NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	Safety and Effectiveness of Piperacillin/Tazobactam (Zosyn®) for the Treatment of Pediatric Hospital Acquired Pneumonia (HAP) in the United States: A Retrospective Cohort Study
Protocol number	B2361001 (Formerly 0910K2-4015)
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EU Post Authorisation Study (PAS) register number	EU PAS 8352
Medicinal product	Piperacillin/Tazobactam (Zosyn®)
Research question and objectives	**Primary objective** To estimate the risk of serious events, including mortality, among pediatric patients with hospital acquired pneumonia (HAP) in the US treated with P/T as compared to other HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin).

	Secondary objective To evaluate "effectiveness" of the antibiotic therapy (using binary treatment outcome "clinically improved" or "did not improve") in pediatric patients with HAP in the US, comparing P/T to Comparator HAP appropriate antibiotics.
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LIST OF STAND ALONE DOCUMENTS

- Appendix 1. Study Protocol (including CRF)
- Appendix 2. Statistical Analysis Plan
- Appendix 3. Copies of De-Identified Medical Charts Requested by the FDA
- Appendix 4. Pilot Study Report
- Appendix 5. A copy of the IRB Letter declining the Request to provide de-identified copies of Medical Charts

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CAP	Community Acquired Pneumonia
CICU	Cardiac Intensive Care Unit
CBC	Complete Blood Count
CHOP	Children Hospital of Philadelphia
CI	Confidence Interval
CNS	Central Nervous Systems
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRAs	Clinical Research Associates
CRNs	Clinical Research Nurses
CXR	Chest x-Ray
DF	Degrees of Freedom
dl	Deciliter
e-HRD	Electronic Health Related Databases
Egfr	Estimated Glomerular filtration rate
EMA	European Medicines Agency

Abbreviation	Definition
EMR	Electronic Medical Records
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GGT	Gamma-Glutamyl Transferase
GPP	Good Pharmacoepidemiology Practices
gm	Gram
HAP	Hospital Acquired Pneumonia
Hgb	Hemoglobin
Hmpv	Human Metapneumovirus
IAI	Intra-abdominal Infections
ICD	International Classification of Diseases
IQR	Interquartile Range
IRR	Incidence Rate Ratio
IEA	International Epidemiological Association
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
KDIGO	Kidney Disease Improving Global Outcomes
LFTs	Liver Function Tests
LL	Log likelihood
MRSA	Methicillin-resistant Staphylococcus aureus
mEq/Dl	Milliequivalent/deciliter

Abbreviation	Definition
mmol/Ul	Millimole/microliter
mg/kg	Milligram/kilogram
mg/dl	Milligrams/deciliter
NCHS	National Center for Health Statistics
NICU	Neonatal Intensive Care Unit
NDI	National Death Index
OR	Odds Ratio
PHIS	Pediatric Hospital Information System
PICU	Pediatric Intensive Care Unit
PhRMA	Pharmaceutical Research and Manufacturers Association
POR	Physician of record
P/T	Piperacillin/Tazobactam
pRIFLE score	Pediatric Risk, Injury, Fail, Loss, End stage renal disease score
SAE	Serious Adverse Event
SOPs	Standard Operating Procedures
SCr	Serum creatinine
TBD	To Be Determined
THOU/uL	Thousand/microliter
UTI	Urinary Tract Infection
U/L	Units per liter

3. INVESTIGATORS

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5. MILESTONES

Milestone	Planned date	Actual date
Study Protocol		
Final Protocol		13 October 2009 (IND filing: 21 October 2009)
Protocol Amendment-I		18 September 2012
Protocol Amendment-II		16 December 2014
Protocol Amendment-III		1 November 2016
Protocol Amendment-IV		21 September 2017
Protocol Endorsement by the FDA		31 August 2013
Registration in the EU PAS Register	Prior to start of data collection	13 January 2015
Start of Study Data Collection	2 March 2015	2 March 2015
End of Study Data Collection	31 March 2018	26 Sept 2018
Study Progress Reports		
Progress Report-I	22 December 2014	18 December 2014
Progress Report-II	21 December 2015	24 November 2015
Progress Report-III	19 December 2016	19 December 2016
Progress Report-IV	18 December 2017	29 November 2017
Final Study Report	29 March, 2019	29 March, 2019

6. RATIONALE AND BACKGROUND

Pneumonia is a common source for hospital acquired infection in children and adults.[1,2] Hospital acquired pneumonia (HAP) is often categorized as associated or not associated with invasive ventilation. Estimates of overall HAP rates are limited but a recent multicenter surveillance study estimated the ventilator associated pneumonia (VAP) rate to be 0.7 per 1,000 ventilator days. While this rate has been steadily decreasing it still approximates the rate of central line associated bloodstream infection.[2] HAP often complicates the care of vulnerable children with prolonged hospital stay, those in the intensive care unit (ICU), and/or those with complex underlying illnesses. [3,4] Furthermore, a variety of Gram-positive or Gram-negative organisms can be the source of HAP which challenges the initial therapeutic decision for selecting appropriate antibiotics for treatment. [1,5,6,7] This constellation of factors makes it important to better understand the safety and effectiveness of empiric HAP antibiotic therapeutic options to reduce subsequent morbidity and mortality.[1,8]

Piperacillin/tazobactam (P/T) (Zosyn®) is an injectable antibacterial combination medication consisting of the semisynthetic antibiotic piperacillin sodium and the ß-lactamase inhibitor tazobactam sodium for intravenous administration. P/T was first approved by the US Food and Drug Administration (FDA) in 1993. Currently, P/T is approved for several adult indications in the US, including:

- Appendicitis (complicated by rupture or abscess),
- Uncomplicated and complicated skin and skin structure infections,
- Postpartum endometritis or pelvic inflammatory disease,
- Community-acquired pneumonia (CAP) (moderate severity only), and
- Nosocomial pneumonia (moderate to severe).

P/T is frequently utilized by pediatric clinicians to treat HAP because it has relatively broad coverage for pathogens linked to HAP. The safety and effectiveness of P/T in the treatment of HAP among pediatric patients has not been formally studied in either comparative observational studies or randomized controlled trials (RCTs). It is expected that P/T will have a similar incidence of serious adverse events (SAEs) and similar effectiveness to that of other current antibiotic therapies for HAP in pediatric patients i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin (hereafter referred to as "Comparator HAP appropriate antibiotics").

A previous RCT in hospitalized children with pneumonia presented challenges with recruitment of pediatric patients. [9] It is likely that prospective recruitment of pediatric patients with HAP would ultimately result in inadequate recruitment even over an extended period of time. Furthermore, recent data suggest that HAP rates are decreasing in pediatric institutions [2]. Given these data, it was not considered feasible to conduct a large and adequately powered RCT or a prospective observational study to evaluate the safety and effectiveness of P/T in treating pediatric HAP. In the interim pediatricians have continued to administer P/T to patients with HAP.

A retrospective cohort study using secondary data was designed to evaluate the safety and effectiveness of P/T in pediatric patients treated for HAP. This study design offers certain advantages. First, it evaluates the treatment of pediatric HAP in a real-world setting, which offers generalizability of study findings. Second, a secondary data collection study utilizing retrospective data can be completed in less time compared to a prospective study.

This retrospective cohort study evaluating the safety and effectiveness of P/T in pediatric patients with HAP was a Post-Authorization Safety Study (PASS) commitment to the US FDA.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Primary Objective

To estimate the risk of serious events, (9.6.2.1 Serious Events) including mortality, among pediatric patients with HAP in the US treated with P/T as compared to other HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin).

Specifically, to evaluate serious adverse events (referred to as "serious events"):

- Among pediatric patients with HAP 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 HAP appropriate antibiotic at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients.

- Among pediatric patients with HAP who received at least one dose of P/T ("Any dosing") to patients who received at least one dose of a Comparator HAP appropriate antibiotic.

7.2. Secondary Objective

To evaluate effectiveness of the antibiotic therapy (using a binary treatment outcome of "patient clinically improved" or "did not improve") in pediatric patients with HAP in the US, comparing P/T to Comparator HAP appropriate antibiotic therapies.

Specifically, to estimate the proportion of patients classified into the binary treatment effectiveness outcome:

- Among pediatric patients with HAP who received P/T at a dose 80-100 mg/kg piperacillin/ 10-12.5mg/kg tazobactam every 6 hours (HAP dosing).

- Among pediatric patients with HAP who received a Comparator HAP appropriate antibiotic at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients (HAP dosing).

8. AMENDMENTS AND UPDATES

The study protocol was amended four times; details of each amendment are provided in the protocol Amendment-IV (Appendix 1). Briefly:

- Amendment I was implemented to incorporate FDA's feedback on the draft protocol with regard to inclusion/exclusion criteria, sample size, and other comments relevant to study methods.

- Amendment II was performed to update the inclusion/exclusion criteria and the case report form (CRF) based on lessons learned from the pilot study.

- Amendments III and IV were primarily implemented to maximize patient enrollment (in an attempt to achieve the sample size) by expanding the study period and allowing local site staff to abstract data at additional study sites, respectively.

9. RESEARCH METHODS

9.1. Study design

This was a retrospective cohort study of pediatric patients receiving antibiotics for the indication of HAP at multiple pediatric hospitals across the US. Pediatric patients with an indication of HAP receiving P/T were included in the exposed group and those receiving Comparator HAP appropriate antibiotics were included in the Comparator group (i.e., Unexposed to P/T) (9.5 Exposed and Unexposed/Comparator groups).

9.2. Setting

Pediatric patients aged 2 months to <18 years diagnosed with HAP constituted the study population. The potential pediatric patients with HAP were initially identified from the Pediatric Health Information System (PHIS), an administrative database that collects patient-level data from pediatric hospitals across the US, and then confirmed as HAP through review of patient medical charts at each of the participating sites (9.7 Data Sources and Measurement).

9.3. Index Date and Follow Up

The index date was the "date of initiation of HAP treatment". The follow-up time for a patient outcome, which measures the person-time at risk, is defined as the time interval from the index date until one of the following:

- For the outcome of all-cause mortality, a period of 30-days after the first dose of P/T or Comparator antibiotics (at which time all surviving patients were considered censored),

- For all other serious events, completion of 40 days after the first dose of P/T or Comparator HAP antibiotics, or discharge from the hospital (or death), whichever occurs first (after which time all surviving patients were considered censored), and

- For the assessment of treatment effectiveness outcome, up to 14 days from initiation of HAP therapy.

9.4. Study Population

There is no specific International Classification of Diseases (ICD) -9 code for HAP. Therefore, a two-step process was followed to identify pediatric patients diagnosed and treated for HAP. As described in detail below, **Step-I** consisted of screening the PHIS database for potentially eligible patients, and **Step-II** included review of individual patient medical charts to confirm the diagnosis of HAP before inclusion in the study.

Step-I: PHIS database screening to identify potential patients with HAP

During the first step, the PHIS database was screened to identify patients with a potential diagnosis of HAP with the inclusion criteria, as follows:

- 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 discharge ICD-9 code consistent with bacterial pneumonia (Additional Table A), and
- Received at least 1 dose of P/T or Comparator HAP appropriate antibiotic during the hospitalization.

The following patients were excluded during the PHIS database screening:

- Patients who received an antibiotic(s) consistent with treatment of CAP (i.e., 2nd or 3rd generation cephalosporins, ampicillin/amoxicillin, amoxicillin/clavulanic acid, ampicillin/sulbactam, azithromycin, clindamycin, or penicillin) during the first two days of hospitalization,
- Patients with a diagnosis of cystic fibrosis based on ICD-9 codes (Additional Table B); these patients were excluded because they are frequently admitted for cystic fibrosis pulmonary exacerbations and receive similar antibiotic therapy but likely do not have HAP,
- Patients treated with two HAP appropriate antibiotics (including P/T or two comparator HAP antibiotics) simultaneously (within one day). These patients were excluded because they are likely clinically different than patients treated with just one HAP appropriate antibiotic,

- Patients who received P/T or Comparator antibiotics for other infection(s) any time during the admission prior to the diagnosis of HAP, or,
- Patients with missing pharmacy data in the PHIS.

As noted in 9.7 Data Sources and Measurement, the PHIS database does not contain information on daily patient physical exams, medication doses and daily physician impression and management plans. Therefore, for each patient meeting the inclusion and exclusion criteria described above, the patient's medical charts was reviewed to confirm that the patient received an antibiotic for the indication of HAP. If the patient was confirmed to have been initiated on therapy for HAP, the medical chart review was continued to obtain information on the administered doses of P/T and Comparator HAP appropriate antibiotics, and to document the onset of serious events and treatment outcomes related to effectiveness of the initial HAP therapy.

Step-II: Review of individual patient medical charts to confirm initiation of antibiotic for HAP

A review of the medical chart for each of the potential cases of HAP identified from the PHIS database screening was performed either at the respective sites or remotely accessing their electronic medical records (EMR) system to systematically confirm the receipt of an antibiotic for the indication of HAP, as follows:

- Confirmation of an absence of a diagnosis of CAP in the physician of record (POR)'s documentation at any time in the first two days of hospitalization,
- Confirmation of pneumonia diagnosis in daily progress notes any time after the first two days of hospitalization,
- Confirmation of receipt of P/T or Comparator HAP appropriate antibiotic(s) administered within one day of the pneumonia diagnosis,
- Confirmation that patient did not receive two HAP appropriate antibiotics simultaneously (within one day), and
- Confirmation that patient did not receive P/T or Comparator antibiotics for other infection(s) any time during the admission prior to the diagnosis of HAP.

Once the diagnosis of HAP was confirmed, a detailed chart abstraction was performed to gather data on exposure to P/T and Comparator HAP appropriate antibiotic(s), data on serious events including mortality and treatment effectiveness outcomes, and other relevant data (9.6 Variables). Of note eligible patients could not receive two of the study HAP antibiotics at the onset of therapy but other adjunctive antibiotics such as vancomycin or aminoglycosides were allowed. Data on these concomitant antibiotics exposures were collected and assessed in the analysis.

9.5. Exposed and Unexposed (i.e., Comparator Groups)

9.5.1. P/T Exposed Groups

The following are the two P/T groups:

- **P/T HAP Dosing Group:** Pediatric patients 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 as the first antibiotic administered for treatment of HAP were included in this group. This "P/T HAP dosing group" was considered as the primary P/T exposed group.

- **P/T Any Dosing Group:** Pediatric patients who received at least one dose of P/T any dose as the first antibiotic administered for treatment of HAP were included in the "P/T Any dosing group".

9.5.2. Comparator Groups

The following are the three comparator groups:

- **Comparator HAP Dosing Group:** Pediatric patients who received at least one dose of one of the Comparator HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime or ciprofloxacin) at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients as the first antibiotic administered for treatment of HAP were included in this group. These antibiotics are from different classes (cephalosporins, anti-pseudomonal penicillin, fluoroquinolone, carbapenems). This group was considered as the "Primary Comparator Group".

- **Comparator Any Dosing Group:** Pediatric patients who received at least one dose of one of the Comparator HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime or ciprofloxacin) (Any dose) as the first antibiotic administered for treatment of HAP were included in this group.

- **Comparator subset: carbapenems HAP Dosing Group:** Pediatric patients who received at least one dose of a carbapenem at a dose consistent with the product label indicated for moderate to severe infections in pediatric patients as the first antibiotic administered for treatment of HAP were included in this group. The carbapenem subset only included the Comparator patients who were administered a carbapenem as the first antibiotic administered for treatment of HAP, and therefore provided an additional and more focused Comparator group to P/T. Similar to P/T, carbapenems are broad spectrum antibiotics that are commonly used in patients with serious hospital-acquired infections. The carbapenem medications of interest in this study included meropenem and imipenem.

9.6. Variables

9.6.1. Exposures

The following data on P/T and Comparator HAP antibiotics were collected from each patient's medical chart:

- **Dose/frequency of HAP antibiotics**

P/T dosing: As noted in 6.0 Rationale and Background, P/T is not currently approved for the treatment of pediatric HAP. Therefore, it is likely that prescribing dose and frequency of P/T in pediatric patients with HAP will vary by hospital. Currently, P/T is approved for use in pediatric patients ≥ 2 months of age for the treatment of intra-abdominal infections (IAI) at a dose of 240/30 to 300/37.5 mg/kg/day divided and administered every 8 hours.[10] However, adult data suggest that higher and more frequent dosing is necessary when *Pseudomonas aeruginosa* is a concern, such as in HAP.[11] Therefore, in the setting of pediatric HAP it was expected that P/T is being prescribed at higher and more frequent dosing regimens than what is recommended for IAI.

Patients receiving P/T 80 to 100 mg/kg every 6 hours for the piperacillin component up to the maximum of 4 gm every 6 hours for the piperacillin component were included in the P/T Group (HAP dosing[1]). However, data on patients receiving P/T other than at a dose 80-100 mg/kg piperacillin/ 10-12.5mg/kg tazobactam every 6 hours (Any P/T dosing) were also collected. Recognizing that there could be modest rounding when calculating medication doses, a dose within 10% of the 80-100 mg/kg piperacillin/ 10-12.5mg/kg tazobactam dose range was considered to meet the definition of the HAP dosing. Further, renal function at baseline was considered and adjusted HAP dosing was included among patients with renal impairment.

Comparator HAP appropriate antibiotics dosing: There are currently no available dosing recommendations for any of the comparator medications that are specific to the treatment of HAP in pediatric patients. However, it is likely that most clinicians will consider HAP as a moderate to severe infection and will dose antibiotic treatments accordingly. As such, pediatric dosing included in the respective product label for moderate to severe infections was used (summarized in Table 1). Similar to the P/T group, a dose within 10% of the respective product label dosing was considered to meet the definition of the HAP dosing. Renal function at baseline was also considered and adjusted HAP dosing was included

[1] The HAP dosing is derived from the approved pediatric febrile neutropenia (FN) dosing in the harmonized EU label. Also, this is the dosing used in the Harriet Lane handbook by John Hopkins dating back to the 1990s for pediatric HAP. Finally the FN dosing in adults is the same as the HAP dosing in adults, and thus this assumption is made for treating children as well. Similar to FN, there is concern for resistant organisms, including Pseudomonas.

among patients with renal impairment. Further, data on patients receiving comparator antibiotic(s) at a dose other than the respective product label(s) indicated for moderate to severe infections in pediatric patients (i.e., Any Comparator dosing) were also collected.

In addition to data on dose of P/T and Comparator antibiotics, start and end dates were collected to estimate the duration of therapy. If a patient was treated for HAP more than once during the follow-up period, only data on the first treatment episode were collected.

9.6.2. Outcomes

Data on serious events, including mortality and treatment outcomes related to effectiveness, were collected directly from each patient's medical chart and are described below.

9.6.2.1. Serious Events

The primary study outcome was the development of "serious events" within 40 days of HAP treatment initiation. A serious event was defined as any untoward medical occurrence documented in a physician's progress note in patients taking P/T or Comparator HAP appropriate antibiotics 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 HAP patients treated with P/T or Comparator HAP appropriate antibiotics (irrespective of 'causal' relationship to therapy) have been reported in clinical studies and post-marketing data for P/T, and were specifically focused upon:

- 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

The trained research personnel (physicians, clinical research nurses [CRNs], or research assistants), performed chart reviews and collected all untoward medical events documented in the daily progress notes of the POR/problem list or impression section of the chart from the day of initiation of P/T or Comparator HAP appropriate antibiotics through the duration of hospitalization or 40 days after the first dose of the HAP antibiotic(s), 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 catalogued as pdf documents for each patient sustaining a serious event (Appendix 3). Worsening of pre-existing conditions (i.e., present prior to the diagnosis

of HAP) during HAP treatment was captured as a serious event if it met any of the criteria for a serious event described above. Subsequently, the pdfs documenting the serious events from each chart were reviewed by one of two study physicians, who were blinded to the antibiotic that each patient received for HAP, to determine whether the event meets the above definition of a serious adverse event, specified above.

Additionally, for all patients that died, a death certificate was requested from either the site where the patient was hospitalized or from the National Death Index (NDI) (details below). 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 POR daily progress notes.

9.6.2.1.1. Ascertainment of all-cause mortality at 30-days after initiation of HAP treatment

Vital status at 30-days after initiation of treatment for HAP was ascertained for all patients, as planned in the protocol. The vital status at 30-days after initiation of treatment for HAP was not available in medical charts for patients who stayed in hospital less than 30-days after initiation of HAP treatment. The following sequential approach was used to determine vital status at 30-day after initiation of HAP treatment:

1. Queried the PHIS database and/or reviewed 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 HAP therapy.

2. If no medical encounter was identified in step 1, then the NDI was queried as detailed below.

The 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. 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, if available. The patient's date of birth was already contained in the study database. Of note individual IRB approval for the provision of first and last name was necessary for this step. Not all sites were able to secure this level of IRB approval. These data elements for patients with unknown 30-days vital status were submitted to the NCHS, with a request to search the NDI for a matching record. In case of a matching record (i.e., patient's death), the 'date of death' from the NDI report was used to ascertain the vital status of the patient at 30-days after initiation of HAP treatment. These data were stored and transferred in a password protected file. Additionally, the death certificate was requested from the NDI or hospital of record for any patient who was found to have died in the window of interest.

9.6.2.2. Treatment Effectiveness

The secondary study outcome was the effectiveness of the antibiotic therapy. In addition to collecting daily pertinent laboratory, radiographic and co-morbid condition data, the trained research personnel also reviewed the medical record documentation (e.g., daily progress notes from physicians caring for the child) and concluded based on the available information whether the patient 'clinically improved' or 'did not improve" from HAP diagnosis (up to 14 days from initiation of HAP treatment). Research personnel were provided guidance for the designation of this outcome through consultations with the study physicians, and recorded one of these two treatment outcomes in the case report form (CRF) (also see 9.12.4 Amendments to the SAP and Study Procedures).

9.6.3. Covariates

In addition to data on exposures and outcomes, data on covariates and potential confounders were collected.

The following data were collected from the PHIS database for all patients with a potential diagnosis of HAP:

- Admission date
- Discharge date

The following data were collected from medical charts in the pre-and post-HAP diagnosis period, when available, only for patients with a confirmed diagnosis of HAP:

- Date of birth
- Date of diagnosis
- Sex
- Race
- Ethnicity
- Pre-existing medical conditions as reported in the POR's admission notes by medical system (e.g., CNS, cardiovascular, respiratory, renal, hepatic, gastrointestinal, hematological)
- Presence of co-infectious processes at time of diagnosis
- Floor/hospital unit the patient was admitted to prior to diagnosis and at the time of HAP diagnosis (e.g., Oncology, pediatric intensive care unit [PICU], neonatal intensive care unit [NICU], cardiac intensive care unit [CICU])
- Laboratory results (e.g., complete blood count [CBC], metabolic panels, liver function tests [LFTs])
- Imaging results (e.g., chest radiography)
- Dosage and duration of use (ie., #of days) for P/T and Comparator HAP appropriate antibiotics administered during the study period.

- Comprehensive list and duration of use of all other enteral, intravenous, and inhaled medications
- For patients admitted to the intensive care unit (ICU) admission and discharge dates from the ICU
- Use of mechanical ventilator, including start and stop dates
- Endotracheal intubation, including start and stop dates
- Tracheostomy, including start and stop dates
- Any respiratory or sputum cultures that were taken within 24 hours of diagnosis and their results
- Vital status at end of 30-days (if Unknown, NDI was to be queried)
- Date of death
- Clinical impression of the patient (pertinent to treatment effectiveness) at 14 days by the POR
- Discharge location at the end of the study period (up to 40 days from HAP diagnosis/treatment initiation)

9.7. Data Sources and Measurement

As described earlier in 9.2 Setting, data were obtained from the PHIS database and patients' medical charts. The PHIS database is a comprehensive pediatric database containing clinical and financial details of more than six million pediatric patients from 43 pediatric hospitals across the US. The PHIS member hospitals represent most of the major metropolitan areas nationwide, with only one children's hospital representing each city. Updated quarterly, data are available for PHIS member institutions on every inpatient since January 1, 2003. The member institutions can access PHIS data via a virtual private network or modem. There are two levels of data within the PHIS database. **Level-I** data contain patient identification, demographics, dates of admission and discharge, physician profiles, clinical classification and primary discharge diagnosis and primary procedure codes coded in International Classification of Diseases-9-Clinical Modification (ICD-9-CM). **Level-II** data contain detailed information about the patient encounter including up to 40 ICD-9-CM discharge diagnosis and procedure codes and specific financial/ utilization data i.e., medical supply, laboratory, radiology/imaging, and clinical services. However, the PHIS database does not contain information on daily patient physical exams, medication doses and daily physician impression and management plans. The PHIS member hospitals have access to the multi-center database (the Peer database) and their hospital-specific database. All aforementioned data are contained in the Peer and hospital-specific databases.

A total of 19 PHIS affiliated hospitals were considered for inclusion in the study; 11 sites were invited[2], 7 sites participated and 4 declined to participate in the study (Table 2). The following 7 sites participated in the study:

1. The Children's Hospital of Philadelphia (CHOP), PA (**principal study site**)
2. Rady Children's Hospital, San Diego, CA
3. Columbia University Medical Center, New York, NY
4. Children's National Medical Center, Washington, DC
5. Cincinnati Children's Hospital Medical Center, OH
6. St. Louis Children's Hospital, MO
7. Children's Healthcare of Atlanta, GA

As described in 9.4 Study Population, the PHIS database was queried with the screening inclusion/exclusion criteria (Step-I) to identify potential HAP patients in the respective hospital after the hospital agreed to participate and obtained approval from the Institutional Review Board (IRB) and hospital administration, where applicable. The data on potential HAP patients were downloaded at the principal study site, CHOP, Philadelphia, PA.

Subsequently, trained research personnel/data abstractors performed a review of the medical chart of each patient identified from the PHIS database screening to confirm the diagnosis of HAP (Step-II). After confirming the diagnosis of HAP, the data abstractors proceeded with a detailed chart review and data abstraction. If HAP was not confirmed by initial chart review, no further data abstraction was performed. The data abstractors underwent formal training by the primary study team at CHOP on how to confirm the diagnosis of HAP and perform detailed chart abstraction on serious events, treatment effectiveness outcomes and covariates/confounders. Further, study physicians were available (in-person or by phone), for advice and consultations. The PI implemented measures such as random validation/ QC check of the completed CRFs to ensure that the abstracted data are reliable and valid, and prevent/minimize variations in data abstraction among study personnel. The sites were enrolled in the study on a rolling basis. Once a site was enrolled, all medical charts of patients with a potential diagnosis of HAP identified from the PHIS database screening during the study period were reviewed. At four of the sites trained research personnel from CHOP completed the data abstraction. The research personnel either traveled to the site, or for sites with capability of remotely accessing the EMR, virtual chart review and data abstraction was performed. The remaining three sites did not allow outside personnel to access medical records at site or remotely; thus, site-specific local personnel were trained by the CHOP team to complete data abstraction.

[2] Nine sites were considered but not invited to participate in the study because of a small number of potential HAP patients based on PHIS database screening

As requested by the FDA and as planned in the study protocol, de-identified copies of a random sample of approximately 5% of the medical charts of HAP patients were obtained and are being submitted with this final study report (Appendix 3). The approval to process de-identified copies of a patient chart at each site was contingent upon local IRB approval. The IRBs at all participating sites agreed to this request with the exception of the IRB at the Rady Children's Hospital in San Diego, CA (also see 9.12.4 Amendments to SAP and Study Procedures). Therefore, de-identified copies of medical records from Rady Children's Hospital patients are not available (see IRB letter from the hospital Appendix 5).

9.8. Bias

This section describes potential sources of bias and efforts to assess and address them in this study.

- **Confounding by indication/severity of illness**: Confounding by indication may take place if the decision to initiate or to stop an antibiotic was influenced by the clinical status of the patient, which impacts the risk of a serious adverse event. This is of particular concern for broad spectrum antibiotics such as P/T, as physicians may be more inclined to start P/T if a patient appears significantly ill. This would result in an inflated association between broad-spectrum antibiotics and worse outcomes. Multivariable analysis was used to control for co-morbid conditions and clinical status at the initiation of the HAP antibiotic to minimize this confounding effect. Additionally, comparison of P/T patients with only patients treated with a carbapenem allowed for a subset analysis that was less vulnerable to confounding by indication (relative to the Comparator group) as these two therapeutic options have similar broad-spectrum coverage.

- **Selection bias**: In a cohort study, selection bias occurs when the choice of exposed and unexposed patients is somehow related to the outcome of interest. A retrospective cohort study is particularly open to this bias since the choice of patients happens after the exposure and outcome of interest have taken place. However, selection bias for this study was less likely because the data in PHIS were collected in real time without knowledge of this study's outcomes of interest. The determination of exposure status for each patient was based on claim records for the antibiotics administered. The claims are recorded in the PHIS database at the time of each hospital admission. Further, the data on exposure status were extracted without simultaneous knowledge of serious events or patient treatment outcome status (i.e. "clinically improved" or "did not improve") thus limiting the potential to select patients in the exposure groups in a manner that would be *differential* by outcome.

- **Misclassification bias**: Misclassification bias occurs when study patients are classified incorrectly according to exposure or outcome status. Data on each patient's antibiotic exposures are susceptible to misclassification secondary to dependence on data from the PHIS database. The chances of misclassification were minimal in this study as determination of antibiotic exposure is dependent on billing documentation, which should

be complete in the database and represents medications actually administered to the patient. Furthermore, if some of the billing is not complete there is no reason to believe that this would be *differential* in nature between the P/T and Comparator groups.

The ability to accurately classify serious events and treatment outcomes related to effectiveness for each patient is dependent on the documentation made in the daily physician notes. The decision to depend on daily physician notes to determine these outcomes was based on the fact that this is a data source that would be available for every patient on every hospital day. Dependence on other data sources such as laboratory results for these outcomes would have the potential to introduce bias as consistent laboratory testing could not be dictated by the study since it was retrospective, and laboratory testing could have been more intense in sicker patients. Nonetheless, even though daily progress notes were expected for all patients, variations in the level of detail of physician documentation/progress notes were expected. Less documentation might have resulted in under-reporting of serious events in some patients. It is not possible to account for the potential under-reporting due to this factor. However, because daily progress notes were used to inform the outcomes and daily progress notes were available for all enrolled patients there is no reason to believe that under reporting of serious events would have occurred *differentially* between the P/T and Comparator groups.

- **Confounding by study site**: This study was designed to include patients from multiple pediatric hospitals across the US making the analysis susceptible to confounding by study site. This type of confounding is possible since the choice of exposure and outcomes can both be associated with the site. Hypothetically, if one site systematically prescribes a specific antibiotic and has a higher mortality rate in HAP patients than other sites, then it could be very difficult to distinguish the effect of the study site from the exposure. Adjustment for this confounding was considered in the analyses by including a variable "participating site" in the multivariable regression model.

- **Data ascertainment bias:** The goal was to have trained research personnel from CHOP abstract data at all sites to maintain data abstraction consistency across the study cohort. However, at three of the study sites (75 P/T patients and 90 Comparator patients), CHOP personnel were not permitted by the site administration to access the EMR systems either remotely or in person. Instead, the CHOP study personnel trained the personnel at these sites to conduct the data abstraction. This difference in personnel performing the abstraction could have led to a difference in the way in which data were collected and/or the way serious events were identified. Potentially the personnel at CHOP abstracting data from four of the sites (66 P/T patients and 181 Comparator patients) could have identified more (or fewer) serious events than the personnel at the three other sites due to a difference in the abstractor(s). As sites may have a preference for certain HAP therapies this difference in data acquisition could have led to under- or over-reporting of serious events that are linked to a specific HAP antibiotic via the site. However, trained data abstractors, a structured CRF, and a commercially developed database tool created by DatSTAT (DatSTAT Illume 6.0, SCI Solutions, Seattle, WA) were all in place for all

sites in order to minimize ascertainment bias. 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 HAP to confirm serious events (primary endpoint).

9.9. Study Size

The target sample size was at least 150 patients with a diagnosis of HAP who received at least one dose of P/T and 300 patients with HAP who received one dose of Comparator HAP appropriate antibiotic(s).

Rates of serious events with 95% confidence intervals (CIs) were computed for both the P/T and Comparator groups. Using the group specific rates, the incidence rate ratios (IRRs) with 95% CIs for serious events (P/T *versus* Comparator) per follow-up days were estimated. The target sample size of 150 patients and 300 Comparator permits estimation of the rate and IRR with the confidence intervals (CI) widths, tabulated for underlying serious event rates ranging from 2% to 10% in Table 3. For example, assuming an underlying serious event rate of 2%, the width of the 95% CI for the serious event rate in the P/T group with 150 patients would be 5.7, and the width of the 95% CI for the IRR (P/T *versus* Comparator) would be 3.9.

9.10. Data Management and Transformation

The final database contained data elements that were collected and compiled in a multistep process. First, potentially eligible patients were identified through a query of the PHIS database. The result of this query was downloaded into Microsoft Excel at CHOP. Each patient identified from the PHIS query had an encrypted Electronic Medical Record Number (EMRN) which served as the unique study ID number for each patient going forward. The encrypted EMRN was decrypted locally by each participating institution's Information Services department in order to gain access to the true medical record number (MRN) for subsequent medical chart review. As detailed above, the medical chart was reviewed to confirm patient eligibility and, if eligible, the necessary data elements were abstracted into a central electronic data collection platform/database designed and supported by DatSTAT. Data were downloaded in various de-identified iterations from the DatSTAT database and saved as.csv files to prepare for data cleaning, evaluation of missing data elements, and eventual data analyses.

Data management, cleaning and statistical analyses were conducted using a combination of software that included Microsoft Excel (Microsoft Office Professional Plus, Microsoft Corporation, 2012), SAS version. 9.4 (SAS Institute, Inc., 2002-2012, Cary, NC) and STATA Statistical Software: Release 15 (StatCorp LLC, 2017, College Station, TX).

Variables transformation/categorization:

Variables were categorized into binary or multiple categories for analysis. Below is the description of categorization for select variables (the reference category for univariable and multivariable analyses specified with [R]):

- Age: (age categories used by the FDA): infant (2-months-< 2 years), child (2 years - <12 years), adolescent (12 years - <16 years), and ≥16 years [R]
- Race: White or Caucasian, Black or African-American, Latino, Asian, other[R] and Unknown
- ICU admission (prior to or after HAP diagnosis): (yes, no [R], unknown)
- Tracheostomy (prior to or after HAP diagnosis): (yes, no[R], unknown)
- Ventilator dependent (prior to or after HAP diagnosis): (yes, no[R], unknown)
- Endotracheal intubation (prior to or after HAP diagnosis): (yes/no[R])
- Laboratory tests (prior to HAP): (abnormal, normal [R] or not available/ordered)
- Laboratory tests (post-HAP): (new single incidence, abnormal at baseline, or normal [R] no measurement at baseline)

All serious events were harmonized into standardized terms by the study physicians e.g., worsening of a Typical Teratoid Rhabdoid tumor or Empendymoma of brain were both classified as "tumor progression" or Left lung collapse and Collapsed lung as "lung collapse".

9.11. Analysis data sets/populations

All patients meeting the study eligibility criteria described above were included in the analysis.

9.11.1. Primary Analysis Set (PAS)

The PAS population included all study patients 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 as the first antibiotic administered for treatment of HAP, OR

- Received at least one dose of one of the Comparator HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime or ciprofloxacin) as the first antibiotic administered for treatment of HAP, at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients.

    - The subgroup of PAS included patients who received at least one dose of a carbapenem (imipenem or meropenem) as the first antibiotic administered for treatment of HAP, at a dose consistent with the product label indicated for moderate to severe infections in pediatric patients.

The PAS population was used to investigate the primary and secondary study objectives.

9.11.2. Full Analysis Set (FAS)

The FAS included all enrolled pediatric patients with HAP who received at least one dose of P/T or one of the Comparator HAP appropriate antibiotics at "Any dose" as the first antibiotic administered for treatment of HAP. The FAS population was planned as a secondary population to evaluate the safety of P/T (primary objective) as described in the protocol (Appendix 1). However, planned analyses using FAS were not conducted because of a very limited number of additional patients (n=5) available for the FAS beyond what was included in the PAS (further described in 10.2.2 P/T Any Dosing *versus* Comparator Any Dosing Groups – FAS, and noted in 9.12.4 Amendments to SAP and Study Procedure).

9.12. Statistical methods

Detailed information on the statistical methods was documented in the Statistical Analysis Plan (SAP) that was developed and completed prior to analysing any outcome data (Appendix 2). Any deviations from the SAP and/or additional analyses (i.e. post-hoc) are documented in section 9.12.4 Amendments to SAP and Study Procedures.

- Descriptive statistics were performed to describe patient demographic characteristics (e.g., age, sex, race) and clinical characteristics (e.g., duration of hospitalization, presence of co-morbid conditions at the time of hospital admission, concomitant medications use and ventilator support) in the P/T and Comparator groups.

- Univariable and multivariable regression analyses were conducted to evaluate the association between P/T HAP dosing and serious events (primary endpoint) compared to the Comparator HAP dosing group

- Univariable and multivariable regression analyses were conducted to evaluate the treatment effectiveness outcome (secondary endpoint) for the P/T and Comparator groups.

9.12.1. Main summary measures

- Counts and frequencies for categorical variables

- Means, median and IQR, where appropriate, for continuous variables

- Crude incidence rate (count of safety events divided by the person-time at risk)

- Unadjusted and adjusted incident rate ratios (IRRs)

- Unadjusted and adjusted odds ratios (ORs)

9.12.2. Main statistical methods

9.12.2.1. Analysis of safety endpoints (Primary Study Objective)

During the study follow up period a patient might have experienced multiple serious events of the same organ/body system (e.g. atrial fibrillation, bradycardia or cardiac failure all from cardiovascular system) or multiple episodes of the same serious event (e.g. atrial fibrillation on two separate occasions). For the former scenario, the first occurrence of each serious event (in this case first occurrence of atrial fibrillation, bradycardia and cardiac failure for a total of 3 events) was counted in the all serious events (i.e., sum of first occurrence of all individual events) incidence rate calculations. For the latter scenario, only the first occurrence of a serious event (in this case the first episode of atrial fibrillation for a total of 1 event) was counted. This construct was used for calculating the following incident measurements:

- All incident serious events (i.e., sum of all individual incident events),
- All incident serious events by body system (e.g., cardiovascular: atrial fibrillation, bradycardia or cardiac failure),
- All incident serious events individually[3],

The above were computed and reported by treatment group as follows:

- Total number of events,
- Cumulative person-time at risk,
- Event rate per 100 person-days [4]with corresponding 95% CI as appropriate.

Comparative analyses of serious event incident rates per person time by treatment group were done for all incident serious events and by body system. This comparison was done using an inverse probability weighted (IPW) informed Poisson regression model with an offset for person-time at risk and robust variance estimate. An IPW informed Poisson regression model was conducted due to the large number of covariates that might be unbalanced across the groups being compared and the inability to include all covariates in a multivariable model (further described in 9.12.4 Amendments to SAP and Study Procedures).

Due to the large number of baseline covariates that might be unbalanced across the HAP treatment groups being compared (P/T *versus* Comparator, and P/T *versus* carbapenems) and the inability to include all covariates in a multivariable outcome model, the development of weights was deemed an efficient approach to control for differences in baseline

[3] Only the number of individual serious events was reported. Incidence rate of individual serious events was not calculated because of a small number of individual events

[4] The SAP outlines that incidence rate of safety events will be reported using “per 1,000 person years” as the denominator. However, the incidence rates are being presented using “per 100 person days” for easier interpretation.

characteristics between study treatment groups. These weights were obtained from propensity score models used to predict the probability of receipt of a specific HAP antibiotic (P/T or Comparator) conditional on observed demographic and clinical characteristics. The weights were then included in the final Poisson models. Additionally, any variable that was still unbalanced after weighting and was thought to be a confounder of the treatment and outcome relationship was to be placed as a covariate in the model. Model adjusted incidence rate ratios (IRR) with corresponding 95% CI were reported from these models.

The following groups were compared using the above Poisson modeling approach:

- P/T HAP dosing *versus* Comparator HAP dosing — Primary safety comparison
- P/T HAP dosing *versus* Comparator subset: carbapenems HAP dosing – Subgroup analysis

Analysis of All-cause Mortality

All-cause mortality rates (%) at 30-days post initiation of HAP treatment were calculated by treatment group and key subgroups such as age and sex.

9.12.2.1.1. Safety Endpoints Sensitivity Analysis

Due to the potential rarity of safety endpoints, there were concerns that the assumption of the Poisson modeling may be violated. Therefore, sensitivity analyses utilizing a Negative binomial model were planned and conducted. The fit of the Poisson model was compared to the fit of the Negative binomial model for the same comparative analysis using goodness of fit statistics and a likelihood ratio test.

A sensitivity analysis exploring the impact of duration of treatment on the comparison of serious event incidence rates by treatment group was conducted. Using similar Poisson and Negative binomial regression modeling approaches described above, the rate of serious events was compared between P/T HAP dosing and Comparator HAP dosing groups, and P/T HAP dosing and Comparator subset: carbapenems HAP dosing groups for the subset of patients who received at least 2 days, at least 5 days and at least 7 days of the initial HAP antibiotic.

9.12.2.2. Analysis of Treatment Effectiveness (Secondary Study Objective)

For descriptive reporting, counts and proportions (%) of HAP patients categorized as "clinically improved" or "did not improve" were calculated and also stratified by select patient characteristics (e.g., age race, sex).

For comparative analysis, a logistic regression model was developed to assess the adjusted comparative effectiveness of P/T *versus* Comparator antibiotics (P/T HAP dosing *versus* Comparator HAP dosing groups, and P/T HAP dosing *versus* Comparator subset:

carbapenems HAP dosing) on failure to clinically improve. This adjusted analysis considered possible confounding from various baseline covariates (using same weights from propensity models that were used in the Poisson regression analysis conducted for the primary endpoint described above). Adjusted odds ratios (OR) and associated 95% CIs were reported for each model.

9.12.2.2.1. Effectiveness Outcome Sensitivity Analysis

For the primary effectiveness comparison, sensitivity analyses were conducted examining the duration of initial HAP antibiotic treatment (i.e. at least 2 days, at least 5 days and at least 7 days of therapy) (also noted in 9.12.4 Amendments to SAP and Study Procedures).

9.12.2.3. Post Hoc Sensitivity Analyses

- An additional sensitivity analysis for the safety endpoints was performed because of concerns of residual confounding by participating site. Although including site as a fixed effect allowed the model to converge, there was still a concern about potential for confounding by site because some sites exhibited a strong preference for one therapy over the other (P/T *versus* any Comparator antibiotics). As a result, a sensitivity analysis that excluded all patients from sites that chose one treatment over 90% of the time was performed. This sensitivity analysis allowed for comparison of P/T HAP dosing and comparator HAP dosing treated patients at three sites and for comparison of P/T HAP dosing and carbapenem HAP dosing treated patients from four sites. Of note, for the latter analysis, two of the four sites had small numbers of patients (also noted in 9.12.4 Amendments to SAP and Study Procedures).

- Finally, a novel measure called the E-value was computed to determine the degree/quantification of unmeasured confounding that would need to exist to move the point estimates from that which was measured to the values 1 (the null) and also to 1.25 (an arbitrary value of a positive association between exposure and outcome). The latter 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. The objective was to quantify the strength of an unmeasured confounder that would need to exist to influence the conclusions of the primary analysis by moving the study results to the null or to completely invert the point estimate identified in the primary adjusted analysis. This analysis is also noted in 9.12.4 Amendments to SAP and Study Procedures.

9.12.3. Missing values

The covariate adjusted regression models were based on complete data except for the number of days spent in the ICU prior to HAP diagnosis. There were nine patients in whom the number of ICU days was not abstracted during the data collection (three from Atlanta, one from Columbia, three from CHOP, and two from St. Louis sites). These nine patients were given an imputed value for this variable, through a single imputation using the sample mean, so that they were not dropped from the logistic regression used to create the propensity score weights (also noted in 9.12.4 Amendments to SAP and Study Procedures)..

9.12.4. Amendments to the Statistical Analysis Plan (SAP) and study procedure

Deviations from the SAP and/or additional analyses conducted (i.e. post-hoc) are documented below:

- **Development of inverse probability weights from propensity score models:** The comparative analysis for serious events between treatment groups (P/T *versus* Comparator, and P/T *versus* carbapenems subset) was conducted using an inverse probability weighted (IPW) informed Poisson regression model, which was not specified in the SAP.
  As described in 9.12.2.1 Analysis of Safety Endpoints (Primary Study Objective), due to the large number of covariates that might be unbalanced across the groups being compared and the inability to include all covariates in a multivariable model, the development of weights was considered an efficient approach to control for differences in demographic and clinical characteristics between the treatment groups. These weights were obtained from propensity score models used to predict the probability of receipt of a specific HAP antibiotic (P/T or Comparator) conditional on observed demographic and clinical characteristics. The weights were then included in the final Poisson (and also in Negative binomial and Logistic) regression models.

- **Inclusion of participating site as a "random effect" in the regression model**: As stated above, there was a concern about confounding by participating site and thus the analytic plan (i.e., SAP) anticipated including study site as a covariate in the regression model. However, prior to performing the analysis, it was not clear whether regression models would converge with participating site in the model as a "fixed effect" covariate. Therefore, it was planned to include site as a "random effect" only if inclusion of site as a fixed effect would not allow the model to converge. The latter was possible and thus a model with participating site as a random effect was not necessary. Further, incidence rates of all serious events by site were calculated to complete the descriptive data report.

- **Analysis using FAS population:** The planned analysis of the primary study objective using FAS, as specified in the SAP, was not conducted because of a very limited number of additional patients (n=5) available for the FAS beyond what was included in the PAS (further described in Section 10.2.2 P/T Any Dosing *versus* Comparator Any Dosing Groups – FAS). However, descriptive analysis of select demographic characteristics was compared between P/T Any dosing *versus* Comparator Any dosing groups, and P/T Any dosing *versus* Comparator subset: Carbapenem Any dosing groups using FAS.

- **Effectiveness Outcome Sensitivity Analysis:** In the SAP, a sensitivity analysis for the treatment effectiveness outcome was planned by excluding patients who received ≤ 2 days of HAP treatment. However, the effect of duration of HAP treatment (i.e. at least 2 days, at least 5 days and at least 7 days of therapy) on the treatment effectiveness outcome was assessed instead to comprehensively analysis this secondary endpoint.
- **Missing data imputation:** Imputation of missing data was not planned in the SAP. There were nine patients for whom data on the number of ICU days were not abstracted/unavailable (three from Atlanta, one from Columbia, three from CHOP, and two from St. Louis sites). These nine patients were given an imputed value for this variable, through a single imputation using the sample mean, so that they were not dropped from the logistic regression used to create the propensity score weights.

- **Additional post hoc sensitivity analyses**
  - An additional sensitivity analysis was performed to assess confounding by participating site, which was not in the SAP. Although including site as a fixed effect allowed the model to converge, there was still a concern about potential for confounding by participating site because some sites exhibited a strong preference for one therapy over the other (P/T *versus* any Comparator). As a result, a sensitivity analysis that excluded all patients from participating sites that chose one treatment over 90% of the time was performed. This sensitivity analysis allowed for comparison of P/T HAP dosing *versus* Comparator HAP dosing groups at three hospitals and for comparison of P/T HAP dosing *versus* Comparator HAP dosing: carbapenems groups from four sites. Of note, for the latter analysis, two of the four sites had small numbers of patients.

  - A novel measure called the E-value, not described in the SAP, was computed to determine the degree/ quantification of unmeasured confounding that would need to exist to move the point estimates (i.e., IRR) from that which was measured to the null and also to 1.25. This analysis was conducted to further assess the role of confounding in the association between P/T and all serious events (primary endpoint).

- **Data collection at Rady Children's Hospital, San Diego:** It was planned in the protocol that a second trained research person would perform a repeat data abstraction of 5% of the study patients from participating sites that were unable to provide de-identified copies of the medical charts requested by the FDA. In case of discrepancies in the abstracted data points in the two CRFs, each data abstractor was to revisit the medical charts to determine the reason for discrepancies and was to agree on the appropriate information to be recorded in the CRF/DatSTAT database prior to lockdown. However, during conduct of the study it was not possible to complete the process as planned due to a limited number of trained research personnel/data abstractors and the extensive and time-consuming data collection process. Therefore, only one CRF was completed for each medical chart. A sample of approximately 5% of the medical charts of study patients are being submitted with this report (Appendix 3). The IRBs at 6 of the 7

participating sites agreed to this request and provided de-identified copies of the medical charts. The IRB from the Rady Children's Hospital did not approve the request to provide de-identified copies of medical charts. A copy of the IRB letter declining the request to provide de-identified copies of medical charts at this site is enclosed for reference. (Appendix 5).

- **Assessment of treatment effectiveness outcomes by study physicians**: As outlined in the protocol and SAP, it was planned to have a study physician, blinded to treatment group, review POR's progress notes to confirm the appropriateness of the outcome designation. However, review of medical charts showed that a substantial proportion of patients did not have a progress note within 14 days of diagnosis in which the POR specifically stated that the patient had improved from their HAP diagnosis. Instead, the trained research personnel had to make a decision about clinical status based on the comprehensive review of the chart. Capturing the entirety of the chart/clinical status for central study physician confirmation of this designation was not possible. As a result, this outcome measure was dependent on the trained research personnel review without study physician's confirmation.

9.13. Pilot Study

A pilot study in a subset of patients at CHOP (principal site) was conducted prior to the actual study. The objective of the pilot study was to identify potential issues, if any, in the planned study methodology/processes e.g., to evaluate the study's algorithm for eligibility screening by first identifying potential HAP patients from the secondary database (Step-I) and then review the medical charts to confirm the diagnosis of HAP (Step-II), and to test adequacy of the draft CRF/capability of electronic study database to collect the required data.

Overall, the pilot study demonstrated the feasibility of applying the inclusion and exclusion criteria/algorithm developed to identify pediatric patients with HAP using PHIS and confirm HAP diagnosis via chart reviews, and also confirmed the capability of the draft CRF to capture the necessary study data. The study protocol was amended to incorporate changes based on lessons learned from the pilot study. The pilot study report was submitted to the FDA on December 24, 2014 and is included as Appendix 4.

9.14. Quality control

The study database had built-in data validity checks for most variables to ensure data capture and accuracy. Additionally, the data collected from various sites were periodically checked for consistency and completeness by the central study coordinator. Internal quality checks of all study data, analytic results, and written materials were conducted. Quality review of the final analytic dataset, statistical analyses results, and study report were documented and retained by the PI and his team, as follows:

- Checked the internal consistency of any data reported in the document, and

- Confirmed that the study conclusions were supported by the results.

9.15. Protection of Human Subjects

9.15.1. Informed Consent

This study utilized existing data from medical charts), which were de-identified data. Informed consent from each patient was not required in this study.

9.15.2. Approval from IRB

The final protocol, any amendments, and informed consent documentation were reviewed and approved by IRBs for each site participating in the study. The Children's Hospital of Atlanta (Emory University) was overseen by the CHOP IRB for this protocol. All other sites received approval from their own individual IRBs.

9.15.3. Ethical conduct

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor, and 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.*

10. RESULTS

A total of 7 PHIS affiliated sites provided data for 412 patients. The largest number of patients was enrolled from the Children's Healthcare of Atlanta, GA (n=84), followed by the CHOP, PA (n=77) and the Children's National Medical Center, Washington, DC (n=71).

Table 2 lists sites that participated in the study (n=7), sites that declined to participate (n=4), and sites considered for inclusion but not invited to participate (n=8) because of the small number of potential HAP treated patients based on screening of the PHIS database.

10.1. Participants

Section 9.4 Study Population described a two-step process that was followed to identify pediatric patients diagnosed and treated for HAP.
During screening of the PHIS database (Step-I), 1,899 patients were identified with a presumed diagnosis of HAP. These patients were admitted between January 01, 2003 and June 30, 2016 at the 7 participating sites (Figure 1). An initial review of the medical chart (Step-II) for each of these 1,899 potential HAP cases, confirmed the diagnosis of HAP in 412 patients (21.7%= 412/1899) that were subsequently included in the study (Figure 2).

Primary analysis set (PAS): Of 412 patients included in the study, 407 (98.8%) patients received HAP dosing as defined in 9.5 Exposed and Unexposed (Comparator groups). This analysis population (n=407) was used to address the primary objectives of study (Figure 2).

Median follow up time for study patients treated with HAP dosing was 17 days (IQR: 10-35 days).

Full analysis set (FAS): Five (1.21%) of the 412 patients included in the study were treated with P/T or Comparator antibiotics outside of the HAP dosing range defined in 9.5 Exposed and Unexposed (Comparator groups). Given the small number of patients (n=5) treated outside the range of HAP dosing, only descriptive statistics were calculated for select demographic variables to compare P/T Any dosing *versus* Comparator Any dosing groups, and P/T Any dosing *versus* Comparator subset: carbapenem Any dosing groups..

10.2. DESCRIPTIVE DATA

Of 407 patients treated with HAP dosing (PAS), 141 (34.64%) patients received P/T as the first antibiotic administered for treatment of HAP and were included in the P/T HAP dosing group, and 266 (65.35%) patients received one of the compactor antibiotics as the first antibiotic administered for HAP and were included in the Comparator HAP dosing group. Among 266 patients in the Comparator group, 92 (22.60%) received cefepime, 55 (13.51%) ceftazidime, 50 (12.29%) ticarcillin-clavulanate, 55 (13.51%) meropenem, 13 (3.19%) ciprofloxacin and 1 (0.25%) patient received imipenem as the first antibiotic administered for the treatment of HAP (Table 2.1.1).

Below are the descriptive statistics comparing demographic and clinical characteristics between the following:

- P/T HAP dosing *versus* Comparator HAP dosing groups—PAS.
- P/T Any dosing *versus* Comparator Any dosing groups —FAS (select variables only)
- P/T HAP dosing *versus* Comparator subset: carbapenems HAP dosing groups —PAS.

10.2.1. P/T HAP dosing *versus* Comparator HAP dosing groups—PAS

Tables 4.1.1 through Tables 4.1.7 present data on demographic characteristics, pre-and post-HAP clinical characteristics including hospitalization, laboratory, radiology, and medication data comparing P/T HAP dosing (n=141) and Comparator HAP dosing (n=266) groups.

- ***Demographic characteristics by P/T versus Comparator HAP dosing groups (PAS)***

Mean age (range) of patients in the P/T HAP dosing group was 7.65 years (0.21-20.53) compared to 6.57 years (0.19-18.87) in the Comparator HAP dosing group. The proportion of infants (2-months to < 2 years) was numerically lower in the P/T compared to the

Comparator HAP dosing group (34.04% *versus* 40.98%). Overall, patients in the two groups were comparable with regards to the distribution of sex and race—about half of the patients were White and >55% males in both groups. 15.60% of patients in the P/T and 19.92% of patients in the Comparator HAP dosing group had missing/unknown data on ethnicity. Among patients with information on ethnicity, 73.76 % in the P/T and 56.77% in the Comparator HAP dosing groups were non-Hispanic or Latino (Table 4.1.1).

The antibiotics used for HAP treatment varied by site. All of the patients (100%; 36/36) at the Columbia University Medical Center, and most patients (81.13%; 43/53) at the Cincinnati Children's Hospital Medical Center were treated with P/T, whereas all or most patients were treated with Comparator antibiotics at the Rady Children's Hospital (100%; 44/44), St. Louis Children's Hospital (95.56%; 43/45) and CHOP (90.67%;68/75) (Table 4.1.1).

- ***Clinical data prior to hospital admission by P/T versus Comparator HAP dosing groups (PAS)***

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. Overall, numerically lower proportions of patients in the P/T group than the Comparator group had a hospital admission within the last 30-days (25.53% *versus* 34.21%) and were ventilator dependent prior to this admission (12.06% *versus* 18.05%). The most commonly reported co-morbidities were neurologic/CNS (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 Comparator), 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 (Table 4.1.2).

- ***Hospitalization, admission and medication data prior to HAP diagnosis by P/T versus Comparator HAP dosing groups (PAS)***

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). 10.64% of the patients in the PT group and 13.53% patients in Comparator group were admitted due to respiratory infections.

The majority of patients in both groups were initially admitted to the PICU or to a general inpatient non-ICU floor. The median number of days in the hospital prior to HAP diagnosis was comparable in both groups: 5 days (IQR: 3-11 days) in PT *versus* 6 days (IQR: 4-10 days) in the Comparator group. Prior to the HAP diagnosis, numerically lower proportions of patients in the P/T group than the Comparator group were initially admitted to the ICU (58.87% *versus* 65.41 %) and required endotracheal intubation (40.43% *versus* 56.77 %).

Comparable proportion of patients in both P/T and Comparator groups were treated with vancomycin (29.08% *versus* 27.44 %), vecuronium (5.67% *versus* 4.14 %) and aminoglycosides (9.93% *versus* 8.27 %) on the day of or day after HAP diagnosis (Table

4.1.3). All other medications administered on the day of or day after HAP diagnosis in both treatment groups are presented in Additional Table C.

- ***Laboratory data prior to HAP diagnosis by P/T versus Comparator HAP dosing groups (PAS)***

Table 4.1.4 summarizes laboratory results (with reference values) on the nearest day prior to HAP diagnosis by treatment group. All laboratory tests were not consistently ordered for all patients prior to HAP diagnosis, as expected, in this observational study. As such, specific test results were not available in medical records in a substantial proportion of patients in the P/T and the Comparator groups, for example: WBC: 29.79% and 15.79%; absolute neutrophil count 55.32% and 37.22%; sodium level 34.04% and 17.67% and serum creatinine level 34.04% and 19.17% respectively.

Among patients with laboratory data, 4.96% in the P/T group and 7.89% in the Comparator group had at least one recorded episode of low WBC count. The proportion of patients with low absolute neutrophil count (ANC) was comparable in both groups prior to HAP diagnosis.

Elevated levels of serum creatinine prior to HAP diagnosis was noted in 6.38% of patients in the P/T group and 8.65% in the Comparator group. Median estimated glomerular filtration rate (eGFR) was identical (96.57 mL/min) in both groups however mean eGFR mL/min was 120.00 in the P/T group and 112.72 in the Comparator group. Overall, 51.77% patients had eGFR within the normal range of ≥70mL/min prior to HAP diagnosis in the P/T group and 66.92% in the Comparator group per the pRIFLE (Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease) criteria. LFTs prior to HAP diagnosis were not available for a substantial proportion (≥ 65%) of patients in both groups. Among patients with data, 8.51% in the P/T group and 4.89% in the Comparator group had high levels of aspartate aminotransferase [AST], 8.51% in the P/T and 6.77% in the Comparator group had high levels of alanine aminotransferase [ALT], and 9.93% in the P/T and 4.14% in the Comparator group had high levels of bilirubin level. Comparable proportion of patients in both groups had high glucose levels (>106 ml/dl) (39.01% in the P/T and 42.11% in the Comparator groups.

- ***Hospitalization, microbiology and radiology data at HAP diagnosis by P/T versus Comparator HAP dosing groups (PAS)***

Approximately half (47.52%) of the patients in the P/T and 59.77% of patients in the Comparator groups were located in the PICU at the time of HAP diagnosis. Respiratory or sputum cultures were not ordered/performed for ~36% of patients in both groups. In patients with records of sputum cultures, the proportion of patients with at least one positive respiratory or sputum culture within 24 hours of starting HAP treatment was comparable in both groups (24.11% in the P/T group *versus* 26.69% in the Comparator group). Overall, other bacterial co-infections (e.g., meningitis/encephalitis, sinusitis pyelonephritis/UTI) at the time of HAP diagnosis were not common in both groups.

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 HAP diagnosis in 95.04% of patients in the P/T group and 95.86% of patients in the Comparator group. In the P/T group and Comparator groups, 26.95% *versus* 25.56% showed new infiltrate(s) only, 12.06% *versus* 8.27% showed new infiltrate(s) with atelectasis, 10.64% *versus* 6.77% showed both new infiltrate(s) and effusion/empyema and 7.80% *versus* 15.41% showed atelectasis only. In 8.51% of patients in the P/T group and 12.03% in the Comparator group the chest x-ray was stable without any acute changes (Table 4.1.5).

- ***Laboratory data after HAP diagnosis by P/T versus Comparator HAP dosing groups (PAS)***

The number of specific laboratory test records (e.g., complete blood counts, liver function tests, creatinine levels) accessible in each patient's medical record varied by patient and was likely dependent upon clinical condition and length of hospitalization. Unlike laboratory data prior to HAP diagnosis where labs were not ordered/not available in medical records in a substantial proportion of patients in both groups, all patients had records of at least one pertinent laboratory test record after HAP diagnosis during the study follow up period (Table 4.1.6).

After HAP diagnosis, 10.00% of patients in the P/T group and 12.11% of patients in the Comparator group had at least one episode of new low WBC count (<4.5 $x10^3$/µL) and 9.21% of patients in the P/T group and 9.26% of patients in the Comparator group had at least one episode of new low absolute neutrophil count (<500 $x10^3$/µL). The, proportion of patients with new low Hgb (<9.0 g/dL) was comparable in both groups (27.16% in the P/T group and 27.43% in the Comparator group).

The proportion of patients with at least one new episode of elevated levels of AST (>64 U/L) was 37.84% in the P/T group and 29.31% in the Comparator group. At least one new episode of elevated ALT (> 45 U/L) was observed during the follow up in 51.35% and 44.00% of patients in the P/T and Comparator groups, respectively. The proportion of patients with at least one episode of elevated total bilirubin was 20.00% in the P/T group and 12.73% in the Comparator group. At least one record of a high creatinine level (>1.5x increase from baseline) was observed in 19.86% of patients in the P/T group and 17.29% in the Comparator group during the follow up period (Table 4.1.6).

- ***Hospitalization and medication data after HAP diagnosis by P/T versus Comparator HAP dosing groups (PAS)***

A comparable proportion of patients in the P/T and Comparator groups received vancomycin (27.66% *and* 25.19%), however a lower proportion in the P/T received vecuronium than the Comparator group (5.67% *versus* 12.03%) after HAP diagnosis. A comparable proportion in both groups received aminoglycosides (14.18% *versus* 14.29%). No patient in the P/T group received methotrexate compared to 5 patients (1.88%) in the comparator group (Table 4.1.7).

63.12% of patients in the P/T group and 78.20% in the Comparator group were in the ICU at the time of HAP diagnosis. Overall, a 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%). Overall, tracheostomy was performed in a small number of patients post HAP diagnosis and the proportion was comparable in the two groups (Table 4.1.7). All other medications after HAP diagnosis in both treatment groups are presented in Additional Table C.

10.2.2. P/T Any dosing *versus* Comparator Any dosing groups— Full Analysis Set (FAS) (n=412)

Of the 412 patients included in this study, 5 (1.2%) patients received P/T or Comparator antibiotics outside of HAP dosing range as described earlier (9.6.1 Exposure). All 5 patients were treated with the Comparator HAP antibiotics: 2 patients at CHOP, PA, 2 patients at Rady Children's Hospital, CA and 1 patient at Children's Healthcare of Atlanta, GA.

Overall, patients in the P/T and the Comparator Any dosing groups were very similar with regards to demographic characteristics including age, sex and race (Table 4.1.1a).

None of the 5 patients treated with an antibiotic dose outside the HAP dosing range are in the P/T group as such the proportion of patients across various demographic characteristics was identical in P/T HAP dosing and P/T Any dosing groups (Tables 4.1.1 and 4.1.1a). With only 5 additional patients, the Comparator Any dosing group results were very similar to the Comparator HAP dosing group results (Tables 4.1.1 and 4.1.1a).

Given that the characteristics of the Any dosing and HAP dosing patient groups were very similar, planned analyses (e.g., incidence rate calculation) for the Any dosing group (using FAS) were not performed as they would be expected to yield comparable results to those of the HAP dosing patients because of the small number (n=5) of patients who were treated outside of the HAP dosing range in this study.

10.2.3. *P/T HAP dosing versus Comparator subset: carbapenems HAP dosing groups— (PAS)*

Of the 266 patients in the Comparator group, 56 (21.1%) patients received a carbapenem at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients as the first antibiotic administered for the treatment of HAP. These 56 patients comprised the "Comparator subset: carbapenems group."

Tables 4.1.1 to 4.1.7 present data on demographic and clinical characteristics (pre-HAP, at HAP-and post-HAP diagnosis) including data on hospitalization, laboratory/radiology, and medications comparing P/T HAP dosing group (n=141) and Comparator subset: carbapenems HAP dosing group (n=56). Below is a summary:

- ***Demographic characteristics by P/T versus Comparator subset: carbapenems HAP dosing groups (PAS)***

Mean age (range) of patients was 7.40 (0.21-20.53) years in the P/T HAP dosing group compared to 6.88 (0.21-18.20) years in the Comparator subset: carbapenems HAP dosing group.

The proportion of infants (2-months to < 2 years) was lower in the P/T compared to the Comparator HAP dosing group (34.04% *versus* 41.07%). Overall, patients in the two groups were comparable with regard to the distribution of sex and race—about half of the patients were White and >57% males in both groups. However, the P/T group had a lower proportion of African American patients than the Comparator subset: carbapenems HAP dosing group (29.08% % *versus* 39.29%) (Table 4.1.1).

Of the 56 patients in the Comparator subset: carbapenems HAP dosing group, 31 (55.36%) patients were included from the Children's Healthcare of Atlanta, GA and 13 (23.21%) were from the Rady Children's Hospital, San Diego, CA. None to a few patients were treated with a carbapenem as the first antibiotic for treatment of HAP at the Columbia University Medical Center (0%; 0/36), Cincinnati Children's Hospital Medical Center (5.66%; 3/53) and at the St. Louis Children's Hospital (2.22%; 1/45).

- ***Clinical data prior to hospital admission by P/T versus Comparator subset: carbapenems HAP dosing groups (PAS)***

Overall, a lower proportion of patients in the P/T group than the Comparator subset: carbapenems HAP dosing group had a hospital admission within the last 30-days (25.53% *versus* 35.71%) and were ventilator dependent prior to the admission (12.06% *versus* 19.64%).

The most commonly reported co-morbidities were neurologic/CNS (39.72% in P/T and 35.71% in Comparator subset: carbapenems), cardiovascular diseases (36.88% in P/T and 28.57% in Comparator subset: carbapenems), and respiratory system related co-morbidities (26.95% in P/T and 28.57% in Comparator: subset carbapenems) prior to the hospital admission (Table 4.1.2).

- ***Hospitalization, admission and medication data prior to HAP diagnosis by P/T versus Comparator subset: carbapenems HAP dosing groups (PAS)***

The primary reason/indication for hospital admission was non-infectious illness in the majority of patients in both groups (80.85% in P/T and 80.36% in Comparator subset: carbapenems group). 10.64% of the patients in the P/T group and 12.50% patients in the Comparator subset: carbapenems group were admitted due to respiratory infections.

The majority of patients in both groups were initially admitted to the PICU or a general inpatient -non-ICU floor. The median days in the hospital prior to HAP diagnosis was comparable in both groups, 5 days (IQR: 3-11 days) in P/T group *versus* 6 days (IQR: 4-10.5 days) in the Comparator subset: carbapenems group. Prior to the HAP diagnosis, a comparable proportion of patients in the P/T group and the Comparator subset: carbapenems

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%). Median duration (days) of ICU admission in patients admitted to ICU for at least 1 day was comparable between the P/T and Comparator subset: carbapenems groups (5[IQR:3-9] days *versus* 7.5 [IQR: 5-10] days).

Comparable proportion of patients in both P/T and Comparator subset: carbapenems groups were treated with vancomycin (29.08% *versus* 21.43%) and aminoglycosides (9.93% *versus* 5.36%), however a higher proportion were treated with vecuronium in P/T than Comparator subset: carbapenems groups (5.67% *versus* 1.79%) on the day of HAP diagnosis or one day after diagnosis (Table 4.1.3). All other medications prior to HAP diagnosis in both treatment groups are presented in Additional Table C.

- ***Laboratory data prior to HAP diagnosis by P/T versus Comparator subset: carbapenems HAP dosing groups (PAS)***

Table 4.1.4 summarizes laboratory results (with reference values) on the nearest day prior to HAP diagnosis by treatment group. As such, specific test results were not available in medical records in a substantial proportion of patients in P/T and Comparator subset: carbapenems groups e.g., WBC: 29.79% and 25.00%; absolute neutrophil count 55.32% and 32.14%; sodium level 34.04% and 25.00%, respectively..

Among patients with laboratory data, a comparable proportion of patients in both treatment groups had at least one recorded episode of low WBC count (4.96% *versus* 8.93%), low absolute neutrophil count (4.26% *versus* 5.36%), and low hemoglobin (7.09% *versus* 8.93%) prior to HAP diagnosis.

Among patients with data on serum creatinine levels, 6.38% in the P/T group and 12.50% in the Comparator subset: carbapenems group had an elevated serum creatinine level prior to HAP diagnosis. The proportion of patients with eGFR within the normal range of ≥70mL/min prior to HAP diagnosis was comparable in both groups (51.77% patients in the P/T group and 53.57% patients in the Comparator subset: carbapenems group per the pRIFLE criteria.

Liver function test (i.e., ALT, AST, total bilirubin) values prior to HAP diagnosis were not available for a substantial proportion (> 50%) of patients in both groups. Among patients with data, a comparable proportion of patients in the P/T group than the Comparator subset: carbapenems group had high levels of AST (8.51% *versus* 12.50%) and ALT (8.51% *versus* 10.71%). 39.01% of patients in the P/T group and 35.71%) in the Comparator subset: carbapenems group had elevated glucose levels (>106 ml/dl).

- ***Hospitalization, microbiology and radiology data at HAP diagnosis by P/T versus Comparator subset: carbapenems HAP dosing groups (PAS)***

Approximately half of the patients in the P/T group (47.52%) and the Comparator subset: carbapenems group (53.57%) were in the PICU at the time of HAP diagnosis. Respiratory or sputum cultures were not ordered/performed in 37.59% of patients in the P/T group and 41.07% in the Comparator subset: carbapenems. In patients with reports of sputum cultures, the proportion of patients with at least one positive respiratory or sputum culture within 24 hours of starting HAP treatment was comparable in both groups (24.11% in the P/T group *versus* 21.43% in the Comparator subset: carbapenems). Other bacterial co-infections (e.g., meningitis/encephalitis, sinusitis pyelonephritis/UTI) at the time of HAP diagnosis were not common in both groups.

At least one chest x-ray was performed between 24 hours before and up to 48 hours (day -1 to day 2) after the HAP diagnosis in 95.04% of patients in the P/T group and 98.21% of patients in the Comparator subset: carbapenems. In 8.51% of patients in the P/T group and 19.64% in the Comparator subset: carbapenems, the chest x-ray was stable (showed no acute changes). In the P/T group and Comparator subset: carbapenems group, respectively, 26.95% *versus* 37.50% showed new infiltrate(s) only, 12.06% *versus* 5.36% showed new infiltrate(s) with atelectasis, 10.64% *versus* 10.71% showed both new infiltrate(s) and effusion/empyema, and 7.80% *versus* 7.14% showed Atelectasis only (Table 4.1.5).

- ***Laboratory data after HAP diagnosis by P/T versus Comparator subset: carbapenems HAP dosing groups (PAS)***

All patients had records of at least one pertinent laboratory test result after HAP diagnosis during the follow up period (Table 4.1.6).

After HAP diagnosis, 10.00% in the P/T group and 17.02% in the Comparator subset: carbapenems had at least one episode of new low WBC count (<4.5 $x10^3$/uL). The rate of new low hemoglobin (<9.0g/dL) was 27.16% in the P/T group and 22.86% in the Comparator subset: carbapenems.

The proportions of patients with at least one new episode of elevated levels of AST (>64 U/L), ALT (> 45 U/L) and total bilirubin between P/T and Comparator subset: carbapenems groups were (37.84% *versus* 36.84%; 51.35% *versus* 54.17%; and 20.00% *versus* 9.52%), respectively. The proportion of patients with at least one record of high creatinine levels (>1.5x increase from baseline) was 19.86% in the P/T group when compared to 26.79% in the Comparator subset: carbapenems during the follow up period (Table 4.1.6).

- ***Hospitalization and medication data after HAP diagnosis by P/T versus Comparator subset: carbapenems HAP dosing groups (PAS)***

Overall, a comparable proportion of patients in the P/T group and Comparator subset: carbapenems group received vancomycin (27.66% *versus* 26.79%), vecuronium (5.67% *versus* 8.93%) and aminoglycosides (14.18% *versus* 12.50%). No patients in the P/T group and 2 (3.57%) patients in the Comparator subset: carbapenems group received methotrexate

during the follow up period after HAP diagnosis. All other medications after HAP diagnosis in both treatment groups are presented in Additional Table C.

63.12% of patients in the P/T group and 78.57% in the Comparator subset: carbapenems were in ICU at the time of HAP diagnosis. A comparable proportion of patients in the P/T group and the Comparator subset: carbapenems were admitted to ICU after the HAP diagnosis (14.29% *versus* 9.09 (Table 4.1.7).

10.3. OUTCOME DATA

The analysis of outcome variables (i.e., serious events and treatment effectiveness endpoints) was conducted by treatment group using PAS.

10.3.1. Serious Events—Primary Endpoints

A total of 93 serious events among 48 patients were identified across the P/T HAP dosing and Comparator HAP dosing groups during the follow up period (Table 5.1.1).

10.3.1.1. P/T HAP dosing group - PAS (n=141)

- Median (IQR) follow up time for the 141 patients in the P/T HAP dosing group from HAP diagnosis until either discharge or death was 15 days (8-31 days). Of the 93 serious events identified in this study, 34 serious events among 18 patients were identified in the P/T HAP dosing group during the follow up period. Median (IQR) time from P/T initiation to the onset of a serious event was 9 days (4-14 days) (Table 5.1.1).

  - Serious events by body system were as follows: cardiovascular (10), CNS (3), endocrine (0), gastrointestinal (4), hematologic (1), hepatic (1), infection (2), renal (1), respiratory (10), and skin (2) (Table 5.1.1).

  - There were 5 deaths within 30-days of HAP treatment initiation identified in the P/T HAP dosing group (Table 5.2.1). Median time from P/T initiation to death was 10 days (IQR: 5 to 15 days).

10.3.1.2. Comparator HAP dosing group- PAS (n=266)

- Median (IQR) follow up time for the 266 patients in the Comparator HAP dosing group from HAP diagnosis until either discharge or death was 18.5 days (10-38 days). Of the 93 serious events within 30-days of HAP treatment initiation identified in this study, a total of 59 serious events among 30 patients were identified in the Comparator HAP dosing group during the follow up period. Median (IQR) time from the Comparator treatment initiation to the onset of a serious event was 6 days (3-16 days) (Table 5.1.1).

  - Serious events by body system were as follows: cardiovascular (15), CNS (7), endocrine (1), gastrointestinal (2), hematologic (1), hepatic (3), infection (11), renal (2), respiratory (14), skin (1) and other (2) (Table 5.1.1).

- There were 12 deaths within 30-days of HAP treatment initiation identified in the Comparator HAP dosing group during the follow up period (Table 5.2.1). Median time from Comparator treatment initiation to death was 12 days (IQR: 8.5-19 days).

10.3.1.3. Comparator subset: carbapenems HAP dosing group- PAS (n=56)

- Median (IQR) follow up time for the 266 patients in the Comparator subset: carbapenems HAP dosing group from HAP diagnosis until either discharge or death was 20.5 days (12-40 days). Of the 59 serious events in the Comparator group, a total of 21 serious events among 9 patients were identified in the Comparator subset: carbapenems group during the follow up period. Median time from carbapenem initiation to the onset of a serious event was 14 days (IQR: 6 – 21 days) (Table 5.1.1).

  - Serious events by body system were as follows: cardiovascular (6), CNS (1), hepatic (2), infections (5), renal (2), and respiratory (5) (Table 5.1.1).

  - There were five deaths within 30-days of HAP treatment initiation identified in the Comparator subset: carbapenems HAP dosing group (Table 5.2.1). Median time from carbapenem initiation to death was 13 days (IQR: 8-21 days).

10.3.2. Treatment Effectives Outcomes- Secondary Endpoints

In accordance with the SAP, the PAS population (n=407) was used to evaluate the secondary study objective. Treatment effectiveness outcome was compared between P/T HAP dosing and Comparator HAP dosing groups, and P/T HAP dosing and Comparator subset: carbapenems HAP dosing groups.

10.3.2.1. P/T HAP dosing group - PAS (n=141)

- Of the 141 patients in the P/T HAP dosing group, 128 patients were categorized as clinically improved and 13 patients were categorized as clinically did not improve (Table 7).

10.3.2.2. Comparator HAP dosing group (n=266)

- Of the 266 patients in the Comparator HAP dosing group, 244 patients were categorized as clinically improved and 22 patients were categorized as did not improve (Table 7).

10.3.2.3. Comparator subset: carbapenem HAP dosing group (n=56)

- Of the 56 patients in the Comparator subset: carbapenems HAP dosing group, 47 patients were categorized as clinically improved and 9 patients were categorized as did not improve (Table 7).

10.4. MAIN RESULTS

10.4.1. Analysis of serious events—primary endpoints

This section presents the results of the main analyses pertaining to the serious events for 1) P/T HAP dosing *versus* Comparator HAP dosing groups, and 2) comparing P/T HAP dosing *versus* Comparator subset: carbapenems HAP dosing groups, and includes:

- Crude incidence rate (with 95% CI) of serious events,
- All-cause mortality rate,
- Univariable and multivariable Poisson regression analyses, and
- Sensitivity analyses using Negative binomial regression analyses.

10.4.1.1. P/T HAP dosing *versus* Comparator HAP dosing groups-PAS

10.4.1.1.1. Incidence rate of all serious events

Tables 5.1.1, 5.1.1a, and 5.1.1b present the crude incidence rate (per 100 per-days) of all serious events for the entire cohort, by body system (e.g., cardiovascular, respiratory), by select demographic characteristics (e.g., age, sex), and by participating site (e.g. CHOP, Rady Children's Hospital) respectively for the P/T HAP dosing and Comparator HAP dosing groups.

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 HAP dosing and 1.02 [95% CI: 0.76-1.28] in the Comparator HAP dosing groups (Table 5.1.1).

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) (Table 6.1.1).

The incidence rate (per 100 person- days) of serious events by select body systems was also comparable between the P/T HAP dosing and the Comparator HAP dosing groups: cardiovascular related serious events (0.37 *versus* 0.26), CNS related (0.11 *versus* 0.12), gastrointestinal related (0.15 *versus* 0.03), renal related (0.04 *versus* 0.03) and respiratory related serious events (0.37 *versus* 0.24) (Table 5.1.1).

In a sex-stratified analysis, incidence rate (per 100 person- days) of all serious events in females in the P/T HAP dosing group was 1.30 (95% CI: 0.74-2.12) and in the Comparator group was 0.67 (95% CI: 0.40-1.05). The age-stratified analysis showed similar rates of all serious events in all age groups between the two groups except adolescents (12 to < 16 years)in whom the incidence rate was numerically lower in the P/T dosing group than the Comparator HAP [0.24 (95% CI: 0.01-1.19) *versus* 1.73 (95% CI: 1.00-2.79)] (Table 5.1.1a).

Table 5.1.1b presents the crude incidence rate (per 100 per-days) of all serious events by participating site: 2.73 (95% CI: 0.69-7.42) in the P/T and 0.84 (95% CI: 0.47-1.41) in the Comparator HAP dosing group at the CHOP; 2.44 (95% CI: 1.53-3.70) in the P/T and 4.96 (95% CI: 2.61-8.61) in the Comparator HAP dosing group at the Cincinnati Children's Hospital.

10.4.1.1.2. All-cause mortality rate

All-cause mortality rate within 30-days of HAP treatment initiation was 3.57% (5/140) in the P/T HAP dosing group and 4.53% (12/265) in the Comparator HAP dosing group.

It is to be noted that vital status within 30-days of HAP treatment initiation was not known for 2 patients (1 in each treatment group) and these 2 patients were not included in the number of deceased patients and in the denominators for calculating the all-cause mortality rates (Table 5.2.1). Causes of death by treatment group are presented in Additional Table D.

10.4.1.1.3. Univariable and multivariable regression analyses evaluating the association between P/T and all serious events

As described in 9.12.2 Main Statistical Methods, comparative analyses of all serious events between the treatment groups were conducted using an inverse probability weighted Poisson regression model with an offset for person-time at risk and robust variance estimate. Adjusted IRR were obtained from weighted multivariable Poisson models. The weights were created using propensity score models to predict the probability of receipt of P/T conditional on patient clinical and demographic characteristics including age, race/ethnicity, hospitalized within 30-days prior to HAP admission, ventilator dependent prior to this HAP admission, cardiovascular comorbid condition, respiratory comorbid condition, other congenital or metabolic defect, required a tracheostomy or endotracheal intubation prior to HAP admission, leukopenia, high creatinine, number of days in the ICU prior to admission, indicator for missing ICU days prior to admission, other bacterial co-infection at the time of HAP diagnosis, at least one positive respiratory or sputum culture within 24 hours of HAP admission, vecuronium, vancomycin, aminoglycoside, and methotrexate. We developed two adjusted models: both models were weighted, but one included site as a fixed effect and the other one did not. There were no covariates that were unbalanced after the propensity score weighting and therefore no additional covariates were included in the models.

Table 6.1.1 presents the results of the univariable and multivariable regression analyses. At the univariable level, Poisson regression analysis showed that treatment with P/T HAP dosing was not associated with an increased risk for all serious event compared to the Comparator HAP dosing group (unadjusted IRR: 1.24 (95% CI: 0.65, 2.36; p=0.51).

Two adjusted Poisson regression models were developed to evaluate the association between treatment groups and all serious events. Both of these adjusted models were weighted, but one model adjusts for site and the other model does not. Both of these models showed no

increased risk of having a serious event with P/T HAP dosing group compared to the Comparator HAP dosing group (adjusted IRR for the model without site: 1.21, 95% CI: (0.63, 2.30), p=0.57 and adjusted IRR for the model with site: 0.80 (95% CI: 0.30, 2.12, p=0.65).

Further, there was no increased risk for all serious events noted with P/T exposure regardless of the duration of P/T HAP dosing (i.e., at least 2 days of therapy, at least 5 days of therapy and at least 7 days of therapy) in inverse probability weighted Poisson models when compared with the Comparator HAP dosing group adjusted for covariates described above.

10.4.1.1.4. Serious Events Sensitivity analyses

Overall, the results of the sensitivity analyses using the Negative binomial regression models were consistent with the conclusions reached from using the Poisson models. The Negative binomial model similarly showed that treatment with P/T HAP dosing group was not associated with an increased risk of all serious events compared to the Comparator HAP dosing group in both univariable analysis (unadjusted IRR: 1.09, 95% CI: 0.52-2.28; p=0.83) and multivariable analysis (using the same propensity weights as described above in 10.4.1.1.3 Univariable and Multivariable Analyses) (adjusted IRR including site in the model: 0.92 (95% CI: 0.29-2.90; p=0.89).

Further, no increased risk for a serious event was noted with various durations of P/T HAP dosing (i.e., at least 2 days of therapy, at least 5 days of therapy and at least 7 days of therapy) compared with the Comparator HAP dosing group in the inverse probability weighted Negative binomial regression models.

The post-hoc sensitivity analysis comparing the rate of serious events for P/T HAP dosing *versus* Comparator HAP dosing patients from 3 sites after excluding patients from sites that chose one treatment < 90% of the time were consistent with those of the primary analysis (Additional Table J).

Calculation of the E-value to determine the degree of unmeasured confounding needed to move the point estimate of the IRR for the comparison of P/T HAP dosing to Comparator HAP dosing patients (Additional Table I) found that an unmeasured confounder would need to be associated with the exposure and outcome to a strength of 1.81 to move the point estimate to the null and a strength of 2.50 to move the point estimate to 1.25.

10.4.1.2. P/T Any dosing *versus* Comparator Any dosing groups- FAS

As described earlier in 9.11.2 Full Analysis Set (FAS), the incidence rate of serious events and univariable and multivariable comparative analyses were not conducted for P/T Any dosing *versus* Comparator Any dosing groups (FAS) because of the small number (n=5) of patients who were treated outside of the HAP dosing range in this study.

10.4.1.3. P/T HAP dosing *versus* Comparator subset: carbapenems HAP dosing groups-(PAS)

10.4.1.3.1. Incidence rate of all serious events

Tables 5.1.1, 5.1.1a, and 5.1.1b. present the crude incidence rate (per 100 person-days) of all serious events overall, by body system (e.g., cardiovascular, respiratory), by select demographic characteristics (e.g., age, sex), and by participating site (e.g. CHOP, Rady Children's Hospital, San Diego), respectively, comparing P/T HAP dosing and Comparator subset: carbapenems HAP dosing groups.

Overall, a similar crude incidence rate (per 100 person- days) of all serious events was observed in the P/T HAP dosing and the Comparator subset: carbapenems HAP dosing groups [1.27 (95% CI: 0.84-1.70) *versus* 1.59 (95% CI: 0.91-2.26)] (Table 5.1.1).

Similar incidence rates (per 100 person-days) of serious events by select body system were observed in the P/T HAP dosing and the Comparator subset: carbapenems HAP dosing groups: cardiovascular related serious events (0.37 *versus* 0.45), CNS related (0.11 *versus* 0.08), gastrointestinal tract related (0.15 *versus* none), renal related (0.04 *versus* 0.15) and respiratory related serious events (0.37 versus 0.38) (Table 5.1.1).

In a sex-stratified analysis, incidence rate (per 100 person- days) of all serious events was 1.25 (95% CI: 0.79-1.90) in males in the P/T HAP dosing group and 1.96 (95% CI: 1.11-3.20) in the Comparator subset: carbapenems HAP dosing groups. The rate was 1.30 (95% CI: 0.74-2.12) in females in the P/T HAP dosing and 1.15 (95% CI: 0.50-2.28) in the Comparator subset: carbapenems HAP dosing group). The age-stratified analysis showed, similar rates of all serious events in all age strata in the P/T HAP dosing group compared to the Comparator subset: carbapenems HAP dosing group except 16 years and older in whom the rate was 2.52 (95% CI: 1.17-4.78) in the P/T HAP dosing group and 10.84 (95% CI: 5.29-19.90) and in the Comparator subset: carbapenems HAP dosing group (Table 5.1.1a).

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) (Table 6.1.2).

Table 5.1.1b presents the crude incidence rate (per 100 per-days) of all serious events by participating site: 2.73 (95% CI: 0.69-7.42) in the P/T and 0 cases in the Comparator HAP dosing group at the CHOP; 2.44 (95% CI: 1.53-3.70) in the P/T and 1.98 (95% CI: 0.33-6.54) in the Comparator subset: carbapenems HAP dosing group at the Cincinnati Children's Hospital.

10.4.1.3.2. All-cause mortality rate

All-cause mortality rate within 30-days of HAP treatment initiation was 3.57% [5/140] in the P/T HAP dosing group and 9.09% (5/55) in the Comparator subset: carbapenems HAP

dosing group Vital status within 30-days of HAP treatment initiation was not known for 2 patients (1 in each treatment group); and these 2 patients were not included in the number of deceased patients and in the denominators for calculating the all-cause mortality rates (Table 5.2.1). Cause of death by treatment group is presented in Additional Table D.

10.4.1.3.3. Univariable and multivariable analyses evaluating the association between P/T and all serious events

Table 6.1.2 presents the results of the univariable and multivariable analyses evaluating the association between P/T HAP dosing group and the risk for all serious events compared to the Comparator subset: carbapenems HAP dosing group. At the univariable level, Poisson regression analysis showed that treatment with P/T HAP dosing group was not associated with an increased risk for all serious events (unadjusted IRR: 0.80, 95% CI: 0.34-1.86; p=0.60).

Two adjusted Poisson regression models were developed to test the association between P/T and all serious events. Both of these adjusted models are weighted, but one model adjusts for site and the other model does not. Both of these models showed no increased risk of having all serious event with P/T HAP dosing group compared to the Comparator subset: carbapenems HAP dosing group (adjusted IRR for the model without site: 0.76, 95% CI: (0.32, 1.78), p=0. 53 and adjusted IRR for the model with site: 0.95 (95% CI: 0.35, 2.62, p=0.93).

Further, no increased risk for all serious event was noted with various durations of P/T HAP dosing (i.e., at least 2 days of therapy, at least 5 days of therapy and at least 7 days of therapy) in sensitivity analyses in propensity weighted Poisson models when compared to patients with similar durations of Comparator subset: carbapenems HAP dosing group (Table 6.1.2).

10.4.1.3.4. Serious Events Sensitivity analyses

Overall, the results of the sensitivity analyses using Negative binomial regression modeling were consistent with the Poisson regression models. The Negative binomial models showed that treatment with P/T HAP dosing was not associated with an increased risk of all serious event compared to treatment with Comparator subset: carbapenems HAP dosing in both univariable analysis (unadjusted IRR: 0.48, 95% CI: 0.17-1.40); p=0.18) and multivariable analysis (using the same weights described above in section 10.4.1.1.3 Univariable and multivariable regression analyses evaluating the association between P/T and all serious events) (adjusted IRR for model with site as a fixed effect was 0.42 (95% CI: 0.10-1.71; p=0.22) (Table 6.1.2).

Further, no increased risk for all serious events was noted with various durations of treatment with P/T HAP dosing (i.e., at least 2 days, at least 5 days, and at least 7 days of therapy) compared to patients receiving Comparator subset: carbapenems HAP dosing in unadjusted and propensity score weighted Negative binomial regression models (Table 6.1.2).

The post-hoc sensitivity analysis comparing the treatment outcomes for P/T HAP dosing *versus* Comparator subset: carbapenem HAP dosing patients from 4 sites (two sites having small numbers) after excluding patients from sites that chose one treatment < 90% of the time were consistent with those of the primary analysis (Additional Table K).

Calculation of the E-value to determine/quantify the degree of unmeasured confounding needed to move the point estimate of the IRR for the comparison of P/T HAP dosing to Comparator subset: carbapenem HAP dosing found that an unmeasured confounder would need to be associated with the exposure and outcome to a strength of 1.29 to move the point estimate from that which was measured to the null or a strength of 1.96 to move the point estimate from that which was measured to 1.25 (Additional Table I).

10.4.2. Analysis of treatment effectiveness- Secondary endpoints

This section presents analyses pertaining to the treatment effectiveness outcomes by treatment group. Table 7 presents counts and proportions of patients categorized as "clinically improved" and "did not improve" within 14 days from the start of HAP therapy overall analysis and by select demographic characteristics.

10.4.2.1. P/T HAP dosing *versus* Comparator HAP dosing groups

A high proportion (>90%) of patients in both treatment groups categorized as clinically improved at or before 14 days from the start of HAP therapy: 90.78% in the P/T HAP dosing and 91.73% in the Comparator HAP dosing groups.

Overall, a small number and proportion of patients were categorized as "clinically did not improve" in the study: 13 (9.22%) in the P/T HAP group and 22 (8.27%) in the Comparator HAP dosing group. No substantial differences in the effectiveness rates between treatment groups were observed by sex and by age subgroups. However, there was a higher proportion of infants (2 months to <2 years) in the P/T HAP dosing group than the Comparator HAP dosing group that did not improve (16.67% *versus* 11.01%) (Table 7).

Table 8.1.1 presents the results of the univariable and multivariable logistic regression analyses comparing outcomes of treatment effectiveness between P/T HAP dosing group and the comparator HAP dosing group. At univariable level, the analysis showed that treatment effectiveness outcome was not different between P/T HAP dosing group and the Comparator HAP dosing group (Unadjusted OR: 1.13, 95% CI: 0.55-2.31; p=0.75).

Two inverse probability weighted logistic regression models were developed to evaluate the effect of P/T HAP dosing on the treatment effectiveness outcome compared with the Comparator HAP dosing group (using the same weights described above in section 10.4.1.1.3 Univariable and multivariable regression analyses evaluating the association between P/T and all serious events). The first adjusted model did not include participating site as a fixed effect (adjusted OR: 1.45, 95% CI: 0.65-3.27; p=0.37) and the second model included

participating site as a fixed effect (adjusted OR: 1.23, 95% CI: 0.39-3.85; p=0.72). Neither adjusted model found a significant association between P/T HAP dosing and treatment effectiveness outcome. Additionally, no significant association was noted with various durations of P/T HAP dosing (i.e., at least 2 days of therapy, at least 5 days of therapy and at least 7 days of therapy) and treatment effectiveness in sensitivity analyses that used the same propensity score weighted logistic regression model, described above (Table 8.1.1).

10.4.2.2. P/T HAP dosing *versus* Comparator subset: carbapenems HAP dosing groups

A high proportion (>83%) of patients in both treatment groups were categorized as "clinically improved" at or before 14 days from the start of HAP therapy: 90.78% of patients in the P/T HAP dosing group and 83.93% of the Comparator subset: carbapenems HAP dosing group (Table 7).

Table 8.1.2 presents the results of the univariable and multivariable logistic regression analyses comparing treatment effectiveness outcomes between P/T HAP dosing group and the Comparator subset: carbapenems HAP dosing group. In the univariable analysis, treatment effectiveness outcome was not different between the two treatment groups (unadjusted OR: 0.53, 95% CI: 0.21-1.32; p=0.17). Two logistic regression models were developed using the same weights described above in section 10.4.1.1.3 Univariable and multivariable regression analyses evaluating the association between P/T and all serious events. The first adjusted model is weighted and does not include participating site as a fixed effect in the model (adjusted OR: 0.58, 95% CI: 0.22-1.52; p=0.27) and the second model included participating site as a fixed effect (adjusted OR: 0.59, 95% CI: 0.19-1.86; p=0.37). Neither adjusted model found a significant association between P/T HAP dosing and treatment effectiveness when compared to the Comparator subset: carbapenems HAP dosing group.

Additionally, no significant association was noted with various durations of P/T HAP dosing (i.e., at least 2 days of therapy, at least 5 days of therapy and at least 7 days of therapy) and treatment effectiveness in sensitivity analyses in both inverse probability weighted logistic regression models, described above (Table 8.1.2).

10.5. Other analyses

None

10.6. Adverse events / adverse reactions

There were five AEs identified (with documented attribution to P/T) in four patients during data collection and were reported to Pfizer Drug Safety. The following AEs were identified and reported: leukopenia (1 patient), diarrhea (1 patient), rash (2 patients), and allergy to P/T resulting in possible renal failure (1 patient).

11. DISCUSSION

11.1. Key results

To our awareness, this is the first study conducted to characterize the safety of P/T in pediatric patients (aged 2 months to < 18 years) with HAP by evaluating serious events in patients treated with P/T and patients treated with other HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, ciprofloxacin).

Overall, the crude incidence rate (per 100 person- days) of all serious events was comparable between the P/T HAP dosing and Comparator HAP dosing groups (1.27 [95% CI: 0.84-1.70] *versus* 1.02 [95% CI: 0.76-1.28]. The propensity score weighted multivariable Poisson and Negative binomial regression models showed no association between treatment with P/T and the risk for all serious event when compared with Comparator HAP antibiotics (and separately in the subset of patients treated with carbapenems). Further, these findings are supported by sensitivity analyses assessing the risk in patients treated for 'at least 2 days', 'at least 5 days' and 'at least 7 days' of HAP treatment and in subgroup analyses (e.g., by age, sex). The strengths of the study include the large number of pediatric patients (n=412) who received antibiotic therapy for the indication of HAP from multiple hospitals across the US, and collection of detailed real world data on safety and effectiveness of P/T and Comparator HAP antibiotics. Additionally, the study employed robust statistical analyses including IPW informed Poisson and Negative binomial regression models to control for available potential confounders.

As expected, the results from this cohort suggest that P/T dosing regimens being prescribed by clinicians for the treatment of pediatric HAP are higher than what is recommended for the treatment of IAI. All patients included in the P/T group (n=141) were treated with P/T 80 to 100 mg/kg every 6 hours (or an equivalent renally adjusted dose if renal insufficiency was present) for the piperacillin component up to the maximum of 4 gm every 6 hours for the piperacillin component.

The primary study objective was to estimate the rate of serious events and more specifically to assess the relative rate of serious events in P/T exposed patients as compared to patients prescribed other HAP antibiotics. The target study size was not based on an a priori power calculation. However, a number of factors suggest that the final cohort size of 407 (i.e., 141 patients in the P/T HAP dosing and 266 patients in the Comparator HAP dosing group) was sufficient to adequately inform the resultant point estimates. First, the width of the 95% CI around the point estimates of the incidence of serious events was reasonable for each exposure group. Second, the sample size allowed for multivariable regression analyses to compare the risk of all serious event (primary endpoint) and treatment effectiveness (secondary endpoint) between the two treatment groups while simultaneously controlling for both patient level and hospital level data available on confounders. Lastly, a number of sensitivity analyses were performed and each showed similar point estimates for the comparison of all serious events and successful treatment outcomes between the P/T and the Comparator groups.

Estimates of serious adverse events in pediatric patients treated for HAP are not available in the published literature for comparison. It is possible that the incidence rates of all serious events in both treatment groups are underestimated in this study because of the methodology used to identify these events. As described in 9.7 Data Sources and Measurements, the trained research personnel reviewed the entirety of the daily progress notes (including problem lists, assessment and plan) of the POR (along with the supporting laboratory and radiology data) to identify any untoward medical events. These documents were also reviewed in detail by the study physicians at CHOP (principal study site), who were blinded to the antibiotic that each patient received for HAP treatment, to determine whether the documented event met the study definition, as defined in 9.6.2.1 Serious Events. As stated earlier, the rates of serious events might be underestimated given that the study procedures were designed to capture serious events that were documented in the daily POR progress notes. However, it is expected that most serious events (unlike non-serious adverse events) would have been recorded in the daily progress notes and would therefore have been captured in this study. Furthermore, this approach guards against excessive capture of events that might otherwise have been deemed serious because of a laboratory test result but that are not deemed clinically relevant by the caring physician. As suggested by the FDA, copies of the de-identified daily progress notes that triggered the identification of all serious events after HAP treatment initiation are being submitted (Appendix 3).

While it is possible that this approach underestimated the absolute number of serious events it provided a process that was employed systematically and used a data source that was equally available across treatment groups. In the design phase of the protocol other options for identifying serious events were discussed including use of laboratory results. However, as this was an observational study, local clinicians dictated the frequency and timing of laboratory testing. Because laboratory testing would not be mandated by study protocol, there was a sincere concern that the acquisition of laboratory results would be differential by treatment group and that there would be substantial number of patients with no laboratory results for a given adverse event. These concerns translated into a significant possibility of biased rates of serious events if they were dependent on laboratory results. The daily progress note of the POR was the one consistently available data source for all patients in all treatment groups due to the severity of the underlying illness. There is no reason to conclude that documentation of serious events in these progress notes would occur systematically *differently* between patients treated with P/T and Comparator antibiotics within the same hospital. Ultimately, the goal of this process was to ensure an appropriate relative comparison of incidence of serious events between treatment groups. The primary and sensitivity comparative analyses showed that the IRR of all serious events was comparable between the two treatment groups (and also comparable between the P/T and the Comparator subset: carbapenems group). The assumption of *non-differential* documentation of serious events between the two treatment groups is in part supported by the comparable all-cause mortality rates, which is a well-defined ‘hard endpoint’, observed in the two groups. As such, the conclusion from the analyses was that the incidence rate of serious events is

comparable between the two groups (and also comparable with the Comparator subset: carbapenems group).

As expected, the choice of antibiotics for the treatment of HAP varied by participating site. Some sites primarily used P/T to treat HAP while others used Comparator antibiotics. It is likely that the use of HAP antibiotics was dependent on the formulary and site treatment protocol and/or treating physician. In order to assess the confounding effect due to variation in HAP treatment/clinical practice by participating site, two separate Poisson (and also Negative binomial) regression models were developed. One of the two regression models included propensity score weights but did not include "participating site" in the model, whereas the other model included the propensity score weights as well as "participating site" as a fixed effect in the model. The effect estimate slightly changed (i.e., IRR moved towards null) after adding participating site as a fixed effect in the model but the overall conclusions remained the same (i.e. no difference in the IRR for a serious event between the treatment groups). The movement of the IRR estimate towards the null suggests some confounding by participating site which could in part be due to variation in patient population and resources available for providing care at that institution. Additionally, a sensitivity analysis was performed limiting the cohort to patients at sites that captured patients from both exposure groups. This sensitivity analysis excluded patients from sites that had a clear preference for one HAP treatment and thus left vulnerability to confounding by site. The point estimates from this sensitivity analysis were similar to those determined when the entire cohort (from all sites) was utilized.

In addition to confounding by site there was also concern for confounding by indication (i.e. preference for a specific treatment based on the degree of illness of a patient at the onset of therapy). This concern led the study investigators to collect comprehensive data on enrolled patients that included a number of covariates that were identified a priori as possible confounders of the association between exposure groups and outcome measures. The resultant adjusted IRRs and accompanying 95% CIs for the comparison of P/T to all comparator antibiotics and specifically to carbapenems subset for the primary endpoint of serious events suggested no difference in these outcomes across treatment groups. In fact, the IRRs for each of these comparisons favored P/T after adjustment but notably the CIs around these point estimates included the null.

Of course, despite the extensive attempts to account for confounding by indication it is still possible that an unmeasured covariate exists that could confound the assessed associations. Recent literature has identified a novel approach to leverage a study's existing adjusted point estimates and 95% CI to determine how large an unmeasured covariate would need to be to alter the findings from the original analysis. The quantification of the unmeasured confounder is referred to as the E-value. 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. [12,13] This approach is a form of a sensitivity analysis and can be done using a publicly available online E-value calculator (E-value calculator: https://evalue.hmdc.harvard.edu/app/). This sensitivity analysis assessed how strong an

association between an unmeasured confounder and both the exposure and outcome would need to be to move each of the point estimates from that which was observed to the null value and to a value of 1.25 (an arbitrary value of a positive association between exposure and outcome). 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. The objective was to quantify the strength of an unmeasured confounder that would need to exist to influence the conclusions of the primary analysis by moving the study results to the null or to the point estimate of 1.25. These calculations were performed for the adjusted effect of P/T *versus* Comparator HAP dosing groups (and also for the adjusted effect of P/T *versus* Comparator subset: carbapenems HAP doing groups) for the primary endpoint (i.e., serious events). An output of the E-value calculator provides the strength of the confounder on a relative risk/ risk ratio scale. For the primary endpoint, 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 HAP dosing group (and 1.29 for the comparison of P/T to Comparator subset: carbapenems HAP dosing group) to move the point estimate of the IRR to the null. 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 (Additional Table I). Given the comprehensive nature of data collection and robust a priori analytic plan it would be very unlikely for such an unmeasured confounder to exist or an unmeasured confounder with this possible magnitude of association that was not already included in the propensity score weights/regression models. This provides further confidence in the observed findings.

The treatment effectiveness outcome designation (i.e., clinically improved from HAP and did not improve) was assessed by trained research personnel. It was planned to have a study physician(s), blinded to treatment group, review documentation from POR progress notes to confirm the appropriateness of the outcome designation ascertained by the research personnel. However, a substantial proportion of patients (42.6% patients in the P/T and 50% in the Comparator group) did not have a progress note within 14 days of HAP diagnosis in which the POR specifically indicated either that the patient had improved or did not improve from their HAP diagnosis. For those patients, it was necessary for the trained research personnel to make an independent decision regarding clinical status at the time of performing the on-site comprehensive chart review. In order for a study physician to confirm the designation of the outcome for each patient by the research personnel, it would have been necessary to copy the entirety of the medical chart for each enrolled patient and bring those copies back to the principal site for review by the study physicians. This was not feasible in the context of the study and participating sites. Research personnel consulted with study physicians on as-needed basis and assigned designation of treatment effectiveness into the binary categories, as instructed; however, misclassification of the binary outcome might have occurred in some patients due to the lack of clear evidence in the entire medical record to support clinical improvement or no improvement within 14 days of HAP treatment initiation. While this was a limitation, it should be noted that the assessment of treatment effectiveness/clinical response was a secondary endpoint and that the study was primarily

designed to evaluate the safety of P/T in the treatment of pediatric HAP. As suggested by the FDA, copies of a sample of de-identified daily progress notes with documentation pertaining to treatment effectiveness are being submitted as examples (Appendix 3).

11.2. Limitations

In addition to inherent limitations of an observational study utilizing retrospective data such as possible inaccuracies and incompleteness in medical records, this study was subjected to the following design/data-related limitations:

- **Residual and unmeasured confounding:** The study collected detailed data on demographic and clinical characterizes including admission, hospitalization, laboratory, radiology, procedures and concomitant medications used during pre-and post-HAP diagnosis. Multiple analytic approaches were used to achieve balance in the comparative groups for possible confounding variables. First, baseline covariates that were unbalanced by treatment group were used to inform a model to establish propensity scores for receipt of a specific treatment and these propensity score models were used to establish weights in the multivariable Poisson and Negative binomial models. Any baseline covariate that was still imbalanced after propensity score weighting and deemed to be a possible confounder was to be included in these final regression models. Additionally, an a priori decision was made to compare P/T HAP dosing patients with patients treated with a carbapenem as it was expected that these two groups would be less vulnerable to confounding by indication, relative to the comparator HAP antibiotics group, as they are both sufficiently broad antibiotics. Nonetheless, imbalance of some covariates might have persisted in this comparison and as such similar modeling as detailed above was performed.

  To address confounding by participating site, a post-hoc sensitivity analysis was conducted in which the same models were rerun for the same primary outcome, removing sites with a predilection for either P/T or the comparator treatments in 90% or more of their study patients. Lastly, to examine the effect of any unmeasured confounding, an E-value was calculated to quantify the strength of an association between an unmeasured confounder and both the exposure *and* outcome of interest needed to reverse the findings. Despite the robust and comprehensive nature of the analysis, the study was dependent on data that were available in the stored medical records. Therefore, it is possible that residual confounding from unmeasured covariates might have persisted.

- **Underestimation of incidence rate of serious events:** Given that only documented events that appeared in the POR daily progress notes and met the definition of serious events (9.6.2.1 Serious Events) were included, it is possible that the incidence rates of all serious events and by body system in both treatment groups might be underestimated because not all such events may have been documented in real world clinical practices. However, pediatric HAP is a serious illness for which detailed progress notes/documentations are routine for all patients 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 antibiotics.

- **Misclassification of treatment effectiveness outcome:** As described earlier in 11.1 Key Results, study physicians were not able to confirm the designation of treatment effectiveness outcomes (i.e., clinically improved or did not improve) that was ascertained by the research personnel during review of medical charts. Although the research personnel followed the instructions and consulted with the study physicians to assign the outcome designation on as-needed basis, misclassification (either *differential* or *non-differential*) of the treatment effectiveness outcome in some patients cannot be ruled out due to a lack of clear documentation in a substantial proportion of charts pertaining to clinical improvement (or no improvement) within 14 days of HAP treatment initiation. Further, the research personnel who abstracted the data from medical charts were not blinded to the treatment patients received. As such, data on the treatment effectiveness outcome should be interpreted with caution.

11.3. Interpretation

P/T is an injectable broad spectrum antibacterial agent first approved by the FDA in 1993. The safety and effectiveness of P/T in the treatment of HAP among pediatric patients has not been formally studied in either comparative non-interventional studies or RCTs.

This retrospective cohort study showed that the incidence rate of serious events and all-cause mortality in the P/T HAP dosing (i.e., P/T 80 at a dose 80-100 mg/kg piperacillin/ 10-12.5mg/kg tazobactam every 6 hours) was comparable with Comparator HAP antibiotics (when used alone or in combination with an adjunctive antibiotic such as vancomycin or an aminglycoside) at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients. It is to be noted that data pertaining to the safety of P/T in pediatric patients with HAP from similar studies are not available for comparison. It is possible that this study might have underestimated the absolute incidence rate of serious events in all treatment groups because only events documented by the POR in medical charts that met the definition of serious events were included. However, there is no reason to believe that documentation of serious events in medical records would occur *differentially* between patients treated with P/T and Comparator antibiotics. Therefore, the relative comparison of the incidence of serious events between exposure groups is informative and the results adjusted for important patient and hospital level available confounders support a similar IRR for adverse events between P/T HAP dosing and Comparator HAP dosing groups. However, chances of residual and unmeasured confounding cannot be ruled out and caution must therefore be applied in the interpretation of the results.

11.4. Generalizability

This study included 412 pediatric patients from 7 hospitals across the US to assess safety and effectiveness of P/T in pediatric patients with HAP. As such, the findings from this study are

likely to be generalizable to all pediatric patients in the US treated with P/T or Comparator antibiotics (HAP dosing) for the indication of HAP.

12. CONCLUSIONS

This retrospective cohort study investigated the risk of serious events (primary objective) as well as treatment effectiveness outcomes (secondary objective) among pediatric patients with hospital acquired pneumonia (HAP) by comparing piperacillin/tazobactam (P/T) to Comparator HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin). A total of 412 pediatric patients (aged 2 months to <18 years) with an indication of HAP were included from seven large pediatric hospitals across the US. Of 412 patients included in the study, 407 (98.8%) patients received HAP dosing and were used for the primary analysis: 141 (34.64%) patients in the P/T HAP dosing group, and 266 (65.36%) patients in the Comparator HAP dosing group.

The crude incidence rate (per 100 person- days) of all serious events was comparable between the P/T HAP dosing and Comparator HAP dosing groups (1.27 [95% confidence interval (CI): 0.84-1.70] *versus* 1.02 [95% CI: 0.76-1.28]. Two adjusted Poisson regression models were developed to evaluate an association between P/T HAP dosing and all serious events. Both models were adjusted using propensity score weights, but one model adjusted for participating site and the other model did not. Both Poisson models showed no increased risk of having a serious event with P/T HAP dosing group compared to the Comparator HAP dosing group (adjusted incidence rate ratio [IRR] for the model without participating site: 1.21, 95% CI: (0.63, 2.30), p=0.57 and adjusted IRR for the model with participating site: 0.80 (95% CI: 0.30, 2.12, p=0.65). Findings from subgroups (e.g., by age, sex) and sensitivity analyses (e.g., by various treatment durations such as at least 2 days and at least 5 days of therapy) were also consistent with the results of the main regression analyses. Overall, a small proportion of deaths were observed in treatment groups: 3.57% in the P/T and 4.53% in the Comparator.

A high proportion of patients in both treatment groups were categorized as clinically improved at or before 14 days from the start of HAP therapy: 90.78% in the P/T, and 91.73% in the Comparator HAP dosing groups. Neither of the two covariate adjusted logistic regression models found a significant association between P/T HAP dosing and treatment effectiveness outcome.

The strengths of the study include the large number of pediatric HAP patients included from multiple hospitals across the US, and collection of detailed real world data on safety and effectiveness of P/T and Comparator HAP antibiotics from routine clinical practices. The study attempted to control for all major confounding variables to assess the safety and effectiveness of P/T HAP dosing in pediatric patients with HAP. In order to control for differences in baseline characteristics between P/T and Comparator treatment groups, propensity score models were developed that included unbalanced baseline covariates to inform weights used in final models. While it was attempted to control for major confounding variables, given that this observational study was based on finite data elements

contained in the medical records, chances of residual and unmeasured confounding cannot be ruled out and caution must therefore be applied in the interpretation of the results.

Overall, this study showed that the rate of serious events and all-cause mortality in patients treated with P/T HAP dosing is comparable with Comparator HAP antibiotics. However, it is important to carefully weigh the risk of serious events and benefits of the P/T HAP dosing when prescribing to pediatric patients with HAP.

13. OTHER INFORMATION

Not Applicable

14. LIST OF SOURCE FIGURES AND TABLES

- Figure 1. Step I: Pediatric Health Information System (PHIS) database screening to identify patients with potential HAP admitted to pediatric hospitals across United States between 2003 and 2016
- Figure 2. Step II: Initial review of medical chart to confirm the diagnosis of HAP in pediatric patients admitted across United States between 2003 and 2016
- Table 1. Recommended dosing regimens for HAP appropriate antibiotics for the treatment of moderate to severe infections in children (source: Package Insert of listed products)
- Table 2. Names of sites that participated in the study, sites that declined to participate and the number of enrolled patients by site
- Table 2.1.1. Breakdown of treatment groups by antibiotic, Primary Analysis Set (N=407)
- Table 3. Precision of estimate calculation for a range (%) of serious events with corresponding 95% confidence interval (CI) around the estimate and Incidence rate ratios (IRRs)
- Table 4.1.1. Patient demographic and clinical characteristics by treatment group, Primary Analysis Set (N=407)
- Table 4.1.1a. Patient demographic and clinical characteristics by treatment group, Full Analysis Set (N=412)
- Table 4.1.2. Clinical data prior to admission, by treatment group, Primary Analysis Set (N=407)
- Table 4.1.3. Hospitalization, admission and medication data prior to HAP diagnosis by treatment group, Primary Analysis Set (N=407)
- Table 4.1.4. Laboratory and radiology data prior to HAP diagnosis by treatment group, Primary Analysis Set (N=407)
- Table 4.1.5. Hospitalization and microbiology data at HAP diagnosis by treatment group, Primary Analysis Set (N=407)
- Table 4.1.6. Laboratory data after HAP diagnosis by treatment group, Primary Analysis Set (N=407)
- Table 4.1.7. Hospitalization and medication data after HAP diagnosis by treatment group, Primary Analysis Set (N=407)
- Table 5.1.1. Number of serious events, cumulative person-time at risk and crude incidence rate (per 100 person-days with 95% CI); overall, by body system and individual event type, Primary Analysis Set (N=407)

- Table 5.1.1a. Number of serious events, cumulative person-time at risk and crude incidence rate (per 100 person-days with 95% CI), by select demographic characteristics, Primary Analysis Set (N=407)
- Table 5.1.1b. Number of serious events, cumulative person-time at risk and crude incidence rate (per 100 person-days with 95% CI), by participating site, Primary Analysis Set (N=407)

  Table 5.2.1. All-cause mortality rate overall by treatment group, Primary Analysis Set (N=407)
- Table 6.1.1. Regression analysis evaluating the potential association between treatment group and all serious events – P/T *versus* Comparator HAP dosing groups, Primary Analysis Set (N=407)
- Table 6.1.2. Regression analysis evaluating the potential association between treatment group and serious events– P/T *versus* Comparator: subset: carbapenems HAP dosing groups, Primary Analysis Set (N=197)
- Table 7. Counts and percentages of patients categorized as "clinically improved" *versus* "did not improve" at or before 14 days from the start of HAP therapy, by treatment group and stratified by select patient characteristics, Primary Analysis Set (N=407)
- Table 8.1.1. Logistic Regression analysis evaluating the global response of "clinically improved" *versus* "did not improve"– P/T *versus* Comparator, Primary Analysis Set (N=407)
- Table 8.1.2. Logistic Regression analysis evaluating the global response of "clinically improved" *versus* "did not improve" – P/T *versus* Comparator subset: carbapenems, Primary Analysis Set (N=197)

14.1. ADDITIONAL TABLES

- Table A. ICD 9 codes for bacterial pneumonia (inclusion criterion)
- Table B. ICD 9 codes for cystic fibrosis (exclusion criterion)
- Table C. Other medications pre-and post-HAP diagnosis (N=407)
- Table D. Cause of death, individual events by treatment group (N=407)
- Table E. Goodness of fit and likelihood ratio tests for unweighted and unadjusted regression models in Table 6.1.1 evaluating the potential association between treatment group and all serious events– P/T *versus* Comparator
- Table F. Second Goodness of Fit Table (providing AIC and BIC measures) for all regression models in Table 6.1.1 used to estimate the potential association between treatment group and all serious events– P/T *versus* Comparator
- Table G. Goodness of fit and likelihood ratio tests for unweighted and unadjusted regression models in Table 6.1.2 evaluating the potential association between treatment group and all serious events– P/T *versus* Comparator subset: carbapenems
- Table H. Goodness of Fit Table (providing AIC and BIC measures) for all regression models in Table 6.1.2 used to estimate the potential association between treatment group and all serious events– P/T *versus* Comparator subset: carbapenems
- Table I: 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 Primary outcomes (Tables 6.1.1 & 6.1.2) comparing P/T *versus* Comparator and P/T *versus* Comparator subset: Carbapenems
- Table J: Sensitivity Analysis Table - Modified Table 6.1.1 Regression analysis evaluating the potential association between treatment group and serious events (all serious events limiting to sites with <90% preference for one treatment– P/T *versus* Comparator)
- Table K: Sensitivity Analysis Table - Modified Table 6.1.2 Regression analysis evaluating the potential association between treatment group and serious adverse events (all serious events) limiting to sites with <90% preference for one treatment – P/T *versus* Comparator subset: Carbapenem

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