) and CHOP (68/75, 90.67%). This might have been due to preference of study sites for specific NP therapies. To adjust for this confounder, sonsors' analyses included a variable "participating site" in the multivariable regression model. Further, medical records (e.g. daily progress notes) were reviewed from all sites by study physicians blinded to the antibiotics that each patient received for NP to confirm serious events.

A comparable proportion of patients in the P/T group and Comparator group received vancomycin (27.66% and 25.19%), and aminoglycosides (14.18% versus 14.29%).

Tracheostomy was performed in a small number of patients post NP diagnosis and the proportion was comparable in the two groups.

In terms of diagnostic tests, at least one chest x-ray was performed from 24 hours prior and up to 48 hours (day -1 to day 2) after the day of NP diagnosis in 95.04% and 95.86% of patients in P/T group and comparator group respectively.

One major drawback of the study was that laboratory tests were not consistently ordered for all patients prior to NP diagnosis, however, all patients had records of at least one pertinent laboratory test record after NP diagnosis during the study follow up period. Additionally, respiratory or sputum cultures were not available for majority of patients in both groups, in this observational study.

When evaluating carbapenem subset of comparator group, if one has to assume that perhaps comparatively sicker patients were treated with carbapenem subset, presence of coexisting conditions and co-morbidities in the PT group and carbapenem subset were similar with most common comorbidities being neurologic/CNS (39.72% in P/T and 35.71% in carbapenems), cardiovascular diseases (36.88% in P/T and 28.57% in carbapenems), and respiratory system related co-morbidities (26.95% in P/T and 28.57% in carbapenems) prior to the hospital admission. Primary reason for admission was non-infectious illness in both P/T group and carbapenem subset.

Prior to the NP diagnosis, a comparable proportion of patients in the P/T group and the carbapenem group were initially admitted to the ICU on the first hospital day (58.87% versus 62.50%) or subsequently transferred to the ICU (17.02% versus 16.07 %), and required tracheostomy (13.48% versus 8.93%).

After the NP diagnosis, lower proportion of patients in PT in comparison to carbapenems subset were in ICU (63.12% and 78.57%), and numerically higher proportions of patients in PT group were transferred to ICU after the NP diagnosis (14.29% versus 9.09%). Overall, a comparable proportion of patients in the P/T group and carbapenem subset received vancomycin (27.66% versus 26.79%), and aminoglycosides (14.18% versus 12.50%) after the NP diagnosis.

III. Adequacy of the safety database:

The overall number of patients exposed to P/T in this retrospective study appeared adequate for the target population to perform a safety evaluation.

IV. Deaths

The 30 day timepoint for mortality outcome assessments was predefined in the protocol and statistical analysis plan. Mortality rates were under 5% in both the piperacillin/tazobactam group and the comparator group. Median time from P/T initiation to death was 10 days (IQR: 5 to 15 days). (Table 15)

Table 15 All-cause mortality by treatment group (Primary Analysis Set)

	P/T Group (n = 140) n %	Comparator Group (n = 267) n %	Comparator Subset: Carbapenem Group (n = 57) n %
Deceased within 30 days of HAP diagnosis/treatment	5 (3.6)	12 (4.5)	5 (8.8)

Abbreviations. P/T = piperacillin/tazobactam, HAP = hospital-acquired pneumonia.
Note: One patient in the P/T group and one patient in the comparator group (in the carbapenem subset) had unknown vital status and were not counted as deaths. The table corrects for one subject in the study report whose treatment group was mislabeled.
Source: B2361001 Final Study Report, Table 5.2.1.

A summary of death in P/T group is presented in the table below (Table 16)

Table 16 Summary of Death in P/T group

	P/T Dosing	Cause of Death	Ventilator (Yes/no)
Subjects 2 months to 9 months of age in P/T group (N= 30)			
(b) (6)	97 mg/kg Q 8H *(650 mg/day)*	Down's syndrome, unbalanced atrio-ventricular canal, S/P Glenn anastomosis	No
	143mg/kg Q 6H *(430 mg/day)*	Sepsis, Pulmonary hypertension, bronchopulmonary dysplasia seconmdary to prematurity, ARDS	No
	99 mg/kg Q 12 H *(256 mg/day)*	Pulmonary Hypertension	Yes
Subjects > 9 months to <18 years of age in P/T group (N=110)			
(b) (6)	57 mg/kg Q 6H *(3 Gm/day)*	Pulmonary Hypertension	No
	67 mg/kg Q 6H *(3 Gm/day)*	Hemorrhagic shock, tracheoesophageal fistula	No
*This patient had a domuntation of E. coli as a causative organism for NP; Organism documentation is not available for other cases.			

Source: FDA Reviewer
Abbreviations: ARDS= Acute Respiratory Distress Syndrome

A summary of deaths in comparator group is summarized in Table 17.

Table 17 Summary of Death in Comparator group

Subject	Comparator N=11 (11/267)*	Cause of Death
(b) (6)	Carbapenem	Cardiomyopathy, chronic rejection of cardiac transplant, pulmonary atresia with intact ventricular septum
	Carbapenem	Pulmonary hypertension
	Carbapenem	Cardiac Arrest, Multiple organ failure, Sepsis, Hepatic failure
	Carbapenem	Hepatorenal syndrome, Fulminant acute liver failure

(b) (6)		
	Carbapenem	Respiratory failure
	Carbapenem	Pneumonia
	Non carbapenem	Typical Teratoid Rhabdoid tumor
	Non carbapenem	Pneumonia-pseudomonas, Respiratory failure, Myoclonic encephalopathy
	Non carbapenem	Sepsis, Seizures leading to both cardiac and respiratory arrest
	Non carbapenem	Empendymoma of brain
	Non carbapenem	Pneumonia and overwhelming infection; Cardiac arrest and respiratory failure

Source: FDA Reviewers
*There was one subject for which vital status was not known.

Reviewer's Comment; The rate of death was numerically lower in the P/T group than in the comparator group or carbapenem subset, and thus mortality results in this study did not signal any obvious concerns. The applicant did not perform regression analyses to control for confounding in assessing causal effects on mortality. Cause of deaths were recorded as due to coexisting underlying conditions in all patients receiving P/T, and majority of patients in comparator group, although 5 of 11 deaths in comparator groups were documented as due to worsening of pneumonia or infection.

In terms of P/T dosing and its correlation with deaths, all 3 deaths in 2 months to 9 months of age group occurred in patients receiving >80 mg/kg/day Q 6 hours dosing; whereas, all (2) deaths in older age group occurred in patients receiving doses <100 mg/kg/day Q 6 hours. Therefore, there was no apparent correlation between dosing and deaths in this study.

Case Narratives of Deaths

Narratives of individual cases of deaths were not included in the submission. An information request was sent to the applicant. The applicant responded that they will be unable to provide narratives for SAEs or deaths for this retrospective study. They further clarified that :
"*Case narratives for patients who experienced SAEs or deaths were not prepared for inclusion in the final study report as this is a secondary data collection study using existing data from medical records. Because full charts are not readily available for these cases, to create case narratives PI would need to approach respective sites first, copy full charts and then prepare case narratives. This will take considerable time, and cannot be completed by deadline for this application*".
Thus c*ausality of death could not be re-assessed by this reviewer due to these limitations. (Reader is referred to ' limitations of the safety assessment' in the beginning of this section).*

V. Serious Adverse Events

The table below (Table 18) summarizes the incidence of serious events over time in each treatment group. The rates of serious events per 100 person days were 1.28 in the P/T group, 1.02 in the comparator group, and 1.56 in the carbapenem subset of the comparator group.

Table 18 Cumulative person-time at risk and crude incidence rate per 100 person days (Primary Analysis Set)

	P/T Group (n = 140)	Comparator Group (n = 267)	Comparator Subset: Carbapenem Group (n = 57)
Cumulative person time at risk, days	2655	5791	1349
All serious events, count	34	59	21
All serious events, incidence rate (95% CI)	1.28 (0.85, 1.71)	1.02 (0.76, 1.28)	1.56 (0.89, 2.22)
Patients with any serious event n %	18/140 (12.9)	30/267 (11.2)	9/57 (15.8)

Abbreviations: P/T = piperacillin/tazobactam, CI = confidence interval.
Note: The crude incidence rate per 100 person days was defined by the sum of serious events divided by the number of hospital days. Confidence intervals were calculated by the applicant using the mid-p exact test. The table corrects for one subject in the study report whose treatment group was mislabeled.
Source: B2361001 Final Study Report Amendment, Summary of Changes, Table 5.1.1.

Serious events by body system are shown in the table below, but numbers of specific individual events were too rare to statistically distinguish treatment groups. (Table 19).

Table 19 Number patients with serious events by body system and individual event type (Primary Analysis Set)

Serious event	P/T Group (n = 140)	Comparator Group (n = 267)	Comparator Subset: Carbapenem Group (n = 57)
Cardiovascular			
Atrial fibrillation	0	1	0
Bradycardia	1	1	0
Cardiac arrest	0	2	0
Cardiac failure	1	2	2
Hypertension	0	1	0
Hypotension	2	1	0
Pericardial effusion	1	0	0
Pulmonary hypertension	3	2	1
Transplant rejection (heart)	0	1	1
Tachycardia/ventricular tachycardia	1	2	1
Volume overload	1	0	0
Nervous System Disorders			
Acute neurologic failure	0	1	0
Encephalopathy	1	1	0

Hydrocephalus	0	1	1
Large pseudomeningocele	1	0	0
Tumor progression	0	2	0
Seizure	1	2	0
Endocrine Disorders			
Hyperglycemia	0	1	0
Gastrointestinal Disorders			
Acalculous cholecystitis	0	1	0
Gastric dysmotility	0	0	0
Gall bladder sludging	0	0	0
Hematemesis	1	0	0
Ileus	1	0	0
Pancreatitis	2	0	0
Small Bowel Obstruction	0	1	0
Transaminitis	0	0	0
Blood and Lymphatic System Disorders			
Blood loss	0	1	0
Hemorrhagic shock	1	0	0
Hepatic *Disorders*			
Hepatic failure	1	2	2
Hepatotoxicity	0	1	0
Infections and Infestations			
Bacteremia	0	1	1
Cellulitis	0	1	1
Herpes virus	1	0	0
Sepsis	1	8	3
Viral pneumonia	0	1	0
Renal and Urinary Disorders			
Renal failure	1	2	2
Respiratory, Thoracic and Mediastinal			
ARDS	1	0	0
Collapsed lung	2	2	0
Diaphragmatic paralysis	0	1	0
Hypoxia	3	3	1
Pleural effusion	1	0	0
Respiratory arrest	0	1	0
Respiratory distress	2	0	0
Respiratory failure	1	7	4
Skin/Alleric			

Anaphylactic reaction	0	2	1
Drug eruption	0	1	0
Graft versus host disease	1	0	0
PICC migration	1	0	0
Other			
Unknown fatal event	0	2	0

Abbreviations: P/T = piperacillin/tazobactam, CI = confidence interval.
Note: The crude incidence rate per 100 person days was defined by the sum of serious events divided by the number of hospital days. Confidence intervals were calculated by the applicant using the mid-p exact test. The table corrects for one subject in the study report whose treatment group was mislabeled.
Source: B2361001 Final Study Report Amendment, Summary of Changes, Table 5.1.1.

The subsequent table displays incidence rates of serious events per 100 person days by treatment group and demographic factors. As shown in Table 20, other than patients ≥16 years of age in the carbapenem subset, where there was a relatively high rate of serious events per 100 person days, although there were only 6 patients in this group, there was no clearly meaningful associations between rates of serious events and demographic characteristics.

Table 20 Crude incidence rates for serious events per 100 person days by treatment group and selected demographic characteristics (PAS)

	P/T Group (n = 140) Incidence rate (95% CI)	Comparator Group (n = 267) Incidence rate (95% CI)	Comparator Subset:Carbapenem Group (n = 57) Incidence rate (95% CI)
Age at HAP diagnosis			
Infant 2 months to <2 years	1.6 (0.8 to 2.4)	0.6 (0.3 to 0.9)	0.9 (0.2 to 1.6)
Child 2 years to <12 years	0.9 (0.3 to 1.6)	0.9 (0.5 to 1.4)	0.7 (0.0 to 1.6)
Adolescent 12 years to <16 years	0.2 (0.0 to 0.7)	1.7 (0.9 to 2.6)	1.4 (0.0 to 3.0)
≥16 years	2.5 (0.8 to 4.3)	2.3 (0.9 to 3.6)	10.8 (3.8 to 17.9)
Sex			
Male	1.3 (0.7 to 1.8)	1.3 (0.9 to 1.7)	1.9 (0.9 to 2.9)
Female	1.3 (0.6 to 2.0)	0.7 (0.4 to 1.0)	1.2 (0.3 to 2.0)
Race			
Black	0.8 (0.2 to 1.44)	0.9 (0.5 to 1.3)	0.7 (0.0 to 1.3)
Non-Black	1.5 (0.8 to 2.2)	1.1 (0.8 to 1.5)	2.5 (1.3 to 3.6)
Participating study site			
Children's Hospital of Philadelphia	2.7 (0.0 to 5.8)	0.8 (0.4 to 1.3)	0.0

Randy Children's Hospital, San Diego, CA	N/A: no patients	1.4 (0.6 to 2.2)	3.1 (0.9 to 5.2)
Children's National Medical Center, Washington, DC	1.9 (0.5 to 3.3)	1.6 (0.8 to 2.4)	3.1 (0.1 to 6.0)
Columbia University Medical Center, New York, NY	0.3 (0.0 to 0.8)	N/A: no patients	N/A: no patients
Cincinnati Children's Hospital Medical Center	2.4 (1.4 to 3.5)	5.0 (2.0 to 7.9)	2.0 (0.0 to 4.7)
St. Louis Children's Hospital	0.0	0.2 (0.0 to 0.5)	0.0
Children's Healthcare of Atlanta	0.3 (0.0 to 0.7)	0.6 (0.2 to 1.0)	0.8 (0.2 to 1.5)

Abbreviations: P/T = piperacillin/tazobactam, CI = confidence interval.
Note: The crude incidence rate per 100 person days was defined by the sum of serious events divided by the number of hospital days. This table corrects for one subject in the study report whose treatment group was mislabeled. Confidence intervals are based on the normal approximation and lower confidence limits are truncated at zero.
Source: B2361001 Final Study Report, Tables 5.1.1a and 5.1.1b; and FDA Statistical reviewer

To control for confounding factors in this non-randomized study, the next table summarizes regression analyses examining the association between P/T and serious events. The Table 21 displays the primary analysis of the Poisson regression comparing the P/T group versus the comparator group, as well as the applicant's sensitivity analyses based on negative binomial regression models. The table additionally shows comparisons between P/T and the carbapenem subset of the comparator group. The three columns display unadjusted incidence rate ratios that ignored confounding variables, adjusted rate ratios based on inverse propensity score weighting, and adjusted rate ratios based on inverse propensity score weighting and inclusion of study site as a main effect in the Poisson or negative binomial regression model.

Table 21 Regression analysis evaluating the potential association between treatment group and all serious events (Primary Analysis Set)

Poisson regression analysis: P/T versus comparator group:		
Unadjusted IRR, 95% CI	Adjusted IRR without site 95% CI	Adjusted IRR with site 95% CI
IRR: 1.24 CI: (0.65, 2.36)	IRR: 1.21 CI: (0.63, 2.30)	IRR: 0.81 CI: (0.30, 2.16)
Negative binomial regression analysis: P/T versus comparator group:		
Unadjusted IRR, 95% CI	Adjusted IRR without site, 95% CI	Adjusted IRR with site 95% CI
IRR: 1.09 CI: (0.52, 2.28)	IRR: 1.07 CI: (0.53, 2.16)	IRR: 0.92 CI: (0.29, 2.90)
Poisson regression analysis: P/T versus carbapenem subset:		

Unadjusted IRR, 95% CI	Adjusted IRR without site, 95% CI	Adjusted IRR with site 95% CI
IRR: 0.80 CI: (0.34, 1.86)	IRR: 0.76 CI: (0.32, 1.78)	IRR: 0.98 CI: (0.36, 2.68)
Negative binomial regression analysis: P/T versus carbapenem subset:		
Unadjusted IRR, 95% CI	Adjusted IRR without site, 95% CI	Adjusted IRR with site, 95% CI
IRR: 0.48 CI: (0.17, 1.43)	IRR: 0.49 CI: (0.18, 1.33)	IRR: 0.42 CI: (0.10, 1.71)

Abbreviations: IRR = incidence rate ratio, CI = confidence interval.
Note: The table corrects for one subject in the study report whose treatment group was mislabeled.
Source: B2361001 Final Study Report Tables 6.1.1 and 6.1.2 and Final Study Report Amendment, Summary of Changes.

Reviewer's comment: Propensity score weights were identical to those previously discussed for the logistic regression analysis of clinical improvement, and confidence intervals were likewise constructed by the applicant using robust variance estimators. As previously described in the discussion of efficacy, this standard error estimation did not take into account noise from estimating propensity scores. However, a nonparametric bootstrap analysis performed by the FDA statistical reviewer did not lead to qualitative differences in interpretations.

The analyses in the table did not strongly point to positive or negative association between piperacillin/tazobactam and serious events. The confidence interval for each adjusted and unadjusted incidence rate ratio was consistent with either a positive or negative association. P/T was associated with fewer serious events than the carbapenem subset of the comparator group in both adjusted and unadjusted analyses, but this may have been due to incomplete adjustment for confounding if carbapenem use selected for a sicker underlying patient population.

To account for confounding by an unmeasured covariate, the sponsor conducted quantification of the unmeasured confounder was measured by E-value[5]. The E-value quantifies how strong the association of an unmeasured confounder needs to be with both the exposure *and* outcome of interest to change the findings.[6],[7] The value of 1.25 was chosen as it is a point estimate away from the null, and in the opposite direction of that which was observed in the primary analysis. These calculations were performed for the adjusted effect of P/Tversus comparator groups (and also for the adjusted effect of P/T versus Ccmparator subset: carbapenems groups) for the primary endpoint of serious events.

[5] E-value calculator: https://evalue.hmdc.harvard.edu/app/
[6] VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167:268–274.
[7] Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. Epidemiol. 2016; 27(3): 368-377.

Results of the study data showed that for the primary endpoint of serious events, an unmeasured confounder would need to be associated with the exposure and endpoint to a strength of 1.81 for the comparison of P/T to comparator group (and 1.29 for the comparison of P/T to comparator subset: carbapenems group) to move the point estimate of the IRR to the null.

If there was an effect of unmeasured confounder, an unmeasured confounder would need to be associated with the exposure and outcome to a strength of 2.50 for the comparison of P/T to comparator group (and 1.96 for the comparison of P/T to comparator subset: carbapenems group) to move the point estimate of the IRR to 1.25. This provides further confidence in the observed findings.(Table 22).

Table 22 Quantification of an unmeasured confounder to move each of the analyses' point estimates from their observed values to the null and 1.25 (E-value) for regression models for 'serious events' comparing P/T *versus* comparator and P/T *versus* comparator subset carbapenem

Primary Endpoint Serious Adverse Event	Adjusted Point Estimate including Site		E-value Calculations:					
Observed Association:	IRR (95% CI)	P-value	Hypothesized True Effect	Relative Risk/Rate Ratio for strength of confounder to move observed association to 1*	Lower Confidence Interval for Size of confounder	Hypothesized True Effect	Relative Risk/Rate Ratio for strength of confounder to move observed association to 1.25*	Lower Confidence Interval for Size of confounder
P/T vs. Comparator	0.80 (0.30, 2.12)	0.65	1	1.81	1	1.25	2.50	1
P/T vs. Carbapenem	0.95 (0.35, 2.62)	0.93	1	1.29	1	1.25	1.96	1

6.2.4. Descriptive analysis of Serious Adverse Events: Study B2361001

A total of 93 serious events were reported among 48 patients across the P/T and comparator groups during the follow up period. Of the 93 serious events identified in this study, 34 serious events among 18 patients were identified in the P/T group and a total of 59 serious events among 30 patients were identified in the comparator group during the follow up period. Median (IQR) time from HAP treatment initiation to the onset of a serious event was 9 days (4-14 days) in P/T group and 6 days (3-16 days) in comparator group.

Following Table summarizes serious adverse events in P/T treatment group in descriptive details by age group (2 months to 9 months and >9 months to <18 years of age), P/T dosing, and outcomes (Table 23).

Table 23 Summary of subjects in the P/T group with at least one serious adverse events by age group , causative microorganisms and ventilation status

#	P/T Dosing	Dose received /Day	No. of SAE	SAE(s)	Organism	Ventilator (Y/N)	Clinical Outcome	Death
SAEs in Subjects 2 months to 9 months of age [n=5/30, 16.6%)								
(b) (6)	97 mg/kg/d Q8H (3.5 m)	650 mg	2	Cardiac Failure Encephalopathy	*E. coli*	No	Did not improve	Yes
	143.3 mg/d Q 6 H (6 m)	573 mg	3	Pulm-HTN Sepsis ARDS	N/A	No	Did not improve	Yes
	98.4 mg/kg/d Q 12 H (4 m)	197 mg	1	Pulm-HTN	N/A	Yes	Did not improve	Yes
	149 mg/kg/d Q8hr (3 m)	447 mg	2	Bradycardia Hypoxia	N/A	No	Did not improve	No
	80 mg/kg/d Q8hr (2.5 m)	240 mg	2	Hypotension	*K.pneumoniae* , *S. aureus*	No	Did not improve	No
SAEs in Subjects > 9 months to <18 years of age [n=13/110, 12 %]								
(b) (6)	100 mg/kg/d Q6hr	1050 mg	2	Hypotension Hypoxia	N/A	No	Improved	No
	56.9 mg/kg Q6hr	3000 mg	1	Pulm-HTN	N/A	No	Did not improve	Yes
	66.7 mg/kg Q6hr	3000 mg	2	Shock Pleural Effusion	N/A	No	Improved	Yes
	50.5 mg/kg Q6hr	1530 mg	5	Hepatic Failure Renal Failure Respiratory Failure, GVHD	N/A	No	Did not improve	No
	89.5 mg/kg Q6hr	3375 mg	2	Collapsed Lung Pancreatitis	*P. aeruginosa*	Yes	Improved	No
	96.2 mg/kg Q6hr	500 mg	1	PICC /Rash	N/A	Yes	Improved	No
	100.0 mg/kg Q6	1300 mg	1	Pseudomeningocele	N/A	N/A	Improved	No
	101.5 mg/kg Q6hr	1320 mg	3	Hematemesis Hypoxia Tachycardia	N/A	No	Did not improve	No
	100.0 mg/kg Q6hr	1050 mg	3	Hypotension Hypoxia Volume Overload	N/A	No	Improved	No
	75.5 mg/kg Q6hr	4500 mg	1	Seizure	Normal Flora	No	Improved	No

#	P/T Dosing	Dose received /Day	No. of SAE	SAE(s)	Organism	Ventilator (Y/N)	Clinical Outcome	Death
(b) (6)	75.0 mg/kg Q6hr	1065 mg	1	Ileus	*M. catarrhalis*, *P. aeruginosa*	No	Improved	No
	101.7 mg/kg Q6hr	2400 mg	1	Pancreatitis	N/A	No	Did not improve	No
	93.8 mg/kg Q8hr	1200 mg	1	Pericardial Effusion	N/A	No	Improved	No

Source: FDA Reviewer
Note: # = Subject number; N/A =Not available

Reviewer's Comment: : Among patients 2 months to 9 months age group, 16.6% experienced any serious adverse event; whereas, 12% patients experienced any serious adverse event among older age group. Serious events by body system were as follows: cardiovascular (10), neurologic (3), endocrine (0), gastrointestinal (4), hematologic (1), hepatic (1), infection (2), renal (1), respiratory (10), and skin (2). Causality of serious events were difficult to ascertain due to lack of narratives, and retrospective collection of data. Based on sponsor's notation, none of the serious adverse events were considered directly related to study drug or had led to discontinuation of study drug.

Serious adverse events occurred across varying dosages and frequencies with no apparent correlation between dosing regimen and occurrence of serious adverse events.

In terms of degree of a patient's underlying illness at the onset of NP treatment, the sponsor collected data on enrolled patients that included a number of covariates that were identified a 'priori as possible confounders of the association' between the exposure groups and serious events. The resultant adjusted IRRs and accompanying 95% CIs for the comparison of P/T to all comparator antibacterial and specifically to carbapenems subset for the primary endpoint of serious events suggested no difference in these outcomes across treatment groups.

6.2.5. Additional Safety Explorations

Literature review and analyses of postmarketing safety reports was an essential part of the review process to obtain additional safety information on P/T use in pediatric patients at a dose of 80 mg/10mg/kg to 100/ 12.5/Kg at a frequency of Q 6 hours. P/T has been used in post marketing setting since 1996, therefore, literature and post market safety reports were a readily accessible source of information for the reviewer. In addition, literature was explored to review new safety concerns reported in recent years associated with P/T or its class (betalactam) in general.

This reviewer conducted a systematic literature search and also reviewed adverse events reported in FDA FAERS data, between the calendar year January 1999 to Decemebr 2019.

I. Literature Review

A systematic PubMed search using FDA tool PERIDOT was conducted to identify articles that could provide additional safety information to support the pediatric use of P/T at a dose of 80-100 mg/Kg piperacillin every 6 hours for various clinical indications.

Majority of the studies reported in the literature used P/T at a dosing range of 80 - 100/ Kg piperacillin at a frequency of every 8 hours. There were 4 citations of comparative studies conducted in children with 'febrile neutropenia' where P/T was used at a dose of 80-100 mg/Kg every 6 hours. These studies are briefly summarized in the table below (Table 24) . A thorough information on adverse events associated with study treatments were only provided in study by Cometta et al.

Table 24 Summary of Studies in Literature that utilized 80 mg/10 mg/Kg P/T and maximum of 4.5 gm per dose Q6H in Pediatric patients

Author/ year	Setting	Number of patients	Dose	Study findings/Comment
Cometta et al, 1995[8]	Open label, prospectively randomized study to compare safety, tolerance and efficacy of P/T plus amikacin vs ceftazidime plus amikacin in febrile granulocytopenic children (2 months to 14 years)	N= 146 P/T: 76 Ceftazidime:70 Age Gr: 2m - 14 Y	80mg/10mg/Kg Q6H for children <50kg;* 4.5 Gm Q 6H for children >50kg** *Dose equivalent to younger infants(2m-9 m) proposed for treatment of NP; **Dose equivalent to older children proposed for treatment of NP	-The study subjects had cancer or had undergone bone marrow transplant for a neoplastic disease. -Both treatment groups were comparable in terms of age, and other baseline clinical characteristics. -Duration of treatment was to be a minimum of 7 days -The two treatment arms were equivalent with regard to microbiologically documented infection based on the ITT. Safety Findings: There were 4 deaths in the study, 2 in each treatment arm; only 1 was secondary to infection, which was in the ceftazidime arm. There was higher

[8] A. Cometta et al, THE INTERNATIONAL ANTIMICROBIAL THERAPY COOPERATIVE GROUP OF THE EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER. Piperacillin-Tazobactam plus Amikacin versus Ceftazidime plus Amikacin as Empiric Therapy for Fever in Granulocytopenic Patients with CancerANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1995, p. 445–452

				incidence of AEs in the P/T arm (21/76, 26.3% vs 7/70, 10%; p=0.018). Main difference in AEs between the treatment arms were due to high incidence of *rash /urticaria* (7/21, 26%), and *hypokalemia* (8/21, 10.5%) in PT arm. Additionally, P/T patients had more drug-related AEs (15.8% vs 4.3%; p=0.028), and 5 of those patients were withdrawn from the study all due to moderate rash /urticaria.
Metin Demirkaya 2013 [9]	Propectively, randomized study to compare safety and effectiveness of P/T Plus Amikacin Versus Cefoperazone-Sulbactam Plus Amikacin for Management of FN in Children (0 -18 years of age) With Lymphoma and Solid Tumors	N=46 (1:1 randomization) Age: 0 m -18 Y	90 mg/kg/day Q 6 H* (*Dosage regimen slightly higher than dose proposed for younger infants with NP)	Both groups were comparable in terms of age, and other baseline clinical characteristics. Both combinations were effective and safe as empirical therapy for febrile neutropenic patients. Safety findings: No major side effect were reported in either group during the course of the study.
Corapcioglu et al., 2006[10]	Prospectively, randomized, controlled trial to compare the efficacy and safety of P/T with cefepime monotherapy in children (2 to <18 years of age) with febrile neutropenia	N=50 P/T : 25 Cefepime: 25 Age: 2 Y to <18 Y	80 mg/10 mg/kg every 6 h (maximum 4.5 g /dose)	Both groups were comparable in terms of age, and other baseline clinical characteristics. Microbiologically and clinically documented infection rate was 46%. The treatment success of initial empirical therapy without modification was not different in the two groups (56% in P/T group and 48% in cefepime group). Safety Findings:

[9] Metin Demirkaya, Solmaz Çelebi, Betül Sevinir & Mustafa Hacımustafaoglu (2013) Randomized Comparison of Piperacillin–Tazobactam Plus Amikacin Versus Cefoperazone-Sulbactam Plus Amikacin for Management of Febrile Neutropenia in Children with Lymphoma and Solid Tumors, Pediatric Hematology and Oncology, 30:2, 141-148
[10] Funda Corapcioglu, Nazan Sarper & Emine Zengin (2006) MONOTHERAPY WITH PIPERACILLIN/TAZOBACTAM VERSUS CEFEPIME AS EMPIRICAL THERAPY FOR FEBRILE NEUTROPENIA IN PEDIATRIC CANCER PATIENTS: A Randomized Comparison, Pediatric Hematology and Oncology, 23:3, 177-186

				No fatalities were reported in either treatment arms. Both combinations were found safe and effective.
Yildrim et al., 2008 [11]	Prospective, randomized trial to compare P/T and amikacin with carbapenem monotherapy for the empirical treatment of febrile neutropenic episodes of children with acute leukemia.	N=87 P/T: 46 Meropenem:41 Age: 2 Y to 16 Y	80 mg/10 mg/kg every 6 h	No difference between the two regimens for durations of fever, neutropenia, and hospitalization. Safety Findings: No difference in adverse events reported between the treatment groups.

Abbreviations: m=month; y= year; N= number of subjects; ITT= intent to treat analysis; AE= adverse events
Source: FDA Reviewer

The other articles reviewed used P/T (sometimes in combination with an aminoglycoside) at a dose of 80-100 mg/kg every 8 hours. These articles described use of PT in different age groups in the pediatric population for the treatment of *FN.* The authors would generally provide safety reports (anecdotally) probably *somewhat* relevant to this review. The authors did not provide how many patients received P/T, what dose and, more significantly, what AEs were suffered by these patients during the study, even if to report that none were encountered. Two articles reported the dose of P/T used and adverse events noted during the studies (Le Guyader et al; and Nurnberger et al, briefly summarized below).

Le Guyader et al[12]: This was an observational noncomparative trial in France in which 148 neutropenic episodes in 104 children (mean age 7 years) were treated with P/T (100 mg/12.5 mg/kg) Q 8h, along with netilmicin. When indicated, a glycopeptide and antifungals were added. No deaths occurred; 1 child had a rash in P/T arm that resolved after P/T was discontinued. The authors concluded that P/T was efficacious and well tolerated.

[11] I. Yildirim, S. Aytac, M. Ceyhan, M. Cetin, M. Tuncer, A. B. Cengiz, G. Secmeer & S. Yetgin (2008) PIPERACILLIN/TAZOBACTAM PLUS AMIKACIN VERSUS CARBAPENEM MONOTHERAPY AS EMPIRICAL TREATMENT OF FEBRILE NEUTROPENIA IN CHILDHOOD HEMATOLOGICAL MALIGNANCIES, Pediatric Hematology and Oncology, 25:4, 291-299

[12] Le Guyader N, Auvrignon A, Vu-Thien H, Portier E, Tabone MD, Leverger G. Piperacillin-tazobactam and netilmicin as a safe and efficacious empirical treatment of febrile neutropenic children. Support Care Cancer 2004; 12:720-724.

Nurnberger et al[13]: This was a noncomparative trial in Germany published in 1998, which assessed the tolerability of P/T (80 mg/10 mg/kg Q 8h) in 19 children (aged 2 to 18 years, with 7 children under age 12) who developed fever during aplasia after high-dose radio or chemotherapy and autologous stem cell transplantation (HD-SCT) for primary multifocal or relapsed solid tumours. No severe side effects and no relevant laboratory abnormalities secondary to P/T were reported in this study. Most children did have a mild reversible glultamyltransferase (GGT) elevation, and although P/T cannot be excluded as a cause, this was felt to be secondary to cytoreductive therapy.

Another literature search specifically focused on 'safety profile' of P/T in pediatric population identified five additional citations[14,15,16,17,18] reporting 'acute kidney injury (AKI)' in pediatric patients when P/T was administered concomitantly with vancomycin across various clinical settings (including febrile neutropenia, cystic fibrosis, sepsis, intraabdominal infections). These studies are summarized briefly in Appendix 12.2. In summary, these citations were related to an higher incidence of AKI when P/T was used at approved doses in combination with vancomycin in pediatric patients, especially in the presence of renal insufficiency. Warning for 'AKI when P/T is administered comcomitantly with vancomycin' has already been added recently to Zosyn USPI, based on similar post marketing reports from use in adult population.

II. Safety studies on very low birth weight and premature infants

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[13] Nurnberger W, Bonig H, Burdach S, Gobel U. Tolerability of piperacillin/tazobactam in children and adolescents after high dose radio-/chemotherapy and autologous stem cell transplantation. Infection. 1998;26(1):65-67.
[14] Cook K.M., Gillon J., Grisso A.G., Banerjee R., Jimenez-Truque N., Phillips E.J., Van Driest S.L. Incidence of Nephrotoxicity Among Pediatric Patients Receiving Vancomycin With Either Piperacillin-Tazobactam or Cefepime: A Cohort Study 26 Mar 2018 Journal of the Pediatric Infectious Diseases Society 2018
[15] Joyce E.L., Kane-Gill S.L., Priyanka P., Fuhrman D.Y., Kellum J.A. Piperacillin/Tazobactam and Antibiotic-Associated Acute Kidney Injury in Critically Ill Children 09 Sep 2019 Journal of the American Society of Nephrology : JASN 2019
[16] Kalligeros M., Karageorgos S.A., Shehadeh F., Zacharioudakis I.M., Mylonakis E. The association of acute kidney injury with the concomitant use of vancomycin and piperacillin/tazobactam in children: A systematic review and meta-analysis 07 Oct 2019 Antimicrobial agents and chemotherapy 2019.
[17] Downes KJ et al, Association of Acute Kidney Injury With Concomitant Vancomycin and Piperacillin/Tazobactam Treatment Among Hospitalized Children. JAMA Pediatr. 2017
[18] Abouelkheir M et al; Pediatric acute kidney injury induced by concomitant vancomycin and piperacillin-tazobactam. Pediatr Int. 2018 Feb;60(2):136-141.

A PubMed search was also performed to evaluate any reports on safety information in very low birth weight and premature infants. Search yielded two citations[19,20] where safety of P/T was evaluated in very low birth weight and premature infants. Brief summary of these citations are described below.

Berger et al [19] conducted an open-label, noncomparative safety study of P/T in very low birth weight infants, defined in the study as those having a birth weight ≤ 1500 g. This safety evaluation enrolled 27 preterm infants, with 17 (63%) having suspected necrotizing enterocolitis (NEC), 3 (11%) having other intraabdominal infections, 4 (15%) having nosocomial sepsis with gram negative rods, and another 3 (11%) having a nosocomial infection that did not respond to empiric therapy. The patients were all initially treated with vancomycin plus an aminoglycoside. In the event of clinical failure, defined as a lack of response to empiric therapy in the first 48 hours, patients were given P/T 80/10 mg/kg IV q8h for a minimum of 3 days, in addition to the vancomycin and aminoglycoside combination. The only exception to this was when the growth of gram-negative rods was observed in the blood culture, in which case the vancomycin was discontinued. Clinical evaluation revealed cure or improvement in 17 (63%) patients. There were no study drug-related adverse events, and the authors concluded that P/T was safe and well tolerated in preterm infants with bacterial infections, particularly those involving the gastrointestinal tract.

Flidel-Ramon et al [20] conducted a pharmacokinetics study, where 7 infants (mostly premature newborns) had documented bacterial sepsis. In all of these cases, documented bacterial sepsis resolved with treatment with P/T administered at 100/12.5 mg/kg, however, dosing frequency was not reported in this study. No adverse events were reported. None of the infants were renally impaired in the study.

III. Post marketing adverse events data summary

An Information was requested from the applicant to submit safety reports from global safety database associated with piperacillin and tazobactam use for any indication at a dose of 80-100 mg piperacillin/10-12.5 mg of tazobactam/ kg every 6 hours in pediatric patients 2 months to <18 years of age.

The applicant's search did not yield any safety data in subjects below 1 year of age. Based on applicant's submitted CRFs, a total of 28 subjects with 58 SAEs were identified in pediatric age

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[19] Berger A, Kretzer V, Apfalter P, et al. Safety evaluation of piperacillin/tazobactam in very low birth weight infants. J Chemother. 2004; 16(2):166-171
[20] Flidel-Rimon O, Britzi M, Friedman S, Shinwell ES, Soback S. The pharmacokinetics of piperacillin (PIP) and tazobactam (TAZ) in premature newborn infants [abstract]. Pediatr Res. 2003;53(Suppl 4):561A. Abstract 3179.

group ranging from 1.7 years to 17 years over a period of 1999 to 2019. Of those, 16 SAEs were reported for 7 subjects who received P/T between 1 gm to 2.4 gm Q 6 hours; and 42 SAEs reported in remaining 21 subjects who received doses between 3.375 gm to 4.5 gm every 6 hours (80-100 mg/kg every 6 hours). The CRFs for these subjects were reviewed by the clinical reviewer and summarized in table below. (Table 25)

Table 25 SAEs FAERS Data Base in subjects (<18 years of age) receiving P/T at a dose of 3.375 gm to 4.5 gm Q 6 Hours

#	AER [ISR]	SAEs	Reason for use	Age (year)	Dose
(b) (6)	2018292695	Pyrexia	Sepsis	1.7	1 gm Q 4 hr
	2018292695	Dermatitis allergic	Sepsis	1.7	1 gm Q 4 hr
	8-0940135104	Abdominal pain	Infection/CF exacerbation	3	1 gm Q 6 hr
	8-0940135104	Pyrexia	Infection/CF exacerbation	3	1 gm Q 6 hr
	FR-WYE-G02510508	Drug ineffective	Febrile bone marrow aplasia; Colitis	4	1.2 gm Q 6 hr
	FR-WYE-G02510508	Cholestasis	Febrile bone marrow aplasia; Colitis	4	1.2 gm Q 6 hr
	2008091847	GGT- increased	Febrile bone marrow aplasia	4	1.2 gm Q 6 hr
	2008091847	Rash	Febrile bone marrow aplasia	4	1.2 gm Q 6 hr
	FR-WYE-G02510508	pruritus	Febrile bone marrow aplasia; Colitis	4	1.2 gm Q 6 hr
	FR-WYE-G02510508	Rash morbilliform	Febrile bone marrow aplasia; Colitis	4	1.2 gm Q 6 hr
	8-0940135103	Vomiting	Infection/CF exacerbation	4	1.5 gm Q 6 hr
	8-0940135103	Pyrexia	Infection/CF exacerbation	4	1.5 gm Q 6 hr
	8-0940135103	Dermatitis	Infection/CF exacerbation	4	1.5 gm Q 6 hr
	2016581865	Pyrexia	Psudomonas Infection	7	1.8 g Q 6 hr
	2016581865	Rash maculo-papular	Psudomonas Infection	7	1.8 g Q 6 hr
	HQ5674209DEC2002	Blood glucose decreased	Infection	9	2.4 gm Q 6 hr
	HQ5674209DEC2002	Seizure	Infection	9	2.4 gm Q 6 hr
	2013251540	Neutropenia	Appendicitis perforated	3	3.375 gm Q 6hr
	2013251540	Thrombocytopenia	Appendicitis perforated	3	3.375 gm Q 6hr
	2013251540	Fibrin D dimer increased	Appendicitis perforated	3	3.375 gm Q 6 hr
	2013251540	Serum ferritin increased	Appendicitis perforated	3	3.375 gm Q 6 hr
	2016277872	Acute kidney injury	Pneumonia-Nosocomial	8	3.375 gm Q 6 hr
	8-0940135102	Pyrexia	Infection/CF exacerbation	9.5	3.375 gm Q 6hr
	8-0940135102	Dermatitis	Infection/CF exacerbation	9.5	3.375 gm Q 6 hr
	CO-WYE-H10089809	Eyelid edema	SSTI	12	4.5 gm Q 6 hr
	CO-WYE-H10089809	Anaphylactic reaction	SSTI	12	4.5 gm Q 6 hr
	CO-WYE-H10089809	Product preparation issue	SSTI	12	4.5 gm Q 6 hr
	CO-WYE-H10089809	Pruritus	SSTI	12	4.5 gm Q 6 hr
	2014322901	Tachycardia	Febrile bone marrow aplasia	13	3.6 gm Q 6 hr
	2014322901	Toxic skin eruption	Febrile bone marrow aplasia	13	3.6 gm Q 6 hr
	2014322901	Hypotension	Febrile bone marrow aplasia	13	3.6 gm Q 6 hr
	2012142211	Anemia	SSTI	14	3.375 gm Q 6hr
	2012142211	Thrombocytopenia	SSTI	14	3.375 gm Q 6hr
	GB8897824JAN2002	Hemolysis	Pneumonia	14	4.5 gm Q 6 hr
	HQWYE573522APR04	Hemolytic anemia	Pneumonia	14	4.5 gm Q 6 hr
	8-97345-013L	Tooth discoloration	SSTI	14	3.375 gm Q 6hr

#	AER [ISR]	SAEs	Reason for use	Age (year)	Dose
(b) (6)	FR-WYE-G04061309	Aggression	Febrile bone marrow aplasia	14	4.5 gm Q 6 hr
	FR-WYE-G04061309	Obsessive thoughts	Febrile bone marrow aplasia	14	4.5 gm Q 6 hr
	FR-WYE-G04061309	Dysphonia	Febrile bone marrow aplasia	14	4.5 gm Q 6 hr
	1227926 [8232577]	Febrile neutropenia	Febrile bone marrow aplasia	15	4.5 gm Q 6 hr
	1227926 [8232577]	Tubulointerstitial nephritis	Infection/Pneumonia?	15	4.5 gm Q 6 hr
	FR-WYE-G04958909	Cholestasis	Pneumonia	15	3.2 gm Q 6 hr
	FR-WYE-G04958909	Hepatomegaly	Pneumonia	15	3.2 gm Q 6 hr
	FR-WYE-G04958909	Jaundice	Pneumonia	15	3.2 gm Q 6 hr
	FR-WYE-G04958909	PT prolonged	Pneumonia	15	3.2 gm Q 6 hr
	IL-WYE-H07238308	Septic shock /Drug ineffective	Infection/Unknown	15	4.5 gm Q 6 hr
	2017035104	Toxic epidermal necrolysis	Infection/Unknown	15	4.5 gm Q 6 hr
	HQ2776226OCT2000	Visual impairment	Infection/Unknown	16	3.375 gm Q 6 hr
	HQ2776226OCT2000	Vomiting	Infection/Unknown	16	3.375 gm Q 6 hr
	2016349252	Inflammation	Bacterial Sepsis *	16	4.5 gm Q 6 hr
	2016349252	Pyrexia	Bacterial Sepsis	16	4.5 gm Q 6 hr
	HQ2776226OCT2000	Anxiety	Infection	16	3.375 gm Q 6 hr
	HQ2776226OCT2000	Hypotension	Infection	16	3.375 gm Q 6 hr
	2016349252	Photosensitivity	Bacterial Sepsis *	16	4.5 gm Q 6 hr
	2016349252	Rash	Bacterial Sepsis	16	4.5 gm Q 6 hr
	2016349252	Hypotension	Bacterial Sepsis	16	4.5 gm Q 6 hr
	HQWYE407209APR04	Autoimmune hemolytic anemia	Peritonitis Bacterial	17	3.375 gm Q 6hr
	US-WYE-H00523207	Pancreatitis	Abdominal	17	3.375 gm Q 6 hr
	2013056365	Drug ineffective	Pneumonia, community acquired	17	4.5 gm Q 6 hr

Source: FDA Reviewer/ FAERS Data base
*Pseudomonal sepsis
Abbreviations: hr=hour; PT=prothrombin time

Reviewer's Comment: In majority of cases P/T was used for the treatment of ' unspecified infections' or ' pneumonia' (5/28 [18%]) each; followed by ' febrile bone marrow aplasia' (4/28 [14%]); and 3 cases (11%) each of 'cystic fibrosis exacerbation', 'intra abdominal infections', 'sepsis with pseudomonas'; and 'skin and subcutaneous infections'.

Adverse events were coded most frequently to skin/subcutaneous disorders and hematologic disorders. 12 subjects experienced adverse events related to local or systemic allergic reactions (11 subjects with either rash, pruritus , dermatitis, or phtosensitivity and 1 subject with anaphylaxis); 7 subjects experienced hematologic events (thrombocytopenia (2), hemolytic anemia (3), and neutropenia(2)); 6 subjects experienced pyrexia; 5 subjects experienced events related to hepatic disorders (cholestasis (3), hepatomegaly (2), GGT increased(1)); 3 subjects experienced hypotension; 2 subjects experienced vomiting; 1 subject experienced pancreatitis; 1 subject experienced acute kidney injury; and 1 subject experienced seizures.

Of note, pyrexia and rash were coded AEs in majority of patients who were treated with P/T for cystic fibrosis exacerbation. Similar findings have been reported in adult patients with cysctic findrosis, and is already added to Section 8, 'Use in Specific Population' subsection of Zosyn USPI.

Additional search of FDA FAERS Data

Additional query was run for FDA FAERS data to search for any adverse events reported for infants below 12 months of age who received P/T for any indications at any dose, and where P/T was considered a primary suspect between January 1, 1999 to December 31, 2019. Results yielded a total of 12 reports. In majority of the cases, P/T doses and frequencies were missing which limits this evaluation.(Table 26)

Table 26 Adverse Events from FDA FAERS database reported in Infants <12 months of age where primary suspect drug was "piperacillin/tazobactam"

#	FAERS CASE #	Age	Reported Reason for Use	Dose-Route-Freq	Adverse Events by PT
(b) (6)	4126744	6 m	*E. Coli* infection placenta	N/A	Atrial Flutter
	3414777	12 m	Pneumonia, Lung Abscess	1 G Q 8 hr	Pyrexia; Dermatitis; Diarrhea
	6911948	12 m	UTI Prophylaxis	1.25 G Q 24 hr	Diarrhea
	9542458	12 m	Pneumonia	787.5 mg Q 8 hr	Hepatic function abnormal
	12062143	3 m	"Infection"-unspecified	N/A	Rash/ Injection site erosion
	10905108	6 m	"Infection"-unspecified	N/A	Neutropenia
	9408143	9 m	Pneumonia necrotizing	N/A	Neutropenia
	15531646	8 m	"Infection"-unspecified	N/A	Rash
	4157325	2 m	Bacteremia with Serratia	N/A	Rash
	7442625	3 m	Skin Infection	1 G Q 8 hr	Rash; Urticaria
	10396419	12 m	Pneumonia	N/A	Drug interaction with valproic acid*
	11663425	8 m	Sepsis, Bacteremia	175 mg Q 8 hr	Thrombocytopenia
	15487054	8 m	"Infection"-unspecified	1.2 G Q 24 hr	Seizure; Dyskinesia
	16092192	2 m	"Infection"-unspecified	N/A	Seizure-generalized tonic-clonic
	16114438	12 m	Sepsis	1 G Q 8 hr	Seizure-tonic-Clonic movements
	16178203	2 m	"Infection"-unspecified	N/A	Seizure-generalized tonic-clonic

* Subject experienced SAE of : seizure" which was considered definitely related to the drop in valproic acid levels on day 3 of P/T therapy.

Source: FDA Reviewer

Reviewer's Comment: As shown in table above, P/T is used at varying doses in infants, and in majority of cases (6/16 [37.5%]), reason for use of P/T was not specified and was coded as "Infection-unspecified". Pneumonia was the reason for use in quarter of cases (4 of 16 (25%)); Sepsis or bacteremia in 3/16 (18.7%) cases; Skin infection, and urinary tract prophylaxis was reason for use 1 case each.

With regards to adverse reactions, similar to what was seen in pediatric age group older than 1 year, adverse events were coded most frequently to skin/subcutaneous disorders. Majority of subjects (5/16 [31.3%]) experienced adverse events related to local or systemic allergic skin reactions (rash, dermatitis, urticaria); followed by seizures (4/16 [25%]); hematological adverse

events (3/16 [18.7%]); diarrhea(2/16 [12.5%]); drug interaction with valproic acid, and hepatic function abnormality was experienced by 1 subject each.

Although, SAE of seizures is reported in about a quarter of (25%) infants in this FAERS query, it should be noted that 'febrile seizures' are common in infants and it is difficult to ascertain the causality with P/T without any additional and specific details on subject's case history. Neverthless, a warning of 'seizures' has been added recently to the product USPI (NDA 059684, Supplement-95) based on post marketing reports in adults. *The seizure-inducing potential appears to be one of neurotoxic effect associated with beta-lactam class of antibacterial drugs. Manifestations of CNS toxicity associated with beta- lactam class exposure is primarily linked to the core beta-lactam ring seen within members of this class.[21] Specific precaution is advised in patients with renal imapirement. Elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance, therefore, patients with a medical history of chronic renal impairment may be more susceptible to the neurotoxic effects of piperacillin-tazobactam.*

6.3. Statistical Issues

There were two main statistical limitations in this study that applied to both the safety and efficacy analyses. First, this study was non-randomized, and thus was susceptible to confounding if there were underlying systematic differences between piperacillin/tazobactam group and comparator groups. The Poisson and negative binomial regression modeling of serious events and the logistic regression modeling of clinical improvement attempted to control for confounding factors, and at a high level appeared to be statistically acceptable approaches given the limitations of the observational data. However, measured confounders may not have completely encapsulated group differences. Further, even when confounders are measured causal interpretations can depend on unverifiable assumptions such as correct specification of the propensity score or outcome regression models. The most notable source of potential confounding was the difference between treatment groups in participating study sites, because several large hospitals either included all of their patients in the piperacillin/tazobactam group or all of their patients in the comparator group.

The second main limitation of this study related to prespecification. The statistical analysis plan left room for analyst discretion regarding exactly which covariates to consider for adjustment. The applicant additionally implemented several post-hoc changes to the analyses that had been originally specified in the statistical analysis plan, such as inverse weighting the regression

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[21] Chow KM, et al. Neurotoxicity induced by beta- lactam antibiotics: from bench to bedside. EurJ Clin Micro bio infect Dis. 2005; 24:649–653.

models by propensity scores. Although in principle inverse propensity score weighting is an acceptable statistical strategy, without prespecification it is difficult to gauge possible sources of conscious or unconscious bias.

Despite these statistical limitations, there did not appear to be extreme differences between the piperacillin/tazobactam group and comparator group in terms of safety or efficacy outcomes, irrespective of adjustment for confounding factors. In fact, piperacillin/tazobactam was associated with more frequent clinical improvement and less frequent mortality or serious events than the carbapenem subset of the comparator group. From a statistical perspective, this study did not uncover any obvious signals for piperacillin/tazobactam decrements in pediatric patients. Consequently, determination of efficacy for piperacillin/tazobactam for pediatric HAP will be largely reliant on extrapolation from efficacy in adults, and determination of safety will be largely reliant on clinical assessments of causal relationships between the drug and observed adverse events.

6.4. Safety Summary and Conclusions

The safety profile of P/T in pediatric population with NP was evaluiated in a retrospective comparative study in pediatric patients 2 months of age and older (<18 years) who received P/T at a dose of 80-100 mg/kg piperacillin/ 10-12.5mg/kg tazobactam every 6 hours compared with those who received at least one dose of a comparator antibacterial drugs used at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients. The primary study endpoint was the development of serious adverse events within 40 days of treatment initiation, and all-cause mortality 30 days from the day of study drug initiation. This study included 412 pediatric patients from 7 hospitals across the US to assess safety and effectiveness of P/T in pediatric patients with NP.

Of 412 patients included in the study, 407 (98.8%) patients received proposed NP dosing, and were considered as the primary analysis set (PAS). Of 407 patients, 140 (34%) patients were included in the P/T group, and 267 (65%) patients were included in the comparator group. Mean age (range) of patients in the P/T group was 7.65 years compared to 6.57 years in the comparator group. Overall, patients in the two groups were comparable with regards to the distribution of sex and race. Slightly more than half (55%) of the patients were males, and whites in both groups. The proportion of infants (2 months to 9 months of age) was numerically slightly lower in the P/T group as compared to the comparator group (21.4% versus 29.5%). Overall, the crude incidence rate (per 100 person-days) of serious events was 1.27 [95% CI: 0.84-1.70] in the P/T group and 1.02 [95% CI: 0.76-1.28] in the Comparator groups. A further sensitivity analysis showed no substantial difference in incidence rates (per 100 person- days) of all serious events in the two treatment groups for various treatment durations (i.e., at least 2 days of therapy, at least 5 days of therapy and at least 7 days of therapy). No new or concerning signals surrounding safety or efficacy following P/T treatment were identified in this retrospective study.

Based on the additional review of literature, FAERS reports, and reports from post marketing use of P/T since 1999 in pediatric age group across a variety of indications (on and off label), the adverse events in pediatric age group reported to be associated with P/T use in decreasing order, werecoded to skin/subcutaneous disorders (rash, pruritus , dermatitis, or photosensitivity); followed by hematologic events (thrombocytopenia, hemolytic anemia, and neutropenia); pyrexia; GI and hepatic disorders (cholestasis, hepatomegaly, GGT increased, diarrhea and vomiting); seizures (mostly ininfants), and acute kidney injury when used concomitantly with vancomycin.

Overall, based on the safety results from the retrospective study, product's long history of clinical use in adults with nosocomial pneumonia, use in pediatric patients for various indications, including 'pneumonia' (off label use), literature review and postmarketing reports, no new safety signals were identified in pediatric population at any specific dosing regimen or frequency or when used for any specific indication. Although the retrospective nature of the study and quality of postmarketing data had important limitations, the information provided was adequate to support labeling the product for the treatment of NP in children 2 months of age and older.

7 Advisory Committee Meeting and Other External Consultations

Not applicable.

8 Pediatrics

These sNDAs was submitted to provide safety information with regards to use of Zosyn in pediatric patients with NP. The basis for pediatric use labeling of Zosyn in NP is the following:

1. Zosyn has previously been approved for treatment of "nosocomial pneumonia" in adults. The approved dosing regimen is 4.5 gm every 6 hours.
2. PK information was submitted to the NDA in 2009 in support of the recommended dosage regimen for pediatric patients from 2 months to 9 months of age and >9 months to <18 years of age. This information is based in part on the comparable PK profile for the patients in comparison to the PK for children greater than 2 years of age and adults.
3. Postmarketing safety data and literature reports on use of Zosyn for various indications provided supporting information on the use of Zosyn at a frequency of every 6 hours in pediatric patients. The postmarketing experience described the adverse events

generally consistent with that described in the sponsor's submitted retrospective study on nosocomial pneumonia.

One important limitation of the available data is the lack of information to support the safety and effectiveness of Zosyn in pediatric patients with renal dysfunction. Of particular note, the safety and effectiveness of Zosyn has not been determined in neonates and premature infants in the first 2 months of life, a population with known physiologic renal dysfunction.

Of note, a partial waiver was granted for pediatric patients from birth to 3 months of age from the required PREA study on January 25, 2008, because trials in this young pediatric populationwould be impracticable.

9 Postmarketing Requirements and Commitment

Not applicable.

10 Postmarketing Risk Management Plan

Postmarketing risk management activity should include postmarketing reporting of adverse drug experiences in pediatric population with nosocomial pneumonia as outlined in 21 CFR 314.80.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant proposed labeling (b) (4) The Zosyn prescribing information has been updated to add the pediatric NP indication (1.2), pediatric dosing for NP (2.4), pediatric use in the specific populations section (8.4), and edits to the study information added to clinical trials experience in the adverse reactions section (6.1). (b) (4) During the review cycle, modified warning language incorporating risk of seizures was approved for Section 5.4 (Supplement-95, approved April 13, 2020).

12 Appendices

12.1. Ethical Conduct

Per section 9.15.3 of the study report, the study followed generally accepted research practices described in *Good Pharmacoepidemiology Practices (GPP)* issued by the International Society for Pharmacoepidemiology (ISPE), European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*, and FDA Guidance for Industry and FDA *Staff Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.*

12.2. Acute Kidney Injury in association with P/T and Vancomycin in Pediatric patients

Acute Kidney Injury in association with P/T and Vancomycin

1. Cook K.M., Gillon J., Grisso A.G., Banerjee R., Jimenez-Truque N., Phillips E.J., Van Driest S.L. Incidence of Nephrotoxicity Among Pediatric Patients Receiving Vancomycin With Either Piperacillin-Tazobactam or Cefepime: A Cohort Study 26 Mar 2018 Journal of the Pediatric Infectious Diseases Society 2018
This was a retrospective single-center matched-cohort study of pediatric patients (1 months to <18 years of age), who received vancomycin in combination with P/T or cefepime between January 2015 and June 2016. The patients were matched according to chronic disease, age, sex, and number of concomitant nephrotoxic medications at the time of combination antibiotic therapy. The primary outcome was incidence of acute kidney injury (AKI). Secondary outcomes included differences between groups in time to AKI, resolution of AKI, and effect of vancomycin trough levels on the incidence of nephrotoxicity. Two hundred twenty-eight (208) matched patients were included. AKI developed in 9 (7.9%) of 114 and 33 (28.9%) of 114 patients in the cefepime and P/T groups, respectively (P < .001). Type of combination therapy remained a significant predictor for AKI in multivariate conditional Poisson analysis in which adjustments were made for age, sex, use of concomitant nephrotoxins, and vancomycin dose (relative risk, 2.5 [95% confidence interval, 1.1-5.8]; P = .03). AKI developed almost 3 times sooner in the P/T group than in the cefepime group (hazard ratio, 2.9 [95% confidence interval, 1.3-6.1]; P = .006). Sensitivity analyses in which adjustment was made for antibiotic indication in addition to the aforementioned variables and excluding those with gastrointestinal infection revealed similar results. In conclusion, combination therapy with vancomycin and P/T was associated with an incidence of AKI higher than that associated with vancomycin and cefepime.

2. Joyce E.L., Kane-Gill S.L., Priyanka P., Fuhrman D.Y., Kellum J.A. Piperacillin/Tazobactam and Antibiotic-Associated Acute Kidney Injury in Critically

Ill Children 09 Sep 2019 Journal of the American Society of Nephrology : JASN 2019[22]

This was a retrospective cohort study assessing the risk of AKI in pediatric intensive care unit patients after exposure to vancomycin, TZP, and cefepime, alone or in combination, within 48 hours of admission. The primary outcome was development of stage 2 or 3 AKI or an increase in AKI stage from 2 to 3 within the 6 days after the 48-hour exposure window. Secondary outcomes included lengths of stay, need for RRT, and mortality. Of 5686 patients included, 494 (8.7%) developed stage 2 or 3 AKI. The adjusted odds of developing AKI after medication exposure were 1.56 for P/T (95% confidence interval [95% CI], 1.23 to 1.99), 1.13 for cefepime (95% CI, 0.79 to 1.64), and 0.86 for vancomycin (95% CI, 0.69 to 1.07). The adjusted odds of developing AKI for vancomycin plus P/T versus vancomycin plus cefepime was 1.38 (95% CI, 0.85 to 2.24). In conclusion, this observational data in critically ill children showed that P/T use is associated with increased odds of AKI.

3. Kalligeros M., Karageorgos S.A., Shehadeh F., Zacharioudakis I.M., Mylonakis E. The association of acute kidney injury with the concomitant use of vancomycin and piperacillin/tazobactam in children: A systematic review and meta-analysis 07 Oct 2019 Antimicrobial agents and chemotherapy 2019.

In this systematic review and meta-analysis for pediatric studies, examining the hypothesis, that "concomitant use of vancomycin plus piperacillin/tazobactam (TZP) has been associated with increased risk of acute kidney injury (AKI) in hospitalized adults." In primary analysis, concomitant vancomycin and P/T use yielded a statistically significant association with the development of AKI. More specifically, children with AKI had higher odds to have been exposed to vancomycin plus P/T, in comparison with vancomycin monotherapy (OR 8.15; 95% CI: 3.49-18.99), or vancomycin plus any other beta-lactam antibiotic (OR 3.48; 95% CI: 2.71-4.46). Based on the results of the Newcastle Ottawa Scale quality assessment, a secondary analysis including only higher quality studies (6 out of 10 studies) yielded again higher odds of exposure to vancomycin plus P/T, compared to vancomycin plus another beta-lactam antibiotic (OR 3.76; 95% CI: 2.56-5.51). Notably, even after controlling for possible publication bias, results remained statistically significant (OR 3.09; 95% CI: 2.30-4.14). In conclusion, this metaanalysis showed that the concomitant use of vancomycin and P/T could be associated with AKI development in the pediatric population.

4. Downes KJ et al, Association of Acute Kidney Injury With Concomitant Vancomycin and Piperacillin/Tazobactam Treatment Among Hospitalized Children. JAMA Pediatr. 2017

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[22] Joyce E.L., Kane-Gill S.L., Priyanka P., Fuhrman D.Y., Kellum J.A. Piperacillin/Tazobactam and Antibiotic Associated Acute Kidney Injury in Critically Ill Children 09 Sep 2019 Journal of the American Society of Nephrology : JASN 2019

In this multicenter retrospective cohort study of hospitalized children 6 months to 18 years of age who were given combination therapy, which consisted of IV vancomycin plus 1 antipseudomonal β-lactam agent (ceftazidime sodium, cefepime hydrochloride, P/T, meropenem, or imipenem/ cilastin sodium), on at least days 1 and 2 of hospitalization were enrolled. Patients who received multiple β-lactam agents plus vancomycin on hospital day 1 or 2 were excluded. The KDIGO (Kidney Disease: Improving Global Outcomes) criteria were used to define AKI. Of the 1915 patients, a total of 866 (45.2%) were female and 1049 (54.8%)were male, 1049 (54.8%) were identified as white in race/ethnicity, and the median age was 5.60 years (interquartile range [IQR], 2.12-12.65 years). In this combination therapy cohort, 157 patients (8.2%) developed AKI within the first hospital week, and 74 (47%) of these patients had KDIGO26 stage 2 AKI or higher. Recipients of IV vancomycin plus a β-lactam agent who sustained AKI, compared with those who did not,were older (median age, 12.64 years [IQR, 7.92-15.82 years] vs 5.03 years [IQR, 1.97-11.81 years]; P < .001), more often required ICU level of care on hospital days 0 to 2 (67/157 [42.7%] vs 497/1758 [28.3%]; P < .001), and were more often administered 2 or more nephrotoxic medications (40/157 [25.5%] vs 319/1758 [18.1%]; P = .02) or IV contrast on hospital days 0 to 2 (25/157 [15.9%] vs 168/1758 [9.6%]; P = .01). On multivariable analysis using a discrete-time failure model, receipt of IV vancomycin plus P/T combination therapy was associated with increased odds of AKI each hospital day (adjusted odds ratio [aOR], 3.40; 95% CI, 2.26-5.14. The concomitant administration of intravenous vancomycin plus P/T, compared with vancomycin plus other antipseudomonal β-lactam antibiotics, was significantly associated with an increased risk of acute kidney injury.

5. Abouelkheir M et al; Pediatric acute kidney injury induced by concomitant vancomycin and piperacillin-tazobactam. Pediatr Int. 2018 Feb;60(2):136-141.

This was a retrospective chart review of pediatric patients, aged 0-14 years, who were admitted to the general wards or intensive care unit and developed AKI after receiving vancomycin and P/T concomitantly for >48 h. AKI was defined as a decrease in estimated glomerular filtration rate ≥50% from baseline. Cases were identified by reviewing the Adverse Drug Reaction program database at King Saud University Medical City in Saudi Arabia from January 2015 to June 2016. Eight (8) children received concomitant vancomycin and P/T treatment for pneumonia (n = 7) or febrile neutropenia (n = 1) developed drug-induced nephrotoxicity. Drug Interaction Probability Scale (DIPS) score for causation assessment was 9 in all cases (highly probable).

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