NON-INTERVENTIONAL (NI) STUDY PROTOCOL

MULTINATIONAL **Retrospective Chart Review Study to Assess the Characteristics, Treatment Outcomes and Resource Use Among Adult Patients Hospitalised for Community-Acquired Pneumonia (CAP) or Complicated Skin and Soft Tissue Infections (cSSTI) Treated with Zinforo® (ceftaroline fosamil) in a Usual Care Setting**

Study Information

Title	Multinational Retrospective Chart Review Study to Assess the Characteristics, Treatment Outcomes and Resource Use Among Adult Patients Hospitalised for Community-Acquired Pneumonia (CAP) and Complicated Skin and Soft Tissue Infections (cSSTI) Treated With Zinforo® (ceftaroline fosamil) in a Usual Care Setting
Protocol number	C2661041
Protocol version identifier	2.0
Date of last version of protocol	19 July 2019
Active substance	Other cephalosporins (ATC Code: J01DI02)
Medicinal product	Ceftaroline fosamil (Zinforo)®
Research question and objectives	Primary Objective: To provide real world evidence (RWE) on the characteristics, clinical management, treatment outcomes and healthcare resource use of adult patients aged 18 years and older admitted to the hospital for CAP or cSSTI who received Zinforo® in usual care before 31-May-2019 in Europe and Latin America.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABSSSI	Acute Bacterial Skin and Skin Structure Infections
AE	Adverse event
CABP	Community-Acquired Bacterial Pneumonia
CAP	Community-Acquired Pneumonia
CRF	Case report form
cSSTI	Complicated Skin and Soft Tissue Infections
eCRF	Electronic Case Report Form
EDC	Electronic Data Collection
EMA	European Medicines Agency
GPP	Good Pharmacoepidemiology Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICU	Intensive Care Unit
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
IV	Intravenous
MIC	Minimum Inhibitory Concentration
MDR	Multidrug Resistant
RWD	Real World Data
RWE	Real World Evidence

Abbreviation	**Definition**
RWESA	Real World Evidence Stragety and Analytics
SAP	Statistical Analysis Plan
SOFA	Sequential Organ Failure Assessment
US	United States
WBC	White Blood Cell

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title:	Multinational Retrospective Chart Review Study to Assess the Characteristics, Treatment Outcomes and Resource Use Among Adult Patients Hospitalised for Community-Acquired Pneumonia (CAP) or Complicated Skin and Soft Tissue Infections (cSSTI) Treated With Zinforo® (ceftaroline fosamil) in a Usual Care Setting Version 2.0; 19 July 2019
Rational and background:	cSSTI represents a major clinical problem[1,2,3] and is associated with considerable morbidity, mortality, resource use and healthcare costs.[4-9] Current treatment options are compromised by resistance and tolerability issues. CAP is a common respiratory illness[10-16] that is also associated with considerable morbidity, mortality,[15,17,18] resource use and healthcare costs.[11,14,18,19] In patients with CAP and cSSTI (particularly those at risk of treatment failure), there is a need for an alternative treatment option that will improve empiric treatment success rates by providing activity against a range of suspected causative pathogens (including MRSA and S. pneumoniae) combined with a good tolerability profile. Ceftaroline fosamil (Zinforo®) is a novel 5th generation cephalosporin with rapid bactericidal action against a broad range of common Gram positive and Gram negative pathogens. Zinforo- is approved in the EU in adults and children from the age of two (2) months for the treatment of complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP). For the treatment of cSSTI and CAP, the recommended dose of Zinforo® is 600 mg administered every 12 hours by intravenous infusion over 60 minutes (standard dose). For the treatment of adult patients with cSSTI confirmed or suspected to be caused by S. aureus with a Minimum Inhibitory Concentration (MIC) = 2 mg/L or 4 mg/L to ceftaroline, the dose of Zinforo® is 600 mg administered every 8 hours by intravenous infusion over 120 minutes (high dose). The recommended treatment duration for cSSTI is 5 to 14 days and the recommended duration of treatment for CAP is 5 to 7 days. Zinforo® is an effective treatment for patients hospitalised with CAP or cSSTI, including those at risk of treatment failure and/or with intolerance/contraindications to commonly-used antibiotics.[20,29, 30-32, 33] At present, the real-world use and effectiveness of Zinforo® in treating patients hospitalized with CAP and cSTTI has not been evaluated in a usual care setting in Europe and Latin America.

Research question and objectives:	Study Aim: The overall study aim is to provide real world evidence (RWE) on the characteristics, clinical management, treatment outcomes and healthcare resource use of adult patients aged 18 years and older admitted to the hospital for CAP or cSSTI who received Zinforo® in a usual care setting in Europe and Latin America on or before 31-May-2019. Specific Objectives: • To describe the characteristics of patients hospitalized for CAP or cSSTI who received Zinforo® in a usual care setting in Europe and Latin America on or before 31-May-2019; • To describe physicians' use of Zinforo® in the clinical management of patients hospitalized for CAP or cSSTI in relation to their use of other antibiotics (first-line vs. second-line/salvage, monotherapy vs. combination therapy, empiric vs. definitive therapy); • To estimate the proportion of patients hospitalized for CAP or cSSTI who responded to Zinforo® (clinical response defined as no further intravenous (IV) antibiotic, switch to an oral antibiotic, or IV antibiotic treatment streamlining/de-escalation prior to discharge from the hospital); • To estimate the proportion of patients hospitalized for CAP or cSSTI who had treatment modification of Zinforo® (defined as switch to another IV antibiotic due to an adverse reaction, drug-drug interaction, insufficient response or a microbiological diagnosis indicating that the pathogen is not susceptible to Zinforo);® • To describe the clinical outcomes (eg, hospital readmission, mortality) of patients hospitalized for CAP or cSSTI after starting Zinforo® stratified by clinical response; • To describe the healthcare resource use of patients hospitalized for CAP or cSSTI after starting Zinforo® stratified by clinical response.
Study design:	Multinational, multicenter observational retrospective cohort study
Population:	The target population is adult patients aged 18 years and older hospitalized for CAP or cSSTI who received intravenous (IV)

	Zinforo® treatment in a usual care setting in Europe and Latin America on or before 31-May-2019. Inclusion criteria: 1. Age 18 years or older at admission date to the hospital. 2. Received four (4) or more consecutive IV doses of Zinforo® in usual care on or before 31-May-2019; and 3. Admitting diagnosis to the hospital was either CAP or cSSTI. Exclusion criteria: 1. Patients who were participating in an interventional clinical trial during the same hospital admission in which Zinforo® was administered. 2. Patients whose hospital medical records are missing documentation of the diagnostic criteria for either cSSTI or CAP. 3. Patients whose hospital medical records are missing details of dosing with Zinforo.® 4. Patients whose hospital medical records are missing information on the success/failure of Zinforo® treatment and the reason why treatment was discontinued; and 5. Patients whose hospital medical records are missing discharge date and status information.
Variables	The following data will be collected: • Site Information (country, type of site, hospital size, participating department); • Patient Demographics (sex, age, ethnic origin, height, weight, type of residence/co-habitation, smoking habits); • Medical History (diabetes, respiratory disease, cancer/malignancy, peripheral vascular disease, congestive heart failure, immunosuppressive therapy in the 3 months prior to hospitalization, hospitalization in the prior 3 months, other relevant conditions, multidrug resistance risk score at admission, quick sequential organ failure

	assessment score at admission); • Disease Characteristics for CAP (time from diagnosis to Zinforo initiation, diagnostic criteria met, imaging findings suggestive of bacterial pneumonia, signs of acute illness at diagnosis); • Disease characteristics for cSSTI (time from diagnosis to initiation of Zinforo diagnostic criteria met, cellulitis/fasciitis, abscess, post-traumatic wound, post-surgical wound, diabetic leg ulcer, peripheral vascular disease ulcer, lesion size, lower extremities affected, swelling/induration, skin necrosis, recurrent skin infection episode, nosocomial infection); • Hospitalization Information (duration of hospitalization, discharge destination, discharge status, ICU duration, ICU discharge date); • Microbiological Diagnosis (investigations or diagnostic tests performed, positive microbiological diagnosis obtained, microorganism name, bacteremia diagnosed); • Zinforo® Treatment (treatment duration, line of therapy, time from hospital admission to first dose, empiric vs. definitive therapy, monotherapy vs. combination therapy, daily dose, number of doses administered, treatment duration, clinical response, clinical response definition (Halm criteria, switch to oral antibiotic, other) time to clinical response (days), treatment streamlining/de-escalation, treatment modification, time to treatment modification (days), reason for treatment modification, ICU vs. general medical ward administration); • All Other Antibiotic Treatments during the index hospital admission (each monotherapy/combination antibiotic therapy name, line of therapy, route of administration, duration of treatment, number of doses administered, treatment response, time to treatment modification from initial dose (days), reason for treatment modification, ICU vs. general medical ward administration); • Clinical Outcomes and Healthcare Resource Use after first Zinforo® dose (number of days in the hospital, switch to another IV antibiotic, switch to an oral antibiotic, time to first oral antibiotic dose, admission to ICU, time in ICU,

	mechanical ventilation, surgery, reinfection or recurrence, acute renal failure, length of acute renal failure, blood pressure support, fluid resuscitation, vasopressors, septic shock, isolation required, parenteral nutrition, length of parental nutrition, home-based care after discharge, in-hospital mortality, 30-day mortality, 30-day readmission after discharge).
Data sources	Data will be retrospectively extracted from the hospital medical records of eligible patients. De-identified data will be collected following the Health Insurance Portability and Accountability Act (HIPAA)-compliant safe harbor approach.[34]
Study size	The target sample for recruitment is approximately 600 patients across all sites. The number of eligible CAP and cSSTI patients that each site will provide will vary depending on the historical usage of Zinforo® at that site up to 31-May-2019.
Data analyses	The objective of this retrospective chart review study is descriptive in nature; therefore, no hypothesis testing will be performed. The results of the total study sample will be summarized using descriptive statistics. Data will be summarized by means, standard deviations (SD), medians, minimums and maximums for continuous variables; and by numbers and percentages for categorical variables. All summarized data will be presented in aggregate, and may be stratified by covariates of interest if a subgroup has a minimum sample size of 30 patients (5% of total study size). Clinical outcomes and resource use following the initiation of Zinforo® treatment will be assessed according to patients' observed clinical response time (<72-hours, >72-hours, no response). The mean (SD) and median times to an outcome of interest (eg, length of stay in the hospital measured in days) will be calculated in each patient subgroup.
Milestones	Completion of feasibility assessment: 15 September 2019. Start of data collection: 01 December 2019. End of data collection: 15 June 2020. Final study report: 12 October 2020.

5. AMENDMENTS AND UPDATES

Amendment 1. The study has been updated to expand into Latin America, increasing the sample size from 300 over all sites to approximately 600 patient charts. Additionally, this amendment details an anonymized data collection approach where a waiver of consent will be requested of Institutional review board (IRBs)/Independent ethics committees(IECs). Finally, the recruitment period has been extended to 31 May 2019.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	19-July-2019	4; 9	Expansion into Latin America; increase in sample size and number of sites. Anonymzed data collection approach Extended recruitment period	Expanded area of interest for Pfizer. To help increase likelihood of IRB/IEC's granting the waiver of consent. A waiver is requested to mitigate the risk of sampling bias that may be introduce of consent is required. Allow for additional data to be entered given the change in study timelines.

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	15 September 2019
Start of data collection	01 December 2019
End of data collection	15 June 2020
Completion of data analysis	10 August 2020
Final study report	12 October 2020

7. RATIONALE AND BACKGROUND

Community-acquired pneumonia (CAP) is an acute infection of the lungs for which symptoms include cough, fever and chest pain.[35] CAP is a common respiratory illness[10-16] that is also associated with considerable morbidity, mortality,[15,17,18] resource use and healthcare costs.[11,14,18,19] It is recognized as a leading cause of hospital mortality, for which the incidence appears to be rising.[36,37]

CAP is associated with high patient burden and health resource utilisation including a rehospitalisation rate of up to 20% and a 30-day mortality rate of 23% with elderly patients considered higher risk.[36] Prognosis factors for CAP are thought to be age, severity and comorbidities such as diabetes, while factors related to CAP in-hospital death include comorbidities, age, readmission and mechanical ventilation.[37,38]

Ceftaroline fosamil (Telflaro in the United States [US]; Zinforo® ex-US) is a pro-drug of ceftaroline, which is a broad-spectrum antibiotic with *in vitro* activity against a range of Gram-positive and Gram-negative bacteria commonly associated with CAP or cSSTI. Importantly, ceftaroline is active against resistant phenotypes commonly isolated in CAP including penicillin-resistant *S. pneumoniae* (PRSP), multidrug-resistant *S. pneumoniae*, methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant *S. aureus* (VRSA).

Complicated skin and soft tissue infections (cSSTIs) include infected ulcers, infected burns and major abscesses that require hospitalization among patients who typically are elderly and have underlying comorbidities such as diabetes mellitus, peripheral vascular disease and obesity. The most common etiologic pathogen in cSSTI is *Staphylococcus aureus,* including MRSA. cSSTI represents a major clinical problem[1,2,3] and is associated with considerable morbidity, mortality, resource use and healthcare costs.[4-9] Current treatment options are compromised by resistance in particular countries and tolerability issues.

In patients with CAP or cSSTI (particularly those at risk of treatment failure), there is a need for an alternative treatment option that will improve empiric treatment success rates by providing activity against a range of suspected causative pathogens (including MRSA and *S. pneumoniae*) combined with a good tolerability profile.

Ceftaroline fosamil (Teflaro) was approved by the FDA in 2011 for the indications of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI). The Clinical Assessment Program and TEFLARO Utilization Registry (CAPTURE) is a multicenter retrospective chart review study conducted at 33 hospitals during the first year that Teflaro was marketed in the United States. The sub-study of intravenous Teflaro for ABSSSI collected data from August 2011 to August 2012 among 647 patients who had non-missing data on treatment outcome.[33] Among these patients, 85% (550/647) showed clinical success with Teflaro treatment. The CAPTURE sub-study of intravenous Teflaro for CABP collected data from August 2011 to July 2012 among 398 patients who had non-missing data on treatment outcome.[23] The overall clinical success proportion was 79% (316/398) in this cohort. These data demonstrated that Teflaro, when administered in a "real world" usual clinical care setting at US hospitals, is an effective antibiotic treatment for patients with CABP or ABSSSI. These data also demonstrated that only a small proportion of patients (2% in each sub-study) discontinued Teflaro treatment as a consequence of adverse events (AE).[23,33]

Ceftaroline fosamil (Zinforo®) was approved by the European Commission in August 2012 for the treatment of adult patients with cSSTIs or CAP.® In April 2016, the CHMP extended these two indications to include children from two months old. For the treatment of cSSTI or CAP, the recommended dose is 600 mg administered every 12 hours by intravenous infusion over 60 minutes in patients aged 18 years or older (standard dose). For the treatment of adult patients with cSSTI confirmed or suspected to be caused by *S. aureus* with a MIC = 2 mg/L or 4 mg/L to ceftaroline, the dose of Zinforo® is 600 mg administered every 8 hours by intravenous infusion over 120 minutes (high dose). The recommended treatment duration for cSSTI is 5 to 14 days and the recommended duration of treatment for CAP is 5 to 7 days. Zinforo® is now approved in 52 markets globally.

Zinforo® is an effective treatment for patients hospitalised with CAP or cSSTI, including those at risk of treatment failure and/or with intolerance/contraindications to commonly-used antibiotics.[20-29,30-32,33] At present, the real-world use and effectiveness of Zinforo® in treating patients hospitalized with CAP or cSTTI has not been evaluated in a usual care setting in Europe® and Latin America.

This proposed retrospective chart review study will assess the characteristics, treatment outcomes and resource use of patients hospitalized with CAP or cSSTIs treated with Zinforo® in a "real world" usual care setting in countries within Europe and Latin America.

8. RESEARCH QUESTION AND OBJECTIVES

Study Aim:

The overall study aim is to provide real world evidence (RWE) on the characteristics, clinical management, treatment outcomes and healthcare resource use of adult patients aged 18 years and older admitted to the hospital for CAP or cSSTI who received Zinforo® in a usual care setting in Europe and Latin America on or before 31-May-2019.

Specific Objectives:

- To describe the characteristics of patients hospitalized for CAP or cSSTI who received Zinforo® in a usual care setting in Europe and Latin America on or before 31-May-2019.

- To describe physicians' use of Zinforo® in the clinical management of patients hospitalized for CAP or cSSTI in relation to their use of other antibiotics (first-line vs. second-line/salvage, monotherapy vs. combination therapy, empiric vs. definitive therapy).

- To estimate the proportion of patients hospitalized for CAP or cSSTI who responded to Zinforo® (clinical response defined as no further intravenous (IV) antibiotic, switch to an oral antibiotic, or IV antibiotic treatment streamlining/de-escalation prior to discharge from the hospital).

- To estimate the proportion of patients hospitalized for CAP or cSSTI who had treatment modification of Zinforo® (defined as switch to another IV antibiotic due to an adverse reaction, drug-drug interaction, insufficient response, or a microbiological diagnosis indicating that the pathogen is not susceptible to Zinforo).®

- To describe the clinical outcomes (eg, hospital readmission, mortality) of patients hospitalized for CAP or cSSTI after starting Zinforo® stratified by clinical response.

- To describe the healthcare resource use of patients hospitalized for CAP or cSSTI after starting Zinforo® stratified by clinical response.

9. RESEARCH METHODS

9.1. Study Design

This will be a multinational, multicenter observational retrospective cohort study of patients with cSSTI or CAP treated with Zinforo® in a usual care setting. The hospital medical records of patients who meet the eligibility criteria will be included in this retrospective chart review study. A retrospective chart review study design was chosen as the most efficient method to generate RWE to assess patients' experience with Zinforo® in a usual care setting in Europe and Latin America. The data collected in this study will be obtained in a timelier manner than could be achieved with a prospective study design.

9.2. Setting

The target population will be adult patients aged 18 years and older admitted to the hospital with a documented clinical diagnosis of CAP or cSSTI who received four or more consecutive IV doses of Zinforo® on or before 31-May-2019. This study will be conducted in approximately 35-40 hospitals in multiple countries.

Hospital sites participating in this study will identify all patients dispensed four or more intravenous (IV) doses of Zinforo® in usual care on or before 31-May-2019 by querying their hospital pharmacy dispensing records. Potentially eligible patients treated with Zinforo® for either CAP or cSSTI will be identified by querying hospital discharge records for diagnosis codes indicative of either CAP or cSSTI using the World Health Organization International Classification of Diseases 10th revision (ICD-10; see Annex 3 for the list of ICD-10 codes).

The hospital medical records of potentially eligible patients treated with Zinforo® will be screened manually by site staff to identify the subset of eligible CAP and cSTTI patients who meet all inclusion criteria without meeting any of the exclusion criteria (see below). For most sites, all eligible CAP and cSTTI patients treated with Zinforo® will be selected for chart abstraction. For some sites with a high number of Zinforo-treated patients, the site may be contracted to only abstract the medical records of a prespecified number of their eligible patients in reverse chronological order (most recently treated patients are screened first). The hospital medical records of eligible CAP and cSSTI patients will be abstracted for all clinical outcomes and healthcare resources utilization up to 30-days following the discharge date of the index hospitalization or death, whichever occurs first.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for this retrospective chart review study:

1. Age18 years or older at admission date to the hospital.

2. Received four (4) or more consecutive IV doses of Zinforo® in usual care on or before 31-May-2019.

3. Admitting diagnosis to the hospital was either CAP or cSSTI (see diagnostic criteria below).

Diagnostic Criteria for CAP:

1. Imaging findings (X-ray, ultrasound, etc.) of the chest consistent with a diagnosis of bacterial pneumonia at the date of admission to the hospital.

2. Acute illness at the date of admission to the hospital with at least three of the following:

   - New or increased cough severity;
   - Purulent sputum or change in sputum character;
   - Auscultatory findings consistent with pneumonia;
   - Dyspnea, tachypnea, or hypoxemia (O_2 saturation <90% on room air or pO_2 <60 mm Hg);

- Fever (>38°C oral or 38.5°C rectally or tympanically) or hypothermia (<35°C);
- White blood cell (WBC) count >10,000 cells/mm^3 or < 4,500 cells/mm^3;
- >15% bands irrespective of WBC count.

Diagnostic Criteria for cSSTI:

1. Involvement of deeper soft tissue (eg, cellulitis, fasciitis, etc.) and/or requiring significant surgical intervention (such as wound infection – surgical or traumatic) or developing on a lower limb in a subject with diabetes mellitus or well-documented peripheral vascular disease, a major abscess, infected ulcer or deep or extensive cellulitis, or any surgical site infection.

2. At least two local signs of cSSTI (purulent or seropurulent drainage/discharge, erythema, fluctuance, heat/localised warmth, pain/tenderness to palpation, swelling/induration).

3. At least one systemic sign (temperature of >28°C, WBC count of >10,000/mm^3, >10% immature neutrophils).

cSSTI definitions:

- Cellulitis: advancing erythema, edema and heat. "Deep and extensive cellulitis" affecting deeper soft tissues with a surface area of >10cm^2.
- Significant surgical intervention: a major operative procedure, not including commonly performed minor procedures such as incision and drainage or minor abscesses performed at the bedside, suture removal, needle aspiration, superficial debridement of devitalized tissue or routine wound care.
- Wound infection: purulent/seropurulent discharge or >5cm of erythema (ie, cellulitis) surrounding the wound margin.
- Abscess: loculated fluid collection with >2cm of erythema (ie, cellulitis) extending from the abscess margin. A "major abscess" either extends to deeper soft tissue or requires significant surgical intervention.
- Deeper soft tissue: subdermal tissue, including subcutaneous fat, eg, extension of infection to muscle or fascia constitutes evidence of deeper soft tissue involvement.

9.2.2. General Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be eligible for this retrospective chart review study:

1. Patients who were participating in an interventional clinical trial during the same hospital admission in which Zinforo® was administered.

2. Patients whose hospital medical records are missing documentation of the diagnostic criteria for either cSSTI or CAP (see above).

3. Patients whose hospital medical records are missing details of dosing with Zinforo.®

4. Patients whose hospital medical records are missing information on the success/failure of Zinforo® treatment and the reason why treatment was discontinued.

5. Patients whose hospital medical records are missing discharge date and status information.

CAP-specific Exclusion Criteria:

- Patients admitted hospital for another medical condition who developed signs and symptoms of hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) 48-hours or more after the admission date are not eligible for this study.

cSSTI-specific Exclusion Criteria:

- Patients with uncomplicated SSTI are not eligible for this study.

- Patients with skin and soft tissue infection complicated by the presence of orthopedic or joint replacement prostheses are not eligible for this study.

- Patients with known or suspected endocarditis, osteomyelitis, or septic arthritis are not eligible for this study.

9.3. Variables

Below is a summary of the variables that will be collected for the index hospitalization:

- Site Information (country, type of site, hospital size, participating department).

- Patient Demographics (sex, age, ethnic origin, height, weight, type of residence/co-habitation, smoking habits).

- Quick Sepsis-Related Organ Failure Assessment (qSOFA) at Admission (altererd mental status (Glasgow coma scale <15), low blood pressure (systolic blood pressure <100 mmHg), high respiration rate (>=22 breaths per minute). Risk Factors for having a MDR Pathogen at Admission (chronic renal failure, cerebrovascular disease, diabetes, COPD, hospitalization for >=2 days in the preceding 90 days, residency in a nursing home or extended-care facility, home infusion therapy, home wound care, chronic dialysis within 30 days, immunosuppression, antimicrobial therapy in the preceding 90 days).

- Medical History (other relevant comorbidities such as diabetes mellitus, respiratory disease, cancer/malignancy, peripheral vascular disease, congestive heart failure, immunosuppressive therapy in the 3 months prior to hospitalization, hospitalization in the prior 3 months, invasive surgical treatment in the 3 months prior to hospitalization, other relevant conditions or diseases requiring chronic drug treatment).

- Disease Characteristics for CAP (time from diagnosis to Zinforo initiation, diagnostic criteria met, radiographic findings suggestive of bacterial pneumonia, triggering signs and symptoms of acute illness at diagnosis, , community versus health care associated, severity (PORT, CURB, other), recurrent infection (Y/N).

- Disease Characteristics for cSSTI (time from diagnosis to initiation of Zinforo, diagnostic criteria met, triggering signs/symptoms, , primary anatomic area involved, cellulitis/fasciitis, abscess, post-traumatic wound, post-surgical wound, diabetic leg ulcer, peripheral vascular disease ulcer, lesion extension >50 cm2, lower extremities affected, swelling/induration, skin necrosis, recurrent skin infection episode, nosocomial infection. For wounds: superficial vs. deeper, in joint or organ space, systemic inflammatory response indicators. For cellulitis: deep/extensive).

- Hospitalization Information (duration of hospitalization, discharge destination, discharge status, ICU admission, ICU duration).

    - Microbiological Diagnosis (investigations or diagnostic tests performed, positive microbiological diagnosis obtained, microorganism name, bacteremia diagnosed, the pathogen(s), source(s), and the specimen collection date(s). Pathogens identified by blood, respiratory (eg, sputum, bronchoalveolar lavage), or pleural effusion cultures will be recorded for patients with bacterial pneumonia. Pathogens identified by blood or skin/soft tissue/bone/wound cultures will be recorded for patients with cSSTIs. Minimum inhibitory concentrations (MIC) of antibacterial drugs for pathogens isolated from samples collected within one week before the start of treatment through 24 hours after discontinuation of Zinforo® will be recorded:

        - MIC of ceftaroline for all isolated pathogens;

        - MIC of oxacillin, vancomycin, linezolid, and daptomycin for *S. aureus*;

        - MIC of ceftriaxone for MSSA;

        - MIC of penicillin and ceftriaxone for *S. pneumoniae.*

- Zinforo® Treatment (treatment duration, line of therapy, time from hospital admission to first dose, time from symptom onset to first dose, empiric vs. definitive therapy, monotherapy vs. combination therapy, dose, number of infusions per day, number of doses administered, ICU vs. general medical ward administration, reason for switch to Zinforo® if not 1st line treatment.

- Pre-Zinforo® IVAntibiotic Treatments for the index infection (each monotherapy/combination antibiotic therapy name, line of therapy, route of administration, duration of treatment, time from admission to first dose, time from symptom onset to first dose, empiric vs. definitive therapy, daily dose, number of doses administered, treatment response, time to treatment modification from initial dose (days), reason for treatment modification, ICU vs. general medical ward administration).

- Concurrent IV antibiotic treatments administered with Zinforo® for index infection (antibiotic therapy name, route of administration, treatment duration, daily dose, number of doses administered).

- Post-Zinforo® antibiotic treatments for index infection (antibiotic therapy name, route of administration, treatment duration, daily dose, number of doses administered, reason for switch, treatment response, ICU vs. general medical ward administration).

- Zinforo® Treatment Response: Clinical response (response definition, treatment de-escalation, oral switch, time to symptom resolution, time to clinical stability (Halm criteria), time to oral switch). Clinical failure (treatment modification due to AE, DDI, or insufficient response, death due to index infection, death due to other. Relapse or recurrence. Time to relapse or recurrence.

- Healthcare Resource Use after date of first Zinforo® dose (number of days in the hospital, admission to ICU, time in ICU, surgery, mechanical ventilation, acute renal failure, length of acute renal failure, blood pressure support, fluid resuscitation, vasopressors, septic shock, isolation required, parenteral nutrition, length of parental nutrition, home-based care after discharge, in-hospital mortality, 30-day mortality, 30-day readmission after discharge, readmission for index infection, readmission for other reason).

Derived variables will be calculated from the reported values of other variables entered by sites. For example, type of CAP will be derived as follows:

Variable	Role	Data source(s)	Operational definition
Type of CAP	Effect modifier	Type of residence/co-habitation variable in Patient Demographics CRF.	CAP = Residence in private house or apartment only. HCAP =: residence in a nursing home, home care through a healthcare agency, previous admission to hospital with CAP (last 3 months), haemodialysis or chemotherapy for active cancer, with the exception of immunocompromised/ immunosuppressed.

9.4. Data Sources

Data for this study will be collected by a retrospective medical chart extraction from participating sites. The sites will be hospitals in Europe and Latin America that have treated patients with CAP or cSSTI in usual care during the study period. Approximately 600 patient charts will be included in this study from approximately 35-40 sites in Europe and Latin America (15-20 charts per site). Each chart will be retrieved and screened against the inclusion and exclusion criteria. The sites will be responsible for performing all data extraction. For eligible patients, relevant data will be extracted from the hospital medical records from 3-months before the date of the index hospital admission until 30-days after the hospital discharge date or death, whichever occurs first. All data will be entered by sites into electronic case report forms (eCRFs). De-identified data will be collected following the Health Insurance Portability and Accountability Act (HIPAA)-compliant safe harbor approach.[34]

9.5. Study Size

Given that this study is purely descriptive in nature and there is no a priori hypotheses specified, a formal sample size calculation is not applicable. The number of Zinforo®-treated patients who are eligible for the study will be determined after a site feasibility assessment is conducted. It is anticipated that approximately 600 eligible CAP and cSSTI patients can be obtained from 35-40 participating sites.

9.6. Data Management

Sites will enter data directly into eCRFs. Data extraction will be performed by site staff only. Pfizer and ICON will not have access to patient's medical records for source data verification. Before beginning data collection, all sites will receive training in all study protocol and data collection training materials; this will include attendance at a group training session via teleconference. ICON staff will be available by email and teleconference

to review specific issues and to provide assistance after the initial instructions for completing the eCRF are provided to each site in the form of training documentation.

Depending on eCRF length, the eCRF may be several sheets. Fields of entry will be, where possible, locked to the required data format and free text fields will be used only as necessary in order to collect consistent data, and to assist with data cleaning following data collection.

After the first five charts have been extracted and CRFs transmitted to ICON, the data will be reviewed by the ICON team to determine if any modifications or clarifications are required.

Close-out activities will be performed remotely, via telephone calls to sites. Essential close-out activities include formal communications to sites, collection of any study-related materials from sites, and closure of study with the Institutional Review Board/Independent Ethics Committes (IRB/IEC).

9.6.1. Case Report Form (CRF)/Data Collection Tool (DCT)/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. ICON shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

ICON has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, ICON agrees to keep all study-related records, including" copies of all CRFs, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by ICON according to local regulations or as specified in the contract whichever is longer. ICON must ensure that the records continue to be stored securely for so long as they are retained.

If ICON becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless ICON and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

ICON must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

The primary and secondary study outcomes will be analyzed using descriptive statistics to summarize patient and disease characteristics, treatment patterns, and treatment outcomes and health care resource utilisation. Data will be summarized by means, standard deviations, medians, minimums and maximums for continuous variables; and by numbers and percentages for categorical variables. Data will be presented in aggregate, as well as stratified by patient and disease characteristics of interest, such as geography and indication (sub-group analyses). Missing table will be tabulated. Statistical analyses will be conducted using SAS.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP (along with result table shells) which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality Control

ICON will be responsible for the site contact and ensuring that the data collection is monitored accordingly at each of the participating study sites. Designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative site and ensure collection of high-quality data for this study. All sites will be trained on the protocol, study logistics, and the EDC system. Retraining will be conducted as needed.

All analyses and reporting will be carried out using anonymised data. At the time of data collection completion, all data will be cleaned and the final analyses will be performed by an experienced data analyst. Quality controls performed during statistical analyses will be described in the SAP.

Secure electronic archive of study data will be maintained and will include but will not be limited to: final raw data, analysis datasets, statistical programming performed to generate the results, programs and associated documentation. Access to the archive will be controlled and limited to authorized personnel only. The study data will be stored and archived for an agreed amount of time between Pfizer and ICON in line with the ICON archive policy.

9.9. Limitations of the Research Methods

The target number of patients for inclusion in this study will be largely driven by feasibility, rather than the level of precision. It is considered feasible to include approximately 600 CAP and cSSTI patients since there are many sites participating in this study. However, if this number is not reached after inclusion of patients, this could endanger the generalizability of the results.

The data collected in this study will be retrospective data collected in routine care from the patient's hospital record; there is no way to collect additional information. Therefore if the data was not collected at the time of administering the patient's care it will be recorded as missing. The SAP will include a section on dealing with missing data, and the proportion of missing data will be summarized in the clinical study report.

It is possible to miss a few patients by the inclusion criteria "patients should have had four or more consecutive IV doses of Zinforo".® These criteria were created to match the inclusion criteria of the United States CAPTURE study. It is not likely that many patients will be excluded by these criteria. Zinforo® is taken twice a day, meaning that patients should take Zinforo® for at least two days to be included in the study. Antibiotic regimens are usually applied for two to three days to observe clinical response. Only after this period, a doctor may decide to change the antibiotic regimen.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in the data collection form, any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code.

The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required. The IRB/IEC is requested to grant a waiver for having patients sign an informed consent form (ICF) in order to include their de-identified medical data in this retrospective chart review study on the following grounds:

- This is a non-interventional study that only will abstract data from existing hospital medical records.

- Requesting that patients sign an ICF is not practical because patients will no longer be receiving care at the hospital after discharge and some patients will have died since the index hospital admission.

- Requesting that patients sign an ICF may introduce selection bias, which would have a negative impact on the representativeness of the study results.

- Requesting that patients sign an ICF will cause an unnecessary inconvenience to patients and their families in view that no patient identifiers will be disclosed by the site; and hence, the study data will be fully anonymized to protect the privacy rights of patients (see preceding paragraph).

Should IRBs/IECs reject the request for a waiver of consent, then the investigator will ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. When the informed consent cannot be completed in person, patients or their legal representative will be consented remotely via telephone and will be mailed an ICF to sign, date, and return by mail. The investigator will retain the original of each patient's signed consent form. If local IRBs/IECs require consent for deceased patients, next of kin will be contacted for remote informed consent as described above.

The informed consent form must be in compliance with local regulatory requirements and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

10.3. Patient Withdrawal

Consented patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.4. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE,

but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the CRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer. Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

The data generated from this study will be dissemination in an appropriate peer-reviewed journal and/or a conference. Authorship will be based on the contribution to the study design, data analysis and interpretation of results in line with authorship recommendations by the International Committee of Medical Journal Editors (ICMJE).

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14. LIST OF TABLES

None.

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Community-Acquired Pneumonia(CAP) ICD-10 Codes

A48.1	Legionnaires' disease
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilis influenzae
J15.0	Pneumonia due to Klebsiella pneumoniae
J15.1	Pneumonia due to Pseudomonas sp.
J15.20	Pneumonia due to Staphylococcus sp. unspecified
J15.21	Pneumonia due to Staphylococcus aureus
J15.3	Pneumonia due to Streptococcus sp., group B
J15.4	Pneumonia due to other streptococci
J15.5	Pneumonia due to Escherichia coli
J15.6	Pneumonia due to other aerobic Gram-negative bacteria
J15.7	Pneumonia due to Mycoplasma pneumonia
J15.8	Pneumonia due to other specified bacteria
J15.9	Unspecified bacterial pneumonia
J16.0	Chlamydial pneumonia
J16.8	Pneumonia due to other specified infectious organisms
J18.0	Bronchopneumonia, unspecified organism
Z16	Infection with drug-resistant microorganisms

Complicated Skin and Soft Tissue Infections (cSSTI) ICD-10 Codes

A46	Erysipelas
A48	Gas gangrene
E08.621-622	Diabetes mellitus due to underlying condition with other skin ulcer
E09.621-622	Drug or chemical induced DM with foot ulcer
E11.621-622	DM with foot ulcer
E13.621-622	Other specified DM with foot ulcer
H00.031–H00.039	Abscess and furuncle of eyelid
H05.011–H05.019	Cellulitis of orbit, abscess of orbit
H60.10–H60.13	Cellulitis of external ear
J34.0	Cellulitis and abscess of external nose
K12.2	Cellulitis and abscess of mouth
K61.0–K61.4	Abscess of anal and rectal regions
K68.11	Postprocedural retroperitoneal abscess
K68.12	Psoas muscle abscess
L00-08	Infections of the skin and subcutaneous tissue
L10-L14	Bullous disorders
L76	Intraoperative and post procedural complications of skin and subcutaneous tissue
L89	Pressure ulcer
L97	Non-pressure chronic ulcer of low limb
L98.4XX	Non-pressure chronic ulcer of skin
M60.0XX	Infective myositis
N48.21	Abscess of corpus cavernosum and penis
N48.22	Cellulitis of corpus cavernosum and penis
N61	Inflammatory disorders of breast (includes cellulitis/abscess breast)
N76.4	Abscess of vulva
M72.6	Necrotizing fasciitis
M72.9	Fibroblastic disorder, unspecified
O91.11	Abscess of breast associated with pregnancy
O91.2	Nonpurulent mastitis associated with pregnancy, the puerperium and lactation
S00-01	Superficial injury of head; Open wound of head
S05.X	Injury of eye and orbit
S08	Avulsion and traumatic amputation of part of head
S09	Other and unspecified injuries of head
S10-11	Superficial injury of neck; Open wound of neck
S20-21	Superficial injury of thorax; Open wound of thorax
S30-31	Superficial injury of abdomen, lower back, pelvis and external genitals; Open wound

S40-41	Superficial injury of shoulder and upper arm; Open wound
S50-51	Superficial injury of elbow and forearm; Open wound
S60-61	Superficial injury of wrist, hand and fingers; Open wound
S70-71	Superficial injury of hip and thigh; Open wound
S80-81	Superficial injury of knee and lower leg; Open wound
S90-91	Superficial injury of ankle, foot and toes; Open wound
T14	Injury of unspecified body region
T30	Burn
T79	Certain early complications of trauma, not elsewhere classified
T81.3X	Disruption of wound
T81.4X	Infection following a procedure
T81.89	Other complications of procedures, not elsewhere classified
T87.4	Infection of amputation stump