# CENTER FOR DRUG EVALUATION AND RESEARCH

## *APPLICATION NUMBER:*

# 216974Orig1s000

# INTEGRATED REVIEW

# Integrated Review

**Table 1. Application Information**

| | |
|---|---|
| **Application type** | NDA |
| **Application number** | 216974 |
| **Priority or standard** | Priority |
| **Submit date** | 9/29/2022 |
| **Received date** | 9/29/2022 |
| **PDUFA goal date** | 5/29/2023 |
| **Division/office** | Division of Anti-Infectives (DAI) |
| **Review completion date** | 5/22/2023 |
| **Established/proper name** | Sulbactam and durlobactam |
| **(Proposed) proprietary name** | XACDURO |
| **Pharmacologic class** | Beta-lactam antibacterial and beta-lactamase inhibitor (sulbactam); beta-lactamase inhibitor (durlobactam) |
| **Other product name** | XACDURO (sulbactam and durlobactam) |
| **Applicant** | Entasis Therapeutics Inc |
| **Dosage form/formulation)** | Injection, powder, lyophilized, for solution |
| **Dosing regimen** | **Estimated Creatinine Clearance (mL/min)** / **Dose of Sulbactam and Durlobactam (1g/1g)**<br>≥130 — every 4 hours<br>45-129 — every 6 hours<br>30-44 — every 8 hours<br>15-29 — every 12 hours<br><15 — For patients initiating XACDURO: every 12 hours for the first 3 doses (0, 12, and 24 hours), followed by every 24 hours<br>For patients on XACDURO whose creatinine clearance declines to < 15 mL/min: every 24 hours |
| **Applicant-proposed indication/ population** | XACDURO is indicated for the treatment of adults with infections due to Acinetobacter baumannii-calcoaceticus complex organisms, including multidrug-resistant and carbapenem-resistant strains. |
| **SNOMED CT code for proposed indication disease term(s)[1]** | Acinetobacter pneumonia, SCTID: 1010634002<br>Nosocomial pneumonia, SCTID: 425464007<br>Ventilator-associated pneumonia, SCTID: 429271009<br>Infection due to carbapenem resistant Acinetobacter, SCTID: 44578000 |
| **Regulatory action** | Approval |
| **Approved dosage** | The dosage is provided in the table above. The recommended duration of treatment is 7 to 14 days. |
| **Approved indication/ population** | XACDURO is indicated in patients 18 years of age and older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex. |
| **SNOMED CT code for approved indication disease term(s)[1]** | Acinetobacter pneumonia, SCTID: 1010634002<br>Nosocomial pneumonia, SCTID: 425464007<br>Ventilator-associated pneumonia, SCTID: 429271009<br>Infection due to carbapenem resistant Acinetobacter, SCTID: 44578000 |

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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# Glossary

| | |
|---|---|
| %*f*T > MIC | percent of time that free drug concentrations remain above the MIC |
| ABC | *Acinetobacter baumannii-calcoaceticus* complex |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AP | acute pyelonephritis |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BLQ | below the lower limit of quantitation |
| BPP | Biofire® FilmArray® 2.0 Pneumonia Panel |
| BW | body weight |
| CE | clinically evaluable |
| CFU | colony-forming units |
| CLcr | creatinine clearance |
| CLSI | Clinical Laboratory and Standards Institute |
| $C_{max}$ | maximum plasma concentration |
| CMC | chemistry, manufacturing, and controls |
| COVID-19 | coronavirus disease 2019 |
| CRABC | carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex |
| CRRT | Continuous Renal Replacement Therapy |
| $C_T$ | critical threshold |
| cUTI | complicated urinary tract infections |
| CYP | cytochrome P450 |
| DSMB | Data Safety Monitoring Board |
| DUR | durlobactam |
| ELF | epithelial lining fluid |
| EOT | end of therapy |
| *f*AUC | area under the unbound concentration-time |
| FDA | Food and Drug Administration |
| GLP | good laboratory practice |
| HABP | hospital-acquired bacterial pneumonia |
| HD | hemodialysis |
| ICU | intensive care unit |
| ICH | International Council for Harmonisation |
| IIV | interindividual variability |
| IND | investigational new drug |
| ISR | incurred sample re-analysis |
| ITT | intent-to-treat |
| LFU | late follow-up |
| MAP | mean arterial pressure |
| MDR | multidrug-resistant |
| ME | microbiologic evaluable |
| MIC | minimum inhibitory concentration |

| | |
|---|---|
| m-MITT | microbiologically modified intent-to-treat |
| NDA | new drug application |
| NI | noninferiority |
| NOAEL | no observed adverse effect level |
| NR | normal range |
| OSI | Office of Scientific Investigations |
| PBP | penicillin-binding proteins |
| PD | pharmacodynamic |
| PDUFA | Prescription Drug User Fee Act |
| PI | Prescribing Information |
| PIND | pre-investigational new drug |
| PK | pharmacokinetic |
| PPB | plasma protein binding PTA probability of target attainment |
| QC | quality control |
| q4h | every 4 hours |
| q6h | every 6 hours |
| qSOFA | quick SOFA |
| RIFLE | Risk–Injury–Failure–Loss– End-stage renal disease |
| SAE | serious adverse event |
| SOFA | Sequential Organ Failure Assessment |
| SUL | sulbactam |
| SUL-DUR | sulbactam-durlobactam |
| TEAE | treatment-emergent adverse event |
| TK | toxicokinetic |
| TOC | test of cure |
| ULN | upper limit of normal |
| VABP | ventilator-associated bacterial pneumonia |
| VP | ventilated pneumonia |

# I. Executive Summary

## 1. Summary of Regulatory Action

On September 29, 2022, Entasis Therapeutics Inc. (Applicant) submitted NDA 216974 for sulbactam-durlobactam (SUL-DUR) for injection. SUL-DUR is a copackaged product containing sulbactam (SUL), a beta-lactam antibacterial and beta-lactamase inhibitor, and durlobactam (DUR), a beta-lactamase inhibitor. The Applicant's proposed indication is the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex in patients 18 years of age and older. NDA 216974 is a first cycle NDA review and was filed as a Priority Review classification NDA under the "Program." This NDA was taken to the Antimicrobial Drugs Advisory Committee on April 17, 2023. The PDUFA goal date for NDA 216974 is May 29, 2023.

The SUL-DUR development program is the first example of a streamlined program for a targeted therapy for a high-unmet-need pathogen, namely *Acinetobacter baumannii-calcoaceticus* complex (ABC) including carbapenem-resistant isolates (CRABC). The Applicant submitted a single phase 3, randomized, assessor-blinded, active-controlled noninferiority (NI) study in 177 hospitalized adults, primarily with hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by CRABC. The study met the prespecified 20% NI margin for the primary efficacy endpoint of 28-day all-cause mortality with the upper limit of the 95% CI for the difference in mortality rates of 3.5%. An NI margin of 20% was agreed for this study based on available historical data and considering the high unmet need for antibacterial drugs to treat CRABC. Confirmatory evidence is provided by in vitro and animal data demonstrating the activity of SUL-DUR against *Acinetobacter*. The safety database consists of 158 subjects who received SUL-DUR at the proposed dose and duration.

Under 21 CFR part 312 subpart E, FDA may exercise flexibility in applying statutory standards for drugs intended to treat life-threatening and severely debilitating diseases, while preserving appropriate guarantees for safety and effectiveness. SUL-DUR was developed under a flexible development program given the unmet need for treatment options for serious and life-threatening infections caused by CRABC. Because the flexible development program consisted of a single phase 3 NI study, there is a greater reliance on nonclinical studies of SUL-DUR as well as the known safety profile of sulbactam, one of the components of SUL-DUR to inform the benefit-risk assessment for use of SUL-DUR in the indicated population.

No unexpected safety signals were identified during the development program. The safety profile for SUL-DUR appears consistent with other β-lactam/β-lactamase inhibitor drug products, although the safety assessments of SUL-DUR are limited due to the small size of the safety database.

The overall benefit-risk profile is favorable to support approval of SUL-DUR in adult patients with HABP and VABP caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus*

complex. For detailed information supporting the basis for this approval, please refer to the reviews included in this interdisciplinary assessment document and the product quality review.

# 2. Benefit-Risk Assessment

## 2.1. Benefit-Risk Framework

**Table 2. Benefit-Risk Framework**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of condition | • CRABC infections represent an urgent threat with limited treatment options. Mortality rates in VABP due to CRABC have been reported to be up to 64%. Importantly, while mortality rates in carbapenem-resistant *A. baumannii* infections have been reported to be higher than in carbapenem-susceptible infections, even in susceptible infections mortality rates in VABP can be as high as 46%. | Infections due to *Acinetobacter* spp., especially CRABC infections, represent an urgent threat with limited treatment options. |
| Current treatment options | • Current treatment options for CRABC are limited. Combination therapy is recommended for moderate and severe infections although the superiority of any combination regimen has not been consistently shown. Depending on the susceptibility of the isolate, regimens may include SUL (available in the United States as ampicillin-SUL), cefiderocol, polymyxins, tetracyclines, and aminoglycosides. SUL can be degraded by several *Acinetobacter* β-lactamases.<br>• Limitations of polymyxins and aminoglycosides include their toxicity, especially nephrotoxicity. Limitations of tetracyclines include lower efficacy of some drugs in the class in the treatment of HABP and VABP. Treatment-emergent resistance of CRABC to cefiderocol has been reported. | Treatment options for CRABC are limited. Some of the antibacterial drugs used for the treatment of CRABC are associated with toxicity or have limited efficacy. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Benefit | • A phase 3, randomized, controlled, assessor-blinded study in patients with HABP, VABP, VP and bacteremia caused by CRABC found that SUL-DUR demonstrated noninferiority to colistin on the primary endpoint of 28-Day all-cause mortality within the prespecified noninferiority margin of 20%.<br>• The SUL-DUR group had a 28-Day mortality rate of 19.0% (12/63); the colistin group had a mortality rate of 32.3% (20/62); the difference (95% CI) was −13.2 (−30.0, 3.5).<br>• Confirmatory evidence is provided by in vitro and animal data demonstrating the activity of SUL-DUR against *Acinetobacter*. | The phase 3 study met the agreed primary endpoint for this serious infection. However, there is a degree of uncertainty given that the efficacy has been demonstrated in a single study with a limited sample size and there are no other clinical trials of SUL-DUR in HABP/VABP due to *Acinetobacter* spp., including CRABC. |
| Risk and risk management | • No unexpected safety signals for this β-lactam/β-lactamase inhibitor combination were observed in the SUL-DUR development program although the safety database for SUL-DUR is limited. | While the safety profile of SUL-DUR appears acceptable considering the seriousness of the infection and the safety profile of existing therapy, the safety database for SUL-DUR is limited. |

Abbreviations: CI, confidence interval; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; HABP, hospital-acquired bacterial pneumonia; SUL, sulbactam; VABP, ventilator-associated bacterial pneumonia; VP, ventilated pneumonia.

## 2.2. Conclusions Regarding Benefit-Risk

In NDA 216974 for SUL-DUR for injection, the Applicant is seeking an indication for the treatment of HABP and VABP caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex in patients 18 years of age and older. SUL-DUR is a combination of sulbactam, a beta-lactam antibacterial and beta-lactamase inhibitor that has been approved in combination with ampicillin, and durlobactam, a novel beta-lactamase inhibitor.

Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex infections are associated with high mortality rates and represent an urgent threat with limited treatment options. Clinical efficacy data in the NDA consisted of a single adequate and well controlled phase 3 NI study comparing SUL-DUR with colistin in adult subjects, primarily with HABP (43% of subjects), VABP (53% of subjects), ventilated-pneumonia (VP), or bacteremia caused by CRABC. Subjects were randomized in a 1:1 ratio to either 1 g SUL and 1 g DUR every 6 hours (n=91) or colistin (n=86). Both groups also received imipenem as background therapy. Subjects received up to 14 days of therapy.

The primary efficacy endpoint was 28-day all-cause mortality in the subjects who received any amount of study medication with a confirmed baseline infection with CRABC. The study met the prespecified primary efficacy endpoint with a Day 28 all-cause mortality rate of 19.0% in the SUL-DUR group and 32.3% in the colistin group with the upper limit of the 95% CI for the difference in mortality rate of 3.5% (treatment difference: -13.2%, 95% CI: -30.0, 3.5). Confirmatory evidence is provided by in vitro and animal data demonstrating the activity of SUL-DUR against *Acinetobacter.*

The NDA safety database consists of 158 subjects who received SUL-DUR at the proposed dose and duration, including a phase 2 study in subjects with complicated urinary tract infections (cUTI) and a phase 3 study in subjects with HABP/VABP. The safety of DUR with or without SUL was also evaluated in six phase 1 studies. No unexpected safety signals have been identified during the development program. The safety profile for SUL-DUR appears consistent with other β-lactam/β-lactamase inhibitor drug products, although the safety assessments of SUL-DUR are limited due to the small size of the safety database.

Based on review of the available efficacy and safety data, NDA 216974 for SUL-DUR provides substantial evidence of effectiveness and a favorable benefit-risk profile for the treatment of HABP and VABP caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex in patients 18 years of age and older.

# II. Interdisciplinary Assessment

## 3. Introduction

Sulbactam-durlobactam (SUL-DUR) is a copackaged product containing sulbactam (SUL), a beta-lactam antibacterial and beta-lactamase inhibitor, and durlobactam (DUR), a beta-lactamase inhibitor. SUL has been approved in combination with ampicillin since 1986. DUR is a novel beta-lactamase inhibitor. SUL-DUR is to be administered as 1 g SUL and 1 g DUR every 6 hours up to 14 days of therapy; the dose can be adjusted based on renal function.

*Acinetobacter* spp. are gram-negative, nonlactose-fermenting, oxidase-negative coccobacilli. *Acinetobacter baumannii-calcoaceticus* complex (ABC) species include *A. baumannii*, which is the predominant, clinically significant pathogen in that complex associated with nosocomial infections. ABC also includes *A. calcoaceticus, A. dijkshoorniae, A. seifertii, A. nosocomialis,* and *A. pittii*. These species are biochemically indistinguishable and often grouped together as *A. baumannii* complex, or *A. baumannii-calcoaceticus* or *A. baumannii.*

*A. baumannii* exhibits several resistance mechanisms with the major mechanism of carbapenem resistance being production of Class D and less commonly Class A and Class B carbapenemases. Importantly, in contrast to the oxacillinases of Enterobacterales, which are inhibited by avibactam, *A. baumannii*'s oxacillinases are resistant to all β-lactamase inhibitors currently in clinical use, including but not limited to vaborbactam, relebactam, and avibactam (Karakonstantis et al. 2020).

Infection due to drug-resistant *A. baumannii* is an area of a high unmet need. *A. baumannii* is included in the ESKAPE group of six pathogens causing the majority of resistant bacterial infections in developed and developing countries (Rice 2008). In 2017, the World Health Organization published a list of 12 bacterial pathogens that should be prioritized for research and development, with carbapenem-resistant *A. baumannii* topping the list of the three pathogens ranked as critical. In their latest report on the antibiotic-resistance threats in the United States, the Centers for Disease Control and Prevention escalated the threat level of carbapenem-resistant *Acinetobacter* to urgent (multidrug-resistant [MDR] *Acinetobacter* was listed as serious in the prior report) indicating the lack of treatment options for these infections (CDC 2019).

*A. baumannii* predominantly causes nosocomial pneumonia and bacteremia, although infections at other body sites, including urinary tract and skin and soft tissue infections, may occur. In the United States, 3.2% to 6.6% of ventilator-associated pneumonia cases and 0.4% to 1.9% of central line-associated bloodstream infections are caused by *Acinetobacter* spp. (Weiner-Lastinger et al. 2020). Notably, among *Acinetobacter* spp. isolates causing ventilator-associated pneumonia, 41.3% of intensive-care units and 75.9% of long-term acute-care hospital isolates were carbapenem resistant (Weiner-Lastinger et al. 2020). Overall, it has been estimated that around 23,000 cases of carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CRABC) infection occur annually in the United States (Spellberg and Rex 2013; Lemos et al. 2014). Infections due to carbapenem-resistant *A. baumannii* have been associated with poor outcomes with mortality rates ranging from 38% to 76% (Aydemir et al. 2013; Lemos et al.

2014; Paul et al. 2018). Patients with CRABC infections were found to have a significantly higher risk of mortality than patients with carbapenem-susceptible *A. baumannii* infections, with overall mortality rates in hospital-acquired bacterial pneumonia (HABP) /ventilator-associated bacterial pneumonia (VABP) caused by CRABC of around 45 to 60% (Aydemir et al. 2013; Zheng et al. 2013; Lemos et al. 2014). The proportion of isolates resistant to both ampicillin-SUL and carbapenems among 206 blood isolates of *A. baumannii* was reported to be 25% (Chopra et al. 2013).

Current treatment options for CRABC are limited. Combination therapy is suggested for moderate and severe infections although the superiority of any combination regimen has not been consistently shown in clinical studies (Bartal et al. 2022; Tamma et al. 2022). Ampicillin-SUL is suggested to be a part of a combination therapy when susceptibility has been demonstrated. The activity of ampicillin-SUL against *Acinetobacter* spp. is mediated by the SUL component given that *Acinetobacter* spp. are intrinsically resistant to ampicillin. Because in the United States SUL is approved in combination with ampicillin, ampicillin is nevertheless administered.

SUL has a β-lactam structure and is directly active against *Acinetobacter* spp. by inhibiting penicillin-binding proteins (PBP) 1 and PBP3, the enzymes required for bacterial cell wall synthesis (Penwell et al. 2015). Although SUL is also a class A β-lactamase inhibitor, its β-lactamase inhibitory properties are less relevant for *Acinetobacter* infections.

Resistance to SUL in *Acinetobacter* spp. is primarily due to production of β-lactamases; it may also be mediated by PBP3 mutations and upregulated efflux (Penwell et al. 2015). DUR inactivates several β-lactamases expressed by *Acinetobacter* including those of Ambler Classes A, C, and D, which degrade SUL. DUR does not inhibit Class B metallo-β-lactamases. Compared to other currently approved β-lactamase inhibitors, DUR has extended activity against Class D carbapenemases of the OXA family. DUR in combination with SUL may be an option for the treatment of CRABC resistant to other available therapies. DUR has not been approved in any country.

Other treatment options for CRABC infections include cefiderocol, polymyxins, tetracyclines, and aminoglycosides. The limitations of polymyxins and aminoglycosides include their toxicity, especially nephrotoxicity. The limitations of tetracyclines include lower efficacy of some drugs in the class in the treatment of HABP and VABP (Pfizer 2005). Cefiderocol was recently approved for the treatment of HABP and VABP, including those caused by *Acinetobacter* (Shionogi 2019), but treatment-emergent resistance of CRABC to cefiderocol has been reported (Falcone et al. 2022).

The efficacy of SUL-DUR for the proposed indication is supported by a single phase 3, randomized, assessor-blinded, active-controlled NI study in 177 hospitalized adults, primarily with HABP (43% of subjects) and VABP (53% of subjects) caused by CRABC. Subjects were randomized in a 1:1 ratio to either 1 g SUL and 1 g DUR every 6 hours (n=91) or colistin (n=86). Both groups also received imipenem as background therapy. Subjects received up to 14 days of therapy.

The primary efficacy endpoint was 28-day all-cause mortality in the subjects who received any amount of study medication with a confirmed baseline infection with CRABC. An NI margin of

20% was agreed for this study based on available historical data and considering the high unmet need for antibacterial drugs to treat CRABC.

A total of 125 subjects were assessed in the efficacy population: 63 subjects in the SUL-DUR group and 62 subjects in the colistin group. All-cause mortality at Day 28 was 19% (12/63) in the SUL-DUR group and 32.3% (20/62) in the colistin group, for a treatment difference (95% CI) of −13.2% (−30.0, 3.5), demonstrating that SUL-DUR was noninferior to colistin.

The NDA also included a phase 2 double-blind, randomized, placebo-controlled study evaluating SUL-DUR in the treatment of complicated urinary tract infections (cUTI) that was conducted from January to May 2018. All patients received background therapy with imipenem-cilastatin. The study enrolled 80 adult patients, 53 in the SUL-DUR group and 27 in the placebo group. Because no patients with *A. baumannii* were enrolled, and only one patient in the SUL-DUR group had an isolate resistant to imipenem, the data from this study did not inform the efficacy of SUL-DUR but informed the safety assessments.

The safety database for the NDA includes 158 subjects who received SUL-DUR at the proposed dose and duration, including a phase 2 study in subjects with cUTI and a phase 3 study in subjects with HABP/VABP. The safety of DUR with or without SUL was also evaluated in six phase 1 studies. No unexpected safety signals have been identified during the development program. The safety profile for SUL-DUR appears consistent with other β-lactam/β-lactamase drug products, but it is important to note the limited size of the safety database for SUL-DUR.

The NDA was brought to the Antimicrobial Drugs Advisory Committee meeting to discuss whether the data contained in the NDA for SUL-DUR support a favorable benefit-risk assessment for the treatment of HABP and VABP caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex.

## 3.1. Review Issue List

### 3.1.1. Key Efficacy Review Issues

#### 3.1.1.1. Do the Clinical Data in Phase 3 Study CS2514-2017-0004 Part A Support Labeling for Patients With Bacteremia Caused by ABC or Multidrug-Resistant ABC Pathogens?

### 3.1.2. Key Safety Review Issues

#### 3.1.2.1. Limited Size of the Safety Database

## 3.2. Approach to the Clinical Review

Data for efficacy were from a phase 3 study comparing SUL-DUR with colistin in subjects with HABP, VABP, VP, or bacteremia caused by CRABC. The phase 3 study was considered an adequate and well-controlled study with a prespecified primary endpoint that had been designed consistent with guidance from the Division of Anti-Infectives. Confirmatory evidence is provided by in vitro and animal data demonstrating the activity of SUL-DUR against *Acinetobacter*.

The safety database for the NDA includes 158 subjects who received SUL-DUR at the proposed dose and duration in the phase 3 study and a phase 2 cUTI study. The safety of DUR with or without SUL was also evaluated in six phase 1 studies (123 subjects) and in 12 subjects who received SUL-DUR under an expanded access program. Also, the extensive experience with ampicillin-SUL was considered in the evaluation of the safety of SUL-DUR.

No unexpected safety signals have been identified during the development program. The safety profile for SUL-DUR appears consistent with other β-lactam/β-lactamase inhibitor drug products. Though the integrated safety database was small, the NDA submission was considered adequate from a safety evaluation perspective given the absence of safety signals, supportive data noted above, and the context of clinical use in the population for whom expected benefits outweighed a certain degree of uncertainty with regard to the safety of SUL-DUR.

**Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Sulbactam-Durlobactam**

| Study/Trial Identifier (NCT#) | Study/Trial Population | Study/Trial Design | Regimen (Number Treated), Duration | Primary and Key Secondary Endpoints | Number of Subjects Planned; Actual Randomized[2] | Number of Centers and Countries |
|---|---|---|---|---|---|---|
| NCT03894046<br>ATTACK Trial<br>CS2514-2017-0004 Phase 3 | Subjects ≥18 years of age with HABP, VABP, VP, or bacteremia caused by ABC. | Enrolled in two parallel parts:<br>Part A<br>Pivotal, randomized, comparative portion<br><br>Part B<br>Single-group portion in subjects not eligible for Part A<br><br>Control type: Part A: Active concurrent noninferiority Part B: Uncontrolled<br><br>Randomization: At a 1:1 ratio (Part A)<br><br>Blinding: Assessor blind (Part A)<br>Biomarkers: None<br>Innovative design features: None | Part A<br>Experimental group: 1.0 g SUL/1.0 g DUR IV infused over 3h q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1h q6h; OR<br><br>Control group: 2.5 mg/kg colistin IV infused over 30 minutes every 12h (after an initial loading dose of colistin 2.5 to 5 mg/kg) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1h q6h.<br><br>Part B<br>1.0 g SUL1.0 g DUR IV infused over 3h q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1h q6h.<br><br>Number treated:<br>Part A: 177<br>Part B: 28<br>Duration: 7-14 d | Primary: 28-day ACM in the CRABC m-MITT population;<br><br>Secondary: 28-day ACM in the ITT population;<br><br>Clinical cure at TOC in the CRABC m-MITT population;<br><br>Microbiological favorable assessment at TOC in the CRABC m-MITT population | Planned: 200<br><br>Randomized in Part A: 181<br><br>Transferred to Part B: 2<br><br>Enrolled in Part B: 26<br><br>Completed the study: 152 | Centers: 59<br><br>Countries:16 |

Source: Reviewer.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled."
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; ACM, all-cause mortality; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; h, hours; HABP, hospital-acquired pneumonia; ITT, intention-to-treat; IV, intravenously; m-MITT, microbiologically modified intent-to-treat population, which included subjects randomized in Part A, received any amount of study drug, had an ABC organism isolated as the qualifying culture specimen, confirmed to be carbapenem-resistant, and deemed not to be resistant to SUL-DUR and colistin, had blood culture or respiratory samples collected within 72 hours prior to randomization, not transferred from Part A to Part B, and had HABP, VABP, VP, or bacteremia due to ABC; NCT, national clinical trial; q6h, every 6 hours; SUL, su bactam; TOC, test of cure, that was 7 days (±2 days) after the end of treatment; VABP, ventilator-acquired pneumonia; VP, ventilated pneumonia.

# 4. Patient Experience Data

**Table 4. Patient Experience Data Submitted or Considered**

| **Data Submitted in the Application** | | |
|---|---|---|
| **Check if Submitted** | **Type of Data** | **Section Where Discussed, if Applicable** |
| **Clinical Outcome Assessment Data Submitted in the Application** | | |
| ☐ | Patient-reported outcome | |
| ☐ | Observer-reported outcome | Section 15; definitions of secondary endpoints. |
| ☒ | Clinician-reported outcome | |
| ☐ | Performance outcome | |
| **Other Patient Experience Data Submitted in the Application** | | |
| ☐ | Patient-focused drug development meeting summary | |
| ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) | |
| ☐ | Observational survey studies | |
| ☐ | Natural history studies | |
| ☐ | Patient preference studies | |
| ☐ | Other: (please specify) | |
| ☒ | If no patient experience data were submitted by Applicant, indicate here. | |
| **Data Considered in the Assessment (but Not Submitted by Applicant)** | | |
| **Check if Considered** | **Type of Data** | **Section Where Discussed, if Applicable** |
| ☒ | Perspectives shared at patient stakeholder meeting | |
| ☐ | Patient-focused drug development meeting summary report | |
| ☐ | Other stakeholder meeting summary report | |
| ☐ | Observational survey studies | |
| ☐ | Other: (please specify) | |

# 5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

## 5.1. Nonclinical Assessment of Potential Effectiveness

**Nonclinical Sulbactam-Durlobactam Pharmacokinetics/Pharmacodynamics Information**

XACDURO is a copackaged antibacterial product containing sulbactam and durlobactam. The Applicant conducted several studies examining the nonclinical pharmacokinetics (PK)/ pharmacodynamics (PD) of sulbactam-durlobactam in murine thigh and pneumonia models of MDR ABC infection. Percent of time that free drug concentrations remain above the minimum inhibitory concentration (%*f*T > MIC) was best correlated with sulbactam efficacy, indicating

that antibacterial activity of sulbactam is time dependent, similar to other beta-lactams. Area under the unbound concentration-time (*f*AUC) from time zero to 24 hours post dose curve/MIC ratio ($fAUC_{0\text{-}24}$/MIC) was best correlated with durlobactam efficacy.

To determine the PK/PD target of SUL, it was administered in the presence of DUR at a dose ratio of 4:1 in a murine neutropenic thigh model. The mean plasma %*f*T > MIC magnitudes for SUL were determined as 34.3% (range from 26.2% to 45.7%) to achieve a 1-log10 kill and 38.6% (ranged from 28.8% to 52.9%) for 2-log10 kill, respectively, against five SUL-resistant *A. baumannii isolates*. When SUL was administered in the presence of DUR at a dose ratio of 4:1 in a murine neutropenic lung model, the mean plasma %*f*T > MIC magnitudes for SUL were determined as 45.5% (ranged from 37.1% to 58.1%) to achieve a 1-log10 kill and 55.5% (ranged from 43.9% to 70.9%) for 2-log10 kill, respectively, against four SUL-resistant *A. baumannii* isolates. To determine the PK/PD target of DUR, fixed doses of SUL and varied doses of DUR were administered in a mouse thigh infection model against six SUL-resistant *A. baumannii* isolates. The daily DUR plasma *f*AUC/MIC values associated with 1 log10 kill and 2-log10 kill were determined to be 7.5 and 31.8, respectively. These results are consistent with the *f*AUC/MIC values obtained in the neutropenic thigh and lung studies using the 4:1 SUL:DUR fixed ratio dose. Based on these results, the Applicant chose 50% %*f*T > MIC for sulbactam, and $fAUC_{0\text{-}24}$/MIC of 10 for durlobactam as the PK/PD targets for sulbactam-durlobactam to support the clinical dose selection. For further details on the antibacterial activity of sulbactam-durlobactam, see Sections 19 and 20. For further details on the determination of nonclinical PK/PD targets for sulbactam-durlobactam, see Section 14.1.1.

## 5.2. Clinical Pharmacology / Pharmacokinetics

**Table 5. Summary of Clinical Pharmacology and Pharmacokinetics**

| Characteristic | Drug Information |
|---|---|
| ***Pharmacologic Activity*** | |
| Established pharmacologic class | Sulbactam, a beta-lactam antibacterial and beta-lactamase inhibitor, and durlobactam, a beta-lactamase inhibitor. |
| Mechanism of action | Sulbactam inhibits ABC PBP1 and PBP3, which are essential enzymes required for bacterial cell wall synthesis. The activity of beta-lactam class antibacterial drugs is dependent on the beta-lactam pharmacophore, which is destroyed by β-lactamase enzymes. Durlobactam is a non-β-lactam, β-lactamase inhibitor of Classes A, C, and D serine β-lactamases and it protects sulbactam from degradation by certain serine-beta-lactamases. Durlobactam alone does not have any antibacterial activity against *Acinetobacter* species. |
| Active moieties | Sulbactam and durlobactam |
| QT prolongation | At a dose (4 g) 4-times the maximum recommended single dose, durlobactam does not prolong the QTc interval to any clinically relevant extent.<br><br>The effect of a supratherapeutic dose of durlobactam was evaluated in a phase 1, randomized, partially double-blind, comparative, placebo- and positive-controlled 3-period crossover TQT study conducted in healthy subjects. The QTc effect of durlobactam or moxifloxacin (positive control) was studied following single IV infusion of 4 g durlobactam infused over 3 h, a single IV infusion of placebo for durlobactam infused over 3 h, or a single IV infusion of placebo for durlobactam infused over 3 h and a single oral dose of 400 mg open-label moxifloxacin administered at the end of the infusion. The primary |

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td></td><td>endpoint was based on an analysis of the regression of ΔQTcF as a function of durlobactam plasma concentration to derive the estimated mean placebo-adjusted change of QTcF from baseline (ΔΔQTcF) for a supratherapeutic dose of durlobactam at the geometric mean $C_{max}$. Secondary ECG endpoints for a supratherapeutic dose of durlobactam were change-from-baseline HR, QTcF, PR, and QRS (ΔHR, ΔQTcF, ΔPR, and ΔQRS), placebo-corrected change-from-baseline HR, PR, and QRS (ΔΔHR, ΔΔPR, and ΔΔQRS), categorical outliers for QTcF, HR, PR, and QRS, and frequency of treatment-emergent changes of T-wave morphology and U-wave presence. The estimated mean ΔΔQTcF at the geometric mean plasma concentrations for a supratherapeutic dose of durlobactam had confidence interval upper bounds of <10 ms.</td></tr>
<tr><td>General Information</td><td></td></tr>
<tr><td>Bioanalysis</td><td>Validated HPLC-MS/MS methods were used to determine the concentrations of sulbactam and durlobactam in plasma, urine, and ELF.</td></tr>
<tr><td>Healthy subjects versus patients</td><td>No clinically meaningful differences in sulbactam and durlobactam PK were observed between patients and healthy subjects.</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)</td><td>Table 6. Steady State (Day 3) Plasma PK Parameters in Patients With Normal Renal Function
<table>
<tr><th>PK Parameter</th><th>Sulbactam (n=37)</th><th>Durlobactam (n=37)</th></tr>
<tr><td>$C_{max}$ (µg/mL)</td><td>26.7 (59.1%)</td><td>27.0 (39.3%)</td></tr>
<tr><td>$AUC_{0-24}$ (h·µg/L)</td><td>391 (76.1%)</td><td>418 (53.5%)</td></tr>
</table>
Source: Table 3 from the Applicant's draft label of NDA216974<br>
Note: Parameter values are geometric means (%CV)<br>
Note: CLcr ≥90 to <130 mL/min<br>
Note: Administered sulbactam 1 g and durlobactam 1 g every 6 hours<br>
Abbreviations: $AUC_{0-24}$, area under the curve from 0 to 24 hours; CLcr; creatinine clearance; $C_{max}$, maximum plasma concentration; CV, coefficient of variation; n, number of subjects in category; PK, pharmacokinetic</td></tr>
<tr><td>Range of effective dose(s) or exposure</td><td>The effective dose is 1g sulbactam and 1g durlobactam (phase 2 and 3 studies).</td></tr>
<tr><td>Maximally tolerated dose or exposure</td><td>The highest evaluated dose for durlobactam in humans was 8 g single dose and 2 g q6h (phase 1 study).</td></tr>
<tr><td>Dose proportionality</td><td>The $C_{max}$ and AUC of durlobactam increased in a dose-proportional manner within the dose range from 0.25 to 8 g for single-dose, and 0.25 to 2 g for multiple-dose administration.</td></tr>
<tr><td>Accumulation</td><td>Sulbactam and durlobactam exhibit minimal accumulation over 11 days in a phase 1 multiple-dose study in healthy subjects.</td></tr>
<tr><td>Time to achieve steady state</td><td>Steady state is achieved by day two (administration of four doses).</td></tr>
<tr><td>Bridge between to-be-marketed and clinical trial/study formulations</td><td>The formulation composition proposed for commercial drug products is identical to the phase 3 formulation.</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Volume of distribution</td><td>The geometric mean (%CV) steady-state volume of distribution in patients with normal renal function was 22.0 L (60.8%) and 28.0 L (40.3%) for sulbactam and durlobactam, respectively.</td></tr>
<tr><td>Plasma protein binding</td><td>The binding of sulbactam and durlobactam to human plasma proteins is approximately 38% and 10%, respectively</td></tr>
<tr><td>Drug as substrate of transporters</td><td>Sulbactam and durlobactam are both substrates of OAT1.</td></tr>
</table>

| Characteristic | Drug Information |
|---|---|
| ***Elimination*** | |
| Mass balance results | Following a single IV dose of 1.0 g of nonlabeled durlobactam and 1 µCi of 14C-labeled durlobactam as a 3-hour IV infusion, the mean cumulative recovery of radiolabeled durlobactam over the 168-hour collection period was 93.0% with nearly all the radioactivity recovered in urine. Unchanged parent durlobactam was identified as the major radioactive component in urine (78.1%). The hydrolysis product ETX-014799 accounted for 10.6% of the recovered dose in urine. |
| Clearance | Clearance is 9.98 L/h for sulbactam and 9.40 L/h for durlobactam. |
| Half-life | Terminal half-life is approximately 1 to 3 hours and 2 to 3 hours, respectively, for sulbactam and durlobactam. |
| Metabolic pathway(s) | Both sulbactam and durlobactam are minimally metabolized. |
| Primary excretion pathways (% dose) | Approximately 75 to 85% of administered dose of sulbactam is excreted unchanged in the urine. 78.1% of administered dose of durlobactam was eliminated unchanged in the urine. |
| ***Intrinsic Factors and Specific Populations*** | |
| Body weight | No clinically meaningful differences in sulbactam and durlobactam PK based on body weight (35 kg to 150 kg) were observed. |
| Age | No clinically significant differences in the pharmacokinetics of sulbactam and durlobactam were observed based on age (18 to 91 years of age). |
| Renal impairment | Sulbactam and durlobactam exposures increased with reduced renal function. Dose adjustment is needed in patients with CLcr less than 45 mL/min. Increased sulbactam and durlobactam clearance has been observed in patients with CLcr 130 mL/min or greater. Dose adjustment is needed in patients with CLcr 130 mL/min or greater (see Section 8.1 and 14.2). |
| Hepatic impairment | The effect of hepatic impairment on the pharmacokinetics of sulbactam and durlobactam was not evaluated. However, hepatic impairment is not expected to alter the elimination of sulbactam and durlobactam because sulbactam and durlobactam are mainly excreted by the kidneys. |
| ***Drug Interaction Liability (Drug as Perpetrator)*** | |
| Inhibition/induction of metabolism | In vitro studies showed that durlobactam did not inhibit cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 and did not induce CYP1A2, CYP2B6, or CYP3A4 at therapeutic plasma concentrations. No in vitro studies with CYPs and sulbactam were conducted. |
| Inhibition/induction of transporter systems | In vitro data showed that sulbactam did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, BSEP, OAT1, OAT3, MATE1, or MATE2-K at therapeutic plasma concentrations. In vitro data also indicated that durlobactam did not inhibit P-gp, BCRP, OATP1B1, OAT1, OAT3, or OCT2 at therapeutic plasma concentrations. |

Source: Applicant's module 2.7.2 Summary of Clinical Pharmacology for NDA 216974 and the Applicant's draft label for NDA 216974

Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; AUC, area under the curve; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CLcr; creatinine clearance; $C_{max}$, maximum plasma concentration, CV, coefficient of variation; CYP, cytochrome P450; ECG, electrocardiogram; ELF, epithelium lining fluid; HPLC-/MS/MS, high-performance liquid chromatography with tandem mass spectrometry; HR, heart rate; IV, intravenous; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OCT, organic cation transporter; PBP, penicillin-binding proteins; P-gp, P-glycoprotein; PK, pharmacokinetics; PR, time from the onset of the P wave to the starts of the QRS complex; QT, time between the start of the QRS complex and the end of the T wave; QTc, corrected QT interval; QTcF, corrected QT interval by Fridericia; QRS, combination of the Q, R, and S waves; q6h, every 6 hours; TQT, thorough QT; Δ change-from-baseline; ΔΔ, estimated mean placebo-corrected change-from-baseline

# 6. Efficacy (Evaluation of Benefit)

## 6.1. Assessment of Dose and Potential Effectiveness

**Nonclinical PK/PD Targets and %PTA From the Phase 3 Study**

The Applicant conducted probability of target attainment (PTA) analyses based on nonclinical PK/PD targets to support the adequacy of the proposed dose regimens including the renal function-based dose adjustments throughout drug development phases.

Based on the results from murine thigh and lung infection models against ABC, the PK/PD index that most correlates with sulbactam activity is %*f*T > MIC, with a value of 50% associated with a 1-log10 kill. For durlobactam, *f*AUC$_{0\text{-}24}$/MIC was determined to be the PK/PD index, with ratios of approximately 10 and 30 associated with achieving 1-log10 and 2-log10 kill, respectively, when the unbound sulbactam achieves 50% *f*T > MIC (see Section 5.1).

Based on the observed PK and MIC data from the subjects evaluated in the phase 3 study, the percentage of subjects who achieved the PK/PD targets associated with 1-log kill (i.e., 50% *f*T > MIC for sulbactam and *f*AUC$_{0\text{-}24}$/MIC of 10 for durlobactam) were determined.

**PTA Analyses at the Phase 3 Evaluated Dose Regimen**

The Applicant's proposed dosage of 1.0 g sulbactam/1.0 g durlobactam every 6 hours (q6h) administered as a 3-hour intravenous (IV) infusion was evaluated in the phase 3 study for the treatment of infections caused by ABC, including MDR and carbapenem-resistant strains (Table 7). Of note, renal function-based dose adjustments were revised post NDA submission (see Section 8.1.1).

**Table 7. SUL-DUR Dose Regimens Evaluated in the Phase 3 Study, Study CS2514-2017-0004**

(b) (4)

For the Part A analysis population, the percent of subjects achieving these PK/PD targets ranged from 95.0 to 100% based on the assessment on either Day 1 or the average of Days 1 to 3 free-drug plasma and total-drug epithelial lining fluid (ELF) exposures. For the Part B analysis populations, the percentage of subjects achieving these PK/PD targets ranged from 91.3 to 100%. The ≥90% PTA observed in phase 3 subjects indicates that the dose regimen evaluated in the

phase 3 study provided adequate drug exposure in the majority of subjects to achieve the nonclinical PK/PD targets associated with bactericidal activity against ABC.

# 6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

## 6.2.1. Study CS2514-2017-0004

### 6.2.1.1. Design, Study CS2514-2017-0004

Study CS2514-2017-0004 was composed of two parallel parts: Parts A and B (Figure 1). Part A was the pivotal, randomized, assessor-blinded, comparative, NI portion of the study. It compared the efficacy and safety of IV SUL-DUR versus IV colistin, both in combination with IV imipenem and cilastatin, for the treatment of subjects with ABC HABP, VABP, VP, or bacteremia. Part B was the single-group portion of the study. It enrolled ABC-infected subjects who did not qualify for Part A because the baseline pathogen was known to be resistant to colistin as well as subjects with cUTI and acute pyelonephritis or surgical or post-traumatic wound infections. The efficacy of SUL-DUR was evaluated based on Part A of study CS2514-2017-0004. Therefore, the Agency's efficacy review focuses on Part A unless otherwise stated.

The inclusion criteria for Part A required subjects to be ≥18 years of age; diagnosed with HABP, VABP, VP, or bacteremia caused by ABC based on culture or rapid diagnostic test from a sample collected within 72 hours prior to randomization (see Section 15 for definitions of HABP, VABP, VP, and/or bacteremia); receiving no more than 48 hours of potentially effective antimicrobial therapy prior to the first dose of study drug or clinically failing the prior treatment regimen; and having an Acute Physiology and Chronic Health Evaluation (APACHE) II score between 10 and 30, or a Sequential Organ Failure Assessment (SOFA) score between 7 and 11, or a quick SOFA (qSOFA) score of ≥2 if an APACHE II or SOFA score was unavailable, at the time of diagnosis of infection. Subjects could be transferred from Part A to Part B if their ABC was subsequently determined to be resistant to colistin or polymyxin B.

Subjects were randomized in a 1:1 ratio to one of the following treatment groups:

- Group 1: 1.0 g SUL /1.0 g DUR IV infused over 3 hours every 6 hours.
- Group 2: 2.5 mg/kg colistin IV infused over 30 minutes every 12 hours.

Randomization was stratified by the following three factors:

(1) Baseline infection type (HABP/VABP/VP versus bacteremia).

(2) Severity of illness at baseline, based on the score measured at screening using one of the following three instruments:

(a) APACHE II: (10 to 19 versus 20 to 30), or
(b) SOFA (7 to 9 versus ≥10), or
(c) qSOFA (2 versus 3).

- In case a subject had more than one score reported, the scores were used in the following order: APACHE II, SOFA, and qSOFA.

(3) Region (Mainland China versus the rest of the world).

The study drug was administered daily for 7 days with an extension up to 14 days if clinically indicated. The background therapy in both groups was 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour every 6 hours.

Subjects infected with HABP, VABP, or VP could be eligible for randomization based on a positive result on a Biofire® FilmArray® 2.0 Pneumonia Panel (BPP) rapid test. However, they were withdrawn from the study treatment if their respiratory sample culture subsequently processed by the local microbiology laboratory did not have growth of ABC.

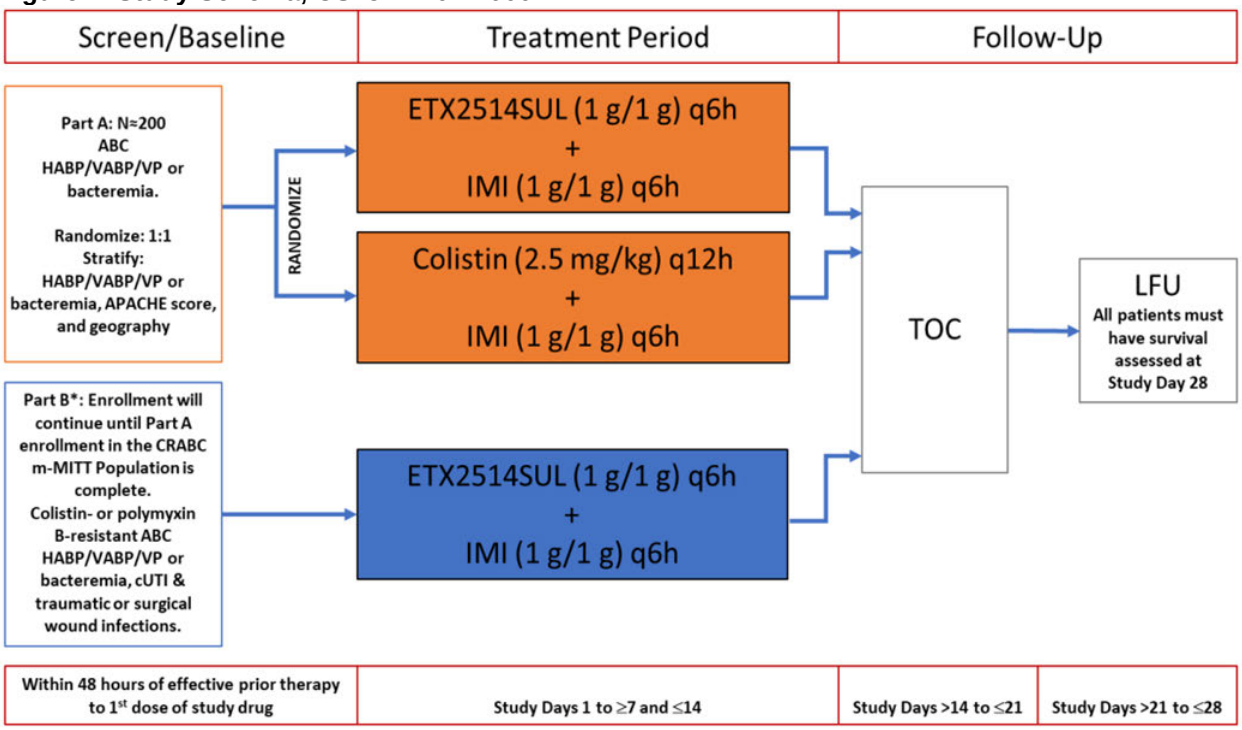
The study duration for a subject was approximately 28 days. If a subject had their late follow-up visit before Day 28, a telephone call on Day 28 or anytime thereafter was made to assess survival status.

The study was unblinded to the principal investigators. A blinded assessor was assigned in each site to assess clinical outcome and causality for adverse events (AEs). If there was a discrepancy between the assessments of the assessor and of the investigator, the assessment of the assessor was used. If an assessment was missing from either the blinded assessor or unblinded investigator, the other available assessment was used. The protocol stated that an adjudication committee may have been organized for endpoint adjudication should it have been deemed necessary as determined by the Data Safety Monitoring Board. However, it was not deemed necessary and therefore no adjudication committee was formed for this study.

Clinical outcome was assessed at visits on Day 5, Day 7, end of therapy (EOT), test of cure (TOC), on Day 7 (±2 days) after EOT, late follow-up (LFU) on Day 14 (±2 days) after the EOT, and early termination. The outcome was categorized into clinical cure, failure, or indeterminate. If a subject was a clinical failure, he/she was automatically a failure at the TOC and LFU visits. Detailed definitions of each category of clinical outcome are provided in Section 15.

Microbiologic outcome was assessed based on the results of blood and/or urine cultures at the Day 5, Day 7, EOT, TOC, and LFU visits. The outcome was classified into microbiologic eradication, presumed eradication, persistence, presumed persistence, indeterminate, or recurrence. A microbiologic favorable assessment included microbiological eradication or presumed eradication. Detailed definitions of the microbiologic outcome categories are provided in Section 15.

**Figure 1. Study Schema, CS2514-2017-0004**




Source: Figure 1 in Clinical Study Report CS2514-2017-0004.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; cUTI, complicated urinary tract infection; ETX2514-SUL, durlobactam-sulbactam; HABP, hospital-acquired bacterial pneumonia; IMI, imipenem/cilastatin; LFU, late follow-up; m-MITT, microbiologically modified intent-to-treat; N, number of subjects; q6h, every 6 hours; q12h, every 12 hours; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia; VP, ventilated pneumonia

## Analysis Populations

The efficacy endpoints were evaluated in various analysis populations. The definitions of the analysis populations are provided in Section 15.

The primary efficacy analysis population was the CRABC microbiologically modified intent-to-treat (m-MITT) population that included subjects who met the following criteria:

(1) Randomized in Part A

(2) Received any amount of study drug

(3) Had an ABC organism isolated as the qualifying culture specimen, as confirmed by the central and/or local microbiology laboratory

(4) Had a baseline ABC organism that was confirmed to be carbapenem-resistant by the central laboratory, or by the local laboratory if the central laboratory was unable to characterize the isolate for any reason

(5) Had isolates that were deemed by the central laboratory not to be resistant to SUL-DUR and colistin

(6) Had blood culture or respiratory samples collected within 72 hours prior to randomization

(7) Not transferred from Part A to Part B

(8) Had HABP, VABP, VP, or bacteremia due to ABC.

**Efficacy Endpoints**

Primary Efficacy Endpoint

- Twenty-eight-day all-cause mortality in CRABC m-MITT population.

Secondary Efficacy Endpoints

- Twenty-eight-day all-cause mortality in the intent-to-treat (ITT), m-MITT, and clinically evaluable (CE) populations.
- Fourteen-day all-cause mortality in the CRABC m-MITT and m-MITT populations.
- Clinical cure at EOT, TOC and LFU in the m-MITT, CRABC m-MITT, CE, microbiologic evaluable (ME), and CRABC ME populations.
- Microbiological favorable assessment at EOT, TOC, and LFU in the m-MITT, CRABC m-MITT, ME, and CRABC ME populations.

### 6.2.1.2. Eligibility Criteria, Study CS2514-2017-0004

The protocol was revised three times. The main change related to eligibility criteria was that the target population was expanded to allow subjects with VP in the study in Protocol Amendment 2 (Version 3). The following inclusion and exclusion criteria were from Protocol Amendment 3 (Version 4) which was the final version of the protocol.

The general inclusion criteria were as follows:

(1) A signed informed consent form;

- Note: If a study patient is unable to provide informed consent due to their medical condition, the patient's legally authorized representative may consent on behalf of the study patient, or the decision can be made according to the procedure permitted by local law and institutional Standard Operating Procedures in compliance with Section 15 in the protocol

(2) Male or female ≥18 years of age;

(3) A confirmed diagnosis of a serious infection and the expectation, in the judgment of the Investigator, that the patient's infection will require treatment with IV antibiotics;

(4) A known infection caused by ABC (bacteremia, HABP, VABP, VP, cUTI or acute pyelonephritis [AP], or surgical or post-traumatic wound infections) as either a single pathogen or member of a polymicrobial infection based on evidence from culture or, if available, rapid diagnostic test from a sample collected within 72 hours prior to randomization (HABP/VABP/VP patients), AND 1 of the following:

(a) Has received no more than 48 hours of potentially effective (i.e., Gram negative coverage) antimicrobial therapy prior to the first dose of study drug; OR

(b) Is clinically failing prior treatment regimens (i.e., clinical deterioration or failure to improve after at least 48 hours of antibiotic treatment);

- Note: Rapid testing of respiratory specimens utilizing FilmArray 2.0 BPP technology should be used to enable early identification of ABC pneumonia. Patients can be randomized based on the results of the BPP rapid test while awaiting results of cultures from the local laboratory. However, if the respiratory sample does not grow ABC in the local microbiology laboratory culture, these patients will be withdrawn from the study drug treatment.
- Note: Isolation of ABC from pleural effusion (empyema) is allowed, if concurrent pulmonary infiltrate is confirmed.

(5) APACHE II score between 10 and 30, inclusive, OR SOFA score between 7 and 11, inclusive, at the time of diagnosis of infection. Patients who are not being treated in an intensive care unit and cannot have an APACHE II or SOFA score performed should have a qSOFA score ≥2 for enrollment;

(6) Expectation, in the judgment of the Investigator, that the patient will benefit from effective antibiotic therapy and appropriate supportive care for the anticipated duration of the study; and

(7) Women of childbearing potential (i.e., not postmenopausal or surgically sterilized) must have a negative highly sensitive urine or serum pregnancy test before randomization. Participating women of childbearing potential must be willing to consistently use one highly effective method of contraception (i.e., condom, combined oral contraceptive, implant, injectable, indwelling intrauterine device, or a vasectomized partner) from Screening until at least 30 days after administration of the last dose of study drug.

In additional to the general inclusion criteria listed above, all subjects enrolled in Part A must have been categorized in one infection type judged to be the primary infection by the Investigator. The definitions of HABP, VABP, VP and/or bacteremia are listed in Section 15.

The exclusion criteria were as follows:

(1) Presence of suspected or confirmed deep-seated infection (e.g., lung abscess in patients with pneumonia, skin abscess, or decubitus ulcer) that is not planned on being drained or debrided within 24 hours after randomization;

- Note: Patients with an empyema who will have drainage within 24 hours of Screening and who are expected to be able to be treated with 14 or fewer days of antibiotics are allowed.

(2) Evidence of active concurrent pneumonia requiring additional antimicrobial treatment caused by *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophila,* respiratory syncytial virus, influenza and parainfluenza viruses, Middle East respiratory syndrome coronavirus, *mycobacteria, aspergillus, mucormycosis,* etc.

- Note: If these organisms are identified but it is deemed by the Investigator that no treatment is warranted and their presence does not significantly change the prognosis of the patient, then the patient may be considered for this study.

(3) Pulmonary disease that precludes evaluation of a therapeutic response (such as lung cancer resulting in bronchial obstruction or on the same side as the pneumonia, active

tuberculosis, cystic fibrosis, granulomatous disease, fungal pulmonary infection, lung abscess, pleural empyema, or post obstructive pneumonia);

- Note: Patients with an empyema who will have drainage within 24 hours of Screening and who are expected to be able to be treated with 14 or fewer days of antibiotics are allowed.

(4) Presence of suspected or confirmed deep seated bacterial infections such as bacterial gram-negative osteomyelitis, endocarditis, or meningitis requiring prolonged therapy, as determined by history and/or physical examination;

(5) Acute infective endocarditis due to gram positive bacteria that require urgent/emergent indication of surgery (i.e., heart failure because of valvular insufficiency or septic shock), or patients in whom surgery is contraindicated due to prohibitive risk for surgery due to comorbidities;

(6) Irremovable implantable device or line thought to be the potential source of ABC infection;

(7) Sustained shock with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥60 mmHg;

- Note: Patients who can maintain MAP ≥60 mmHg on a reasonable dose of pressors or are weaning off of pressors may be considered. Patients who require more than the maximal dose of 2 vasopressors to maintain MAP ≥60 mmHg are ineligible. If vasopressors are weaned to below these levels, patient enrollment can be reconsidered.

(8) For patients to be enrolled with the primary indication of HABP, VABP, or VP, any of the following conditions:

(a) Diagnosis of ventilator-associated tracheobronchitis; or

(b) Inability to provide proper respiratory specimens for culture. Respiratory samples from expectorated or induced sputum should show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per 100 x field;

(9) For patients to be enrolled with the primary indication of cUTI or AP, any of the following urologic conditions:

(a) Likely to receive ongoing antibacterial drug prophylaxis after treatment of cUTI (e.g., patients with vesico-uretal reflux);

(b) Suspected or confirmed prostatitis;

(c) Requirement for bladder irrigation with antibiotics or for antibiotics to be administered directly via urinary catheter;

(d) Previous or planned cystectomy or ileal loop surgery;

(e) Uncomplicated urinary tract infection (e.g., female patients with urinary frequency, urgency, or pain or discomfort without systemic symptoms or signs of infection);

(f) Complete, permanent obstruction of the urinary tract;

(g) Suspected or confirmed perinephric or renal corticomedullary abscess;

(h) Polycystic kidney disease; or

(i) Any recent history of trauma to the pelvis or urinary tract;

(10) Pregnant or breastfeeding women;

(11) APACHE II score >30 and SOFA score >11 at the time of diagnosis of infection;

- Note: A qSOFA score must be calculated for all patients without an APACHE II score. Glasgow coma score for APACHE II calculation should be the best response prior to initiation of sedation/neuromuscular blockade, even if sedation has been in use for >24 hours.

(12) Receiving peritoneal dialysis;

(13) Requirement for temporary or acute onset treatment with antiseizure medication that, in the opinion of the Investigator, would prohibit the patient from complying with the protocol. Patients at risk of seizure or requiring prophylactic antiseizure medications during the study can be considered for enrollment at the discretion of the Investigator. Patients with a history of epilepsy or who are on stable treatment (i.e., no recurrent episodes in the past 30 days) and no history of imipenem-associated seizures may be considered for enrollment in the study;

(14) Requirement for continuing treatment with probenecid, methotrexate, ganciclovir, valproic acid, or divalproex sodium during the study;

(15) Evidence of significant hepatic disease or dysfunction, including known acute viral hepatitis, hepatic cirrhosis, hepatic failure, chronic ascites, or hepatic encephalopathy;

(16) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x upper limit of normal (ULN) AND total bilirubin >2 x ULN at Screening;

- Note: Patients with AST or ALT up to 5 x ULN are eligible if these elevations are acute and are documented as being directly related to the infectious process being treated.

(17) Requirement at the time of randomization for any reason, or likely to require during the patient's participation in the study (from randomization through the LFU Visit), for additional systemic gram-negative antimicrobial therapy.

(18) Requirement for inhaled antibiotics;

(19) Known history of human immunodeficiency virus infection and known recent CD4 count <200/mm3 within the last year or presence of significant immunologic disease or dysfunction, as determined by a current diagnosis of an Acquired Immune Deficiency Syndrome-defining illness;

(20) Presence of neutropenia (absolute neutrophil count <500/mm3) obtained from a local laboratory at Screening;

(21) A QT interval corrected using Fridericia's formula (QTcF) ≥480 msec;

(22) History of significant hypersensitivity or allergic reaction to any beta-lactam, any contraindication to the use of cilastatin based on local approved prescribing information (e.g., Summary of Medicinal Product Characteristics), any contraindication to the

excipients used in the respective formulations, or any contraindication to the use of beta-lactam antibiotics;

(23) Participation in a clinical study involving investigational medication or an investigational device within the last 30 days or 5 half-lives, whichever is longer, prior to Day 1;

(24) Any condition that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of the data or require greater than 14 days of treatment with antibiotics;

(25) Unable or unwilling, in the opinion of the Investigator, to comply with the protocol;

(26) Has previously received SUL-DUR in this study; or

(27) For Part A only, patients with an infection known to be resistant to colistin or polymyxin B (defined as MIC ≥4 mg/L by a nonagar-based method), with a known intolerance to colistin, or taking any drug that prevents them from receiving colistin.

#### 6.2.1.3. Statistical Analysis Plan, Study CS2514-2017-0004

**Primary Efficacy Endpoint**

The primary analysis of the primary efficacy endpoint was conducted among the subjects in the CRABC m-MITT population who did not withdraw consent from participation in the study prior to the assessment of survival status at Day 28. Subjects who did not withdraw consent but had missing survival status were considered as a death in the primary analysis. The 95% CI for the difference (SUL-DUL − colistin) in the mortality rate was calculated, using a continuity-corrected Z-statistic. NI was achieved if the upper limit of the 95% CI was less than the prespecified NI margin of 20%. If the NI was met, superiority would be evaluated and then concluded if the upper bound of the 95% CI was less than 0%.

Noninferiority Margin

The Applicant and the FDA agreed upon a 20% NI margin. The difference in mortality rates between subjects treated with adequate versus inadequate antibacterial therapy was initially estimated at the design stage to be 19% based on literature reviews for HABP/VABP (discussed in the FDA guidance Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment (May 2014)) and subjects with serious ABC infections. Further, due to the impact of the coronavirus disease 2019 (COVID-19) pandemic on enrollment, a 20% NI margin was used to reduce the sample size. Of note, SUL-DUR has met a much narrower NI margin (see Section 6.2.1.4).

**Secondary Efficacy Endpoints**

Similar to the primary analysis, the analyses of the secondary efficacy endpoints included subjects who did not withdraw consent prior to the assessment of survival status at Day 28. Treatment differences for the secondary endpoints were evaluated based on the 95% CIs using the same approach as the primary endpoint. Subjects with a missing value for a secondary

endpoint were considered as nonresponders. Additionally, a clinical failure occurring at an earlier time point was carried forward to the subsequent visits for the secondary endpoints involving clinical cure. The Applicant did not specify how to control multiplicity for testing the secondary efficacy endpoints.

### 6.2.1.4. Results of Analyses, Study CS2514-2017-0004

**Subject Disposition**

A total of 531 subjects were screened for Parts A and B (Table 8). A total of 324 (61%) subjects failed screening, mainly due to not meeting the inclusion/exclusion criteria. Part A randomized 181 subjects. However, two of the subjects were transferred to Part B due to having colistin-resistant ABC by local laboratory results, though the central laboratory results showed that one isolate was colistin-susceptible (Subject# (b) (6)) and the other was colistin-resistant (Subject# (b) (6)). Part B enrolled 26 subjects.

**Table 8. Subject Screening and Enrollment, StudyCS2514-2017-0004**

| Disposition Category | N (%) |
|---|---|
| Subjects screened for Parts A and B | 531 (100.0) |
| Screening failures for Parts A and B | 324 (61.0) |
| Reasons for screening failures | |
| Inclusion/exclusion criteria not met | 308 (58.0) |
| Withdrawal by subject | 11 (2.1) |
| Death | 3 (0.6) |
| Other | 2 (0.4) |
| Subjects randomized in Part A | 181 (34.1) |
| Subjects transferred to Part B | 2 (0.4) |
| Subjects enrolled in Part B | 26 (4.9) |

Source: Table 14.1.1.1 in the CS2514-2017-0004 Clinical Study Report and Statistical Reviewer.
Abbreviation: N, number of subjects

Among the 181 randomized subjects in Part A, approximately 61% completed the assigned treatment (Table 9). The two most common reasons for discontinuation of study treatment were AE (9%) and no growth of ABC (8%) in the SUL-DUR group and AE (11%) and treatment failure (6%) in the colistin group.

Approximately 72% of the randomized subjects completed the study. In both groups, the most common reason for discontinuation from the study was death, which occurred for 23 (16%) subjects in the SUL-DUR group and 21 (24%) subjects in the colistin group.

Approximately 71% of the randomized subjects were included in the CRABC m-MITT primary efficacy analysis population, with 64 subjects per group. The two most common reasons for exclusion from the CRABC m-MITT population were being BPP rapid test positive but culture negative (13% in the SUL-DUR group and 6% in the colistin group), and baseline ABC organism resistant to colistin (9% in the SUL-DUR group and 8% in the colistin group).

**Table 9. Subject Disposition, Study CS2514-2017-0004 Part A**

| Disposition Category | SUL/DUR N (%) | Colistin N (%) | Total N (%) |
|---|---|---|---|
| Randomized | 92 (100) | 89 (100) | 181 (100) |
| Not receiving treatment | 1 (1.1) | 3 (3.4) | 4 (2.2) |
| Death | 0 (0) | 1 (1.1) | 1 (0.6) |
| No growth of ABC | 0 (0) | 1 (1.1) | 1 (0.6) |
| Withdrawal by subject | 0 (0) | 1 (1.1) | 1 (0.6) |
| Did not meet eligibility criteria and randomized in error | 1 (1.1) | 0 (0) | 1 (0.6) |
| Receiving study treatment | 91 (98.9) | 86 (96.6) | 177 (97.8) |
| Discontinuation of study treatment | 24 (26.1) | 31 (34.8) | 55 (30.4) |
| AE | 8 (8.7) | 13 (14.6) | 21 (11.6) |
| Concurrent medical condition | 1 (1.1) | 0 (0) | 1 (0.6) |
| Death | 2 (2.2) | 4 (4.5) | 6 (3.3) |
| No growth of ABC | 7 (7.6) | 4 (4.5) | 11 (6.1) |
| Transferred to Part B | 1 (1.1) | 1 (1.1) | 2 (1.1) |
| Withdrawal by subject | 0 (0) | 2 (2.2) | 2 (1.1) |
| Other | | | |
| Treatment failure[3] | 1 (1.1) | 5 (5.6) | 6 (3.3) |
| ABC colistin resistant | 1 (1.1) | 1 (1.1) | 2 (1.1) |
| Complete resolution or significant recovery of indication and symptoms | 1 (1.1) | 0 (0) | 1 (0.6) |
| Safety concern (imipenem/cilastatin was insoluble) | 0 (0) | 1 (1.1) | 1 (0.6) |
| Site did not have more IMP | 1 (1.1) | 0 (0) | 1 (0.6) |
| PI decision | 1 (1.1) | 0 (0) | 1 (0.6) |
| Discontinuation from study | 23 (25.0) | 28 (31.5) | 51 (28.2) |
| Death | 15 (16.3) | 21 (23.6) | 36 (19.9) |
| Other | 8 (8.7) | 7 (7.9) | 15 (8.3) |
| AE | 0 (0) | 1 (1.1)[1] | 1 (0.6) |
| Prohibited concomitant medication | 1 (1.1) | 0 (0) | 1 (0.6) |
| Noncompliance with protocol | 1 (1.1) | 0 (0) | 1 (0.6) |
| No growth of ABC | 2 (2.2) | 1 (1.1) | 3 (1.7) |
| Withdrawal by subject | 2 (2.2)[2] | 3 (3.4) | 5 (2.8) |
| Transferred to Part B | 1 (1.1) | 1 (1.1) | 2 (1.1) |
| Other[4] | 1 (1.1) | 1 (1.1) | 2 (1.1) |
| Primary efficacy analysis population: CRABC m-MITT | 64 (69.6) | 64 (71.9) | 128 (70.7) |
| Reasons for exclusion from CRABC m-MITT population[5] | 28 (30.4) | 25 (28.1) | 53 (29.3) |
| BPP positive but culture negative | 12 (13.0) | 5 (5.6) | 17 (9.4) |
| Baseline ABC organism resistant to colistin | 8 (8.7) | 7 (7.9) | 15 (8.3) |
| Baseline ABC organism not carbapenem-resistant | 4 (4.3) | 4 (4.5) | 8 (4.4) |
| ABC isolates outside 72-hour window prior to randomization | 3 (3.3) | 0 (0.0) | 3 (1.7) |
| Baseline ABC organism resistant to SUL-DUR | 2 (2.2) | 4 (4.5) | 6 (3.3) |
| Not receiving treatment | 1 (1.1) | 3 (3.4) | 4 (2.2) |
| Transferred from Part A to Part B | 1 (1.1) | 1 (1.1) | 2 (1.1) |

Source: Table 10, Table 14.1.3.2 and Listing 16.2.1.1 in CS2514-2017-0004 Clinical Study Report and the Statistical Reviewer.
[1] Subject# (b) (6) died 5 days after discontinuation of study due to AE.
[2] Subject# died 3 days after discontinuation of study due to withdrawal by subject.
[3] The following are the detailed reasons for "Other" coded in DSTERM in DS.XPT: 1) researchers believe that treatment has failed; 2) the patient's treatment failed, and the investigator decided to stop the administration; 3) symptoms present at study entry have not significantly improved or completely resolved; 4) the researchers determined that the treatment failed; 5) treatment not effective; and 6) PI decision – clinical failure.
[4] Other reasons included: 1) no ABC on local cell culture; and 2) the subject was excluded after it was found that the cultures were drawn outside of the 48-hour window, did not meet inclusion criterion 4 and was randomized in error.
[5] A subject could have more one reason for exclusion from the CRABC m-MITT population.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; AE, adverse event; BPP, Biofire FilmArray 2.0 Pneumonia Panel; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; IMP, imipenem; m-MITT; microbiologically modified intent-to-treat; N, number of subjects; PI, principal investigator; SUL, sulbactam

**Demographics and Baseline Characteristics**

The demographics and baseline characteristics were reasonably balanced between the two treatment groups in the primary efficacy analysis population of the CRABC m-MITT (see Section 16.1). The mean age was 63 years. Most subjects were males (74%); the majority of the subjects were white (49%) or Asian (45%). Only one (0.8%) subject was enrolled in the United States; 40.6% of the subjects were enrolled in Europe, 26.6% in China, 18% in Asia–Pacific, and 14.1% in Latin America.

Regarding the infection type, 53% of subjects had VABP and 43% had HABP. Only three (2%) subjects had bacteremia and two (2%) subjects had VP. Hence, the study population was consistent with a study for a HABP/VABP indication. Approximately 71% of subjects had less severe disease at baseline defined as an APACHE II score of 10 to 19, SOFA score of 7 to 9, or qSOFA score of 2.

There were differences of ≥10% between the SUL-DUR and colistin arms for the following baseline characteristics: age, race, enrollment area and infection type. Of note, the differences were not nominally significant.

- Subjects older than 75 years: 19% (12/64) in the SUL-DUR group and 33% (21/64) in the colistin group.
- Asian subjects: 36% (23/64) in the SUL-DUR group and 53% (34/64) in the colistin group.
- White subjects: 56% (36/64) in the SUL-DUR group and 42% (27/64) in the colistin group.
- Subjects enrolled in Europe: 48% (31/64) in the SUL-DUR group and 33% (21/64) in the colistin group.
- Subjects infected with VABP: 59% (38/64) in the SUL-DUR group and 47% (30/64) in the colistin group.

**Primary and Secondary Efficacy Results**

Primary Efficacy Endpoint

The primary analysis was conducted in 125 subjects in the CRABC m-MITT population who did not withdraw consent before the assessment of survival status at Day 28. The results demonstrated that SUL-DUR was noninferior to colistin using a 20% NI margin (Table 10). The upper limit of the 95% CI for the difference in mortality rate was 3.5%, which was below 20%. It is noted that although the study was designed with a 20% NI margin, SUL-DUR would have met a narrower 10% NI margin. SUL-DUR did not show superiority to colistin because the 95% CI included 0%.

**Table 10. Results of Primary Analysis for 28-Day All-Cause Mortality in the CRABC m-MITT Population Excluding Subjects Who Withdrew Consent Prior to Assessment of Day 28 Survival Status, Study CS2514-2017-0004 Part A**

| | SUL/DUR (N=63) | Colistin (N=62) | Treatment Comparison | |
|---|---|---|---|---|
| Primary Endpoint | n (%) | n (%) | Difference (%) | 95% CI[1] |
| 28-day all-cause mortality | 12 (19.0) | 20 (32.3) | −13.2 | (−30.0, 3.5) |

Source: Table 17 in the CS2514-2017-0004 Clinical Study Report.
[1] The 95% CI was calculated using continuity-corrected Z-statistic.
Abbreviations: CI, confidence interval; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; m-MITT, microbiologically modified intent-to-treat; N, number of subjects; n, number of all-cause mortalities by Day 28; SUL, sulbactam

In the CRABC m-MITT population, three subjects withdrew consent before survival status at Day 28 was obtained and were excluded from the primary analysis, including one subject in the SUL-DUR group and two subjects in the colistin group. Among the subjects who did not withdraw consent, none had missing survival status. Additionally, one subject in the SUL-DUR group who discontinued from the study due to receipt of a prohibited medication on Day 14 and survived to Day 28 was considered as a survivor in the analysis.

To assess the impact of withdrawal of consent and prohibited medication use on the primary analysis, we conducted additional analyses. The most conservative imputation was that subjects who withdrew consent or received a prohibited medication were considered events in the SUL-DUR group and nonevents in the colistin group. This led to the same conclusion as the primary analysis (see Section 16.2).

**Secondary Efficacy Endpoints**

Twenty-Eight-Day All-Cause Mortality in the m-MITT and ITT Populations

The analyses of 28-day all-cause mortality in the m-MITT and ITT populations yielded results similar to those in the CRABC m-MITT population (Table 11). The upper limits of the 95% CIs for the treatment difference in mortality rate were below 10%.

One subject in the colistin group with missing survival status at Day 28 due to loss to follow-up was considered as a death in the analysis. Also, two subjects who transferred to Part B (one subject per group) were excluded from the analysis. Both subjects survived to Day 28. Similar to the CRABC m-MITT population, sensitivity analyses using the most conservative approach to impute the missing data were conducted in the m-MITT and ITT populations (including or excluding the two subjects transferred to Part B). The analyses resulted in the same conclusion (see Section 16.2). The results for mortality in the CE population were consistent with those in the CRABC m-MITT, m-MITT, and ITT populations.

**Table 11. Twenty-Eight-Day All-Cause Mortality in the m-MITT and ITT Populations Excluding Subjects Who Withdrew Consent Prior to Assessment of Day 28 Survival Status, Study CS2514-2017-0004 Part A**

| Analysis Population | SUL-DUR n/N (%) | Colistin n/N (%) | Treatment Comparison Difference (%) | 95% CI[1] |
|---|---|---|---|---|
| m-MITT | 15/76 (19.7) | 25/76 (32.9) | −13.2 | (−28.3, 2.0) |
| ITT | 19/90 (21.1) | 28/85 (32.9) | −11.8 | (−26.0, 2.4) |

Source: Table 14.2.1.2 in the CS2514-2017-0004 Clinical Study Report.
[1] The 95% CI was calculated using continuity-corrected Z-statistics.
Abbreviations: CI, confidence interval; DUR, durlobactam; ITT, intent-to-treat; m-MITT, microbiologically modified intent-to-treat; n, number of all-cause mortalities by Day 28; N, number of subjects in the analysis population excluding subjects transferred to Part B; SUL, sulbactam

Fourteen-Day All-Cause Mortality in the CRABC m-MITT and m-MITT Populations

SUL-DUR had lower 14-day all-cause mortality rates than colistin in the CRABC m-MITT and m-MITT populations (Table 12). The upper limits of the 95% CIs for the differences in mortality rates were <10%.

**Table 12. Fourteen-Day All-Cause Mortality in CRABC m-MITT and m-MITT Populations Excluding Subjects Who Withdrew Consent Prior to Assessment of Survival Status at Day 28, Study CS2514-2017-0004 Part A**

| Analysis Population | SUL/DUR n/N (%) | Colistin n/N (%) | Treatment Comparison Difference (%) | 95% CI[1] |
|---|---|---|---|---|
| CRABC m-MITT | 4/64 (6.3) | 12/63 (19.0) | −12.8 | (−25.7, 0.1) |
| m-MITT[2] | 6/77 (7.8) | 15/77 (19.5) | −11.7 | (−23.7, 0.3) |

Source: Table 22 in the CS2514-2017-0004 Clinical Study Report.
[1] The 95% CI was calculated using continuity-corrected Z-statistics.
[2] Two subjects transferred to Part B were excluded from the analysis.
Abbreviations: CI, confidence interval; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; m-MITT, microbiologically modified intent-to-treat; n, number of all-cause mortalities by Day 14; N, number of subjects in analysis population; SUL, sulbactam

Clinical Cure at EOT, TOC and LFU in the CRABC m-MITT Population

The clinical responses at EOT, TOC, and LFU in subjects in the CRABC m-MITT population who did not withdraw consent prior to assessment of survival status at Day 28 are displayed in Table 13. The clinical cure rates at EOT and TOC for SUL-DUR were nominally significantly higher than the rates for colistin as the lower bounds of the 95% CIs for the treatment differences in the rates exceeded 0% (Table 13). As previously noted, the Applicant did not specify how to control multiplicity for testing secondary efficacy endpoints. The findings in the m-MITT, CE, ME, and CRABC ME populations were consistent with those observed in the CRABC m-MITT population.

**Table 13. Clinical Response at EOT, TOC, and LFU in the CRABC m-MITT Population Excluding Subjects Who Withdrew Consent Prior to Assessment of Survival Status at Day 28, Study CS2514-2017-0004 Part A**

| Assessment Time Clinical Response Category | SUL-DUR (N=63) n (%) | Colistin (N=62) n (%) | Treatment Comparison Difference (%) | 95% CI[1] |
|---|---|---|---|---|
| EOT | | | | |
| Cure | 47 (74.6) | 28 (45.2) | 29.4 | (11.4, 47.4) |
| Failure | 14 (22.2) | 29 (46.8) | | |
| Indeterminate | 2 (3.2) | 5 (8.1) | | |

| Assessment Time Clinical Response Category | SUL-DUR (N=63) n (%) | Colistin (N=62) n (%) | Treatment Comparison Difference (%) | 95% CI[1] |
|---|---|---|---|---|
| TOC | | | | |
| Cure | 39 (61.9) | 25 (40.3) | 21.6 | (2.9, 40.3) |
| Failure | 20 (31.7) | 36 (58.1) | | |
| Indeterminate | 4 (6.3) | 1 (1.6) | | |
| LFU | | | | |
| Cure | 27 (42.9) | 19 (30.6) | 12.2 | (−6.2, 30.6) |
| Failure | 26 (41.3) | 40 (64.5) | | |
| Indeterminate | 10 (15.9) | 3 (4.8) | | |

Source: Table 20 in the CS2514-2017-0004 Clinical Study Report.
[1] The 95% CI was calculated using continuity-corrected Z-statistics.
Abbreviations: CI, confidence interval; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; EOT, end of therapy; LFU, late follow-up; m-MITT, microbiologically modified intent-to-treat; n, number of subjects in the category; N, number of subjects in analysis population; SUL, sulbactam; TOC, test of cure

Microbiologic Favorable Assessment in the CRABC m-MITT Population

A microbiological favorable assessment included microbiologic eradication and presumed eradication, where presumed eradication was defined as meeting clinical criteria for clinical cure if no culture was obtained. The proportion of subjects with microbiological favorable assessment was nominally significantly higher than that in the colistin group at the EOT and TOC visits as the lower limits of the 95% CIs for the treatment difference exceeded 0% (Table 14), although these CIs were not adjusted for multiple comparisons. The nominally significant treatment differences were driven by presumed eradication, which was based on clinical response.

The findings in the m-MITT and ME populations were consistent with those in the CRABC m-MITT population. In the CRABC ME population, the treatment difference for the microbiologic favorable assessment at TOC was nominally significantly higher at TOC in the SUL-DUR group. The treatment difference at EOT was not nominally significant, but the numerical trend in favor of SUL-DUR was maintained. Specifically, 83% (38/46) subjects in the SUL-DUR group achieved a microbiological favorable assessment compared to 64% (28/44) subjects in the colistin group, with a treatment difference of 19% (95% CI −1.2% to 39.1%).

**Table 14. Microbiologic Response at EOT, TOC, and LFU in the CRABC m-MITT Population Excluding Subjects Who Withdrew Consent Prior to Assessment of Survival Status at Day 28, Study CS2514-2017-0004 Part A**

| Assessment Time Microbiological Response Category | SUL/DUR (N=63) n (%) | Colistin (N=62) n (%) | Treatment Comparison Difference (%) | 95% CI[1] |
|---|---|---|---|---|
| EOT | | | | |
| Microbiological favorable assessment | 54 (85.7) | 38 (61.3) | 24.4 | (7.9, 40.9) |
| Eradication | 34 (54.0) | 35 (56.5) | | |
| Presumed eradication | 20 (31.7) | 3 (4.8) | | |
| Persistence | 6 (9.5) | 19 (30.6) | | |
| Presumed persistence | 3 (4.8) | 5 (8.1) | | |
| Indeterminate | 0 (0.0) | 0 (0.0) | | |
| TOC | | | | |
| Microbiological favorable assessment | 43 (68.3) | 26 (41.9) | 26.3 | (7.9, 44.7) |
| Eradication | 23 (36.5) | 22 (35.5) | | |
| Presumed eradication | 20 (31.7) | 4 (6.5) | | |

| Assessment Time<br>Microbiological Response Category | SUL/DUR (N=63)<br>n (%) | Colistin (N=62)<br>n (%) | Treatment Comparison<br>Difference (%) | <br>95% CI[1] |
|---|---|---|---|---|
| Persistence | 7 (11.1) | 28 (45.2) | | |
| Presumed persistence | 9 (14.3) | 8 (12.9) | | |
| Indeterminate | 4 (6.3) | 0 (0.0) | | |
| LFU | | | | |
| Microbiological favorable assessment | 30 (47.6) | 25 (40.3) | 7.3 | (−11.7, 26.3) |
| Eradication | 18 (28.6) | 21 (33.9) | | |
| Presumed eradication | 12 (19.0) | 4 (6.5) | | |
| Persistence | 3 (4.8) | 12 (19.4) | | |
| Presumed persistence | 14 (22.2) | 20 (32.3) | | |
| Recurrence | 6 (9.5) | 2 (3.2) | | |
| Indeterminate | 10 (15.9) | 3 (4.8) | | |

Source: Table 21 in the CS2514-2017-0004 Clinical Study Report.
[1] The 95% CI was calculated using continuity-corrected Z-statistics.
Abbreviations: CI, confidence interval; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; EOT, end of therapy; LFU, late follow-up; m-MITT, microbiologically modified intent-to-treat; n, number of subjects in the category; N, number of subjects in analysis population; SUL, sulbactam; TOC, test of cure

## Subgroup Analyses of the Primary Efficacy Endpoint

Results of subgroup analyses by demographic and some baseline characteristics for the primary endpoint are displayed in Table 15. The sample sizes for many subgroups were small, which limits the ability to identify trends with certainty. Additionally, the subgroup analyses did not adjust for multiplicity and the findings could be influenced by chance. The treatment effect of SUL-DUR versus colistin appeared to be consistent across subgroups. Note that the mortality rates in the SUL-DUR group were numerically higher than the rates in the colistin group in some subgroups, such as subjects aged 65 to 75 years, females, and subjects from the Asia–Pacific region except for Mainland China. However, the sample sizes in these subgroups were small. The subgroup results did not suggest that the study conclusions were driven by any random imbalances in baseline characteristics.

**Table 15. Subgroup Analyses of 28-Day All-Cause Mortality in the CRABC m-MITT Population Excluding Subjects Who Withdrew Consent Prior to Assessment of Survival Status at Day 28, Study CS2514-2017-0004 Part A**

| Demographic or Baseline Characteristic | SUL-DUR n/N (%) | Colistin n/N (%) | Treatment Comparison Difference (%) | 95% CI[1] |
|---|---|---|---|---|
| Age (years) | | | | |
| <65 | 3/36 (8.3) | 7/29 (24.1) | −15.8 | (−36.9, 5.3) |
| ≥65 | 9/27 (33.3) | 13/33 (39.4) | -6.1 | (−33.8, 21.7) |
| 65-75 | 6/16 (37.5) | 2/12 (16.7) | 20.8 | (−18.2, 59.9) |
| >75 | 3/11 (27.3) | 11/21 (52.4) | -25.1 | (-65.9, 15.7) |
| Gender | | | | |
| Male | 8/45 (17.8) | 18/47 (38.3) | −20.5 | (−40.5, −0.5) |
| Female | 4/18 (22.2) | 2/15 (13.3) | 8.9 | (−23.0, 40.8) |
| Race | | | | |
| Asian | 6/22 (27.3) | 9/33 (27.3) | 0.0 | (−27.8, 27.8) |
| White | 6/36 (16.7) | 9/26 (34.6) | −18.0 | (−43.2, 7.3) |
| Other[2] | 0/5 (0) | 2/3 (66.7) | −66.7 | (−100, 13.3) |

| Demographic or Baseline Characteristic | SUL-DUR n/N (%) | Colistin n/N (%) | Treatment Comparison Difference (%) | 95% CI[1] |
|---|---|---|---|---|
| Region | | | | |
| North America | 0/1 (0) | 0/0 | NE | NE |
| Europe | 6/31 (19.4) | 7/21 (33.3) | −14.0 | (−42.5, 14.5) |
| Latin America | 0/9 (0) | 4/8 (50.0) | −50.0 | (−96.5, −3.5) |
| Asia-Pacific except Mainland China | 4/7 (57.1) | 5/15 (33.3) | 23.8 | (−30.4, 78.0) |
| China | 2/15 (13.3) | 4/18 (22.2) | −8.9 | (−40.8, 23.0) |
| North America / Europe | 6/32 (18.8) | 7/21 (33.3) | −14.6 | (−42.8, 13.6) |
| Latin America / Asia | 6/31 (19.4) | 13/41 (31.7) | −12.4 | (−35.1, 10.4) |
| China | 2/15 (13.3) | 4/18 (22.2) | -8.9 | (−40.8, 23.0) |
| Rest of the world | 10/48 (20.8) | 16/44 (36.4) | −15.5 | (−36.0, 4.9) |
| Baseline infection type | | | | |
| Bacteremia | 2/2 (100) | 0/1 (0) | 100.0 | (25.0, 100) |
| HABP | 5/24 (20.8) | 10/30 (33.3) | −12.5 | (−39.7, 14.7) |
| VABP | 5/37 (13.5) | 9/29 (31.0) | −17.5 | (−40.7, 5.7) |
| VP | 0/0 | 1/2 (50.0) | NE | NE |
| Severity of illness | | | | |
| APACHE II (score 10 to 19)/ SOFA (score 7 to 9)/qSOFA (score 2) | 9/47 (19.1) | 13/42 (31.0) | −11.8 | (−32.0, 8.4) |
| APACHE II (score 20 to 30)/ SOFA (score ≥10)/qSOFA (score 3) | 3/15 (20.0) | 7/20 (35.0) | −15.0 | (−49.9, 19.9) |
| BMI (kg/m$^2$) | | | | |
| <25 | 8/32 (25.0) | 13/40 (32.5) | −7.5 | (−31.2, 16.2) |
| 25 to <30 | 1/22 (4.5) | 6/18 (33.3) | −28.8 | (−57.3, −0.3) |
| 30 to <35 | 2/7 (28.6) | 0/2 (0) | 28.6 | (−37.0, 94.2) |
| ≥35 | 1/2 (50.0) | 1/2 (50.0) | 0.0 | (−100, 100) |
| Charlson comorbidity index | | | | |
| <3 | 2/21 (9.5) | 4/19 (21.1) | −11.5 | (−38.8, 15.7) |
| ≥3 | 10/42 (23.8) | 16/43 (37.2) | −13.4 | (−35.1, 8.3) |
| Creatinine clearance group (mL/min) | | | | |
| <30 | 2/6 (33.3) | 2/4 (50.0) | −16.7 | (−99.3, 66.0) |
| 30 to <60 | 5/9 (55.6) | 5/12 (41.7) | 13.9 | (−38.6, 66.4) |
| 60 to <90 | 4/9 (44.4) | 1/9 (11.1) | 33.3 | (−16.2, 82.9) |
| ≥90 | 1/39 (2.6) | 12/37 (32.4) | −29.9 | (−48.4, −11.4) |
| Duration of ICU stay at baseline (days) | | | | |
| No ICU stay | 4/21 (19.0) | 3/19 (15.8) | 3.3 | (−25.2, 31.7) |
| <5 | 1/2 (50.0) | 0/3 (0) | 50.0 | (−61.0, 100.0) |
| 5 to 14 | 4/23 (17.4) | 10/24 (41.6) | −24.3 | (−53.6, 5.1) |
| >14 | 3/17 (17.6) | 7/16 (43.8) | −26.1 | (−62.5, 10.3) |
| HABP/VABP/VP identified as positive ABC by BPP molecular methodology | | | | |
| BPP | 7/41 (17.1) | 14/41 (34.1) | −17.1 | (−38.0, 3.9) |
| Other | 3/20 (15.0) | 6/20 (30.0) | −15.0 | (−45.5, 15.5) |
| Monomicrobial ABC infection vs. polymicrobial infection | | | | |
| Monomicrobial | 6/36 (16.7) | 15/43 (34.9) | −18.2 | (−39.5, 3.1) |
| Polymicrobial | 6/27 (22.2) | 5/19 (26.3) | −4.1 | (−33.8, 25.6) |

| Demographic or Baseline Characteristic | SUL-DUR n/N (%) | Colistin n/N (%) | Treatment Comparison Difference (%) | 95% CI[1] |
|---|---|---|---|---|
| Bacteremia subjects negative blood culture at randomization | | | | |
| Negative blood culture at randomization | 2/2 (100%) | 0/1 (0%) | 100 | (25.0, 100.0) |
| Other | 0/0 | 0/0 | NE | NE |
| Received antibiotics within 24 hours prior to the first dose of study drug vs. not received | | | | |
| Yes | 11/53 (20.8) | 18/58 (31.0) | −10.3 | (−28.2, 7.7) |
| No | 1/10 (10.0) | 2/4 (50.0) | −40.0 | (−100.0, 29.9) |
| Received antibiotics prior to first dose of study drug | | | | |
| Yes | 11/61 (18.0) | 20/62 (32.3) | −14.2 | (−31.0, 2.5) |
| No | 1/2 (50.0) | 0/0 | NE | NE |
| Septic shock status at baseline | | | | |
| Yes | 2/6 (33.3) | 4/12 (33.3) | 0.0 | (−58.7, 58.7) |
| No | 10/57 (17.5) | 16/50 (32.0) | −14.5 | (−32.6, 3.7) |
| Mechanical ventilation status at baseline | | | | |
| Yes | 8/46 (17.4) | 17/48 (35.4) | −18.0 | (−37.6, 1.5) |
| No | 4/17 (23.5) | 3/14 (21.4) | 2.1 | (−33.9, 38.1) |
| COVID-19 status | | | | |
| Positive | 0/2 (0.0) | 1/2 (50.0) | −50.0 | (−100, 69.3) |
| Negative | 2/10 (20.0%) | 0/7 (0.0) | 20.0 | (−16.9, 56.9) |

Source: Tables 14.2.8.1 to 14.2.8.9, 14.2.8.12 to 14.2.8.19 in the CS2514-2017-0004 Clinical Study Report and the statistical reviewer.
[1] The 95% CI was calculated using continuity-corrected Z-statistics.
[2] Other included American Indian or Alaska Native, black or African American, other, and not reported.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; BPP, Biofire FilmArray 2.0 Pneumonia Panel; CI, confidence interval; COVID-19, coronavirus disease 2019; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; m-MITT; microbiologically modified intent-to-treat; n, number of all-cause mortalities by Day 28; N, number of subjects in the analysis; NE, not evaluable; qSOFA, quick Sequential Organ Failure Assessment; SOFA, Sequential Organ Failure Assessment; SUL, su bactam; VABP, ventilator-associated bacterial pneumonia; VP, ventilator pneumonia

# 6.3. Key Efficacy Review Issues

## 6.3.1. Do the Clinical Data in Phase 3 Study CS2514-2017-0004 Part A Support Labeling for Patients With Bacteremia Caused by ABC or Multidrug-Resistant ABC Pathogens?

**Issue**

The Applicant sought a broad indication for the treatment of infections due to ABC complex including multidrug-resistant and carbapenem resistant strains. However, clinical data in the phase 3 study CS2514-2017-0004 do not support this broad indication.

**Background**

Part A of study CS2514-2017-0004 was an NI study to compare SUL-DUR versus colistin for the treatment of subjects with ABC HABP, VABP, VP or bacteremia in terms of reducing 28-day all-cause mortality. Note there was no apparent difference between VABP and VP from a clinical perspective. In Part A, there were few subjects with bacteremia. Additionally, all subjects in the CRABC m-MITT primary analysis population had infections due to ABC complex from carbapenem-resistant strains rather than general types of multidrug-resistant strains. Hence, there were no clinical data to support the proposed broad indication.

**Assessment**

The CRABC m-MITT primary analysis population in Part A only included subjects with infections due to ABC complex with carbapenem-resistant strains. The study did not attempt to enroll subjects with other types of multidrug-resistant infections. Furthermore, among 128 subjects in the CRABC m-MITT population, only three (2%) subjects had bacteremia.

**Conclusion**

In conclusion, data in Part A of study CS2514-2017-0004 did not support the indication including subjects with bacteremia or subjects with infections due to ABC complex due to general multidrug-resistant strains.

# 7. Safety (Risk and Risk Management)

## 7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No specific or serious safety concern was identified based on nonclinical data. Pivotal nonclinical studies were conducted in rats, mice and dogs.

There were no safety signals observed in safety pharmacology studies. Secondary pharmacology data did not reveal any potent activity among 192 pharmacology receptors/enzymes evaluated.

Plasma levels of durlobactam and sulbactam in rats were generally dose proportional after intravenous dosing. Exposure in males and females was comparable and there was minimal accumulation with multiple dosing. In rats, the highest concentrations of durlobactam were observed in those tissues associated with renal excretion of the dose, such as the bladder and the kidneys. Durlobactam metabolism appears to involve hydrolysis of the diazabicyclooctenone core and subsequent decarboxylation in the plasma. In rats dosed with radiolabeled durlobactam, 87.3% of the dose was excreted in the urine, 3.10% in the feces, 5.55% in the cage wash, 0.49% in the carcass, and 0.02% expired in the air. In rats, over 52% of the excreted dose in urine was intact durlobactam. Elimination half-life was less than 1 hour in both rats and dogs. Few details of in vivo nonclinical pharmacokinetics of sulbactam were provided.

Repeated intravenous dosing of sulbactam-durlobactam in rats for 28 days resulted in reversible perivascular inflammation and thrombus at the injection site, as well as mild or marginal changes

in liver, spleen and kidney weights. Transient findings, including decreased food consumption and body weight gain, decreases in mean erythrocytes, hemoglobin, hematocrit, minimal/mild hepatocellular hypertrophy or degeneration, were of questionable toxicological significance or resolved after the cessation of dosing. No adverse findings persisted at the end of a 4-week recovery period. In an embryofetal development study in mice, increased incidence of skeletal variations (unossified calcaneum of the hindlimb and asymmetrical ossification of the sternebrae and supernumerary ribs) were observed at 800 and/or 1600 mg/kg, equivalent to 2- and 4 times the maximum recommended human dose based on area under the concentration-time curve (AUC) comparisons. These findings will be reported in the Physician's Prescribing Information.

An impurity, (b) (4) demonstrated a structural alert for potential mutagenicity. The Applicant evaluated the mutagenic potential of (b) (4) in a bacterial reverse mutation assay but (b) (4) displayed cytotoxicity with all tester strains at (b) (4) µg/plate dose level, except for tester strain WP2 uvrA pKM101 which displayed cytotoxicity at the (b) (4) µg/plate dose levels without metabolic activation. Due to this dose-limiting cytotoxicity at (b) (4) µg/plate dose level, the mutagenicity potential of higher concentrations of (b) (4) were not adequately evaluated. The Applicant conducted a Pig-A assay using the drug/impurity combination, but FDA indicated that this would not be a valid evaluation of the impurity to address a positive QSAR/Ames signal. Impurities should be evaluated in isolation up to an appropriate limit dose. This approach has been confirmed by Agency experts. Conducting a mouse lymphoma toxicokinetic assay or hypoxanthine phosphoribosyl transferase forward mutation assay will determine the mutagenic potential of (b) (4) These data will allow us to determine the genotoxic potential of (b) (4). A postmarketing requirement has been made for the Applicant to conduct such a test of (b) (4) The Applicant should also ensure that any relevant impurities are eventually identified and qualified as appropriate consistent with ICH Guidelines Q3A, Q3B or M7.

## 7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Sulbactam sodium is a derivative of the basic penicillin nucleus. Durlobactam is a β-lactamase inhibitor. The label for UNASYN (ampicillin-sulbactam) (Pfizer 1986), which is the reference drug listed by the Applicant describes safety warnings of hypersensitivity, hepatotoxicity, severe cutaneous reactions and *C. difficile*-associated diarrhea. Hypersensitivity and *C. difficile* colitis have been observed in the pivotal phase 3 study in the SUL-DUR group. Of note, the safety database for the study is limited, with less than 200 subjects in the safety database.

**Adverse Events of Special Interest**

Adverse events of special interest monitored by the Applicant during the clinical development program included drug-related hepatic disorders, hypersensitivity, acute renal failure, infective pneumonia, sepsis, pseudomembranous colitis, and convulsions.

Hepatobiliary Disorders

See Section 7.6.6.

Hypersensitivity

Hypersensitivity reactions were more frequently in the sulbactam-durlobactam group compared with the colistin group (16.5% versus 11.5%), which would be expected with penicillin derivatives. The most common hypersensitivity reaction related to study drug was rash in both groups (3.4% in the sulbactam durlobactam group and 2.3% in the colistin group). These reactions were mild to moderate in nature and resolved with treatment discontinuation. One subject in the sulbactam-durlobactam group discontinued treatment on day 9 due to anaphylactic shock and whole-body rash followed by transient hypotension and oliguria, which resolved after treatment with methylprednisone. One subject in the sulbactam-durlobactam group in the phase 2 study had urticaria, which led to study drug discontinuation.

Other Adverse Events of Special Interest

*C. difficile* colitis and antibiotic-associated colitis were each reported in one subject (0.8%) in the sulbactam-durlobactam group compared with three subjects (3.5%) and two subjects (2.3%), respectively, in the colistin group.

The incidence of seizure was higher in the colistin group (six subjects, 7.0%) compared with the sulbactam-durlobactam group (one subject, 0.8%). The subject in the SUL-DUR group experienced a tonic clonic convulsion on day 5 of study treatment. The subject did not have a history of seizures; however as noted previously the subject was receiving background imipenem-cilastatin, which is known to be associated with seizures. The episode resolved after diazepam treatment; the investigator considered the event related to SUL-DUR and unrelated to imipenem/cilastatin. The dose of SUL-DUR was reduced from 1.5 g/1.5 g to 1 g/1 g and the dose of imipenem/cilastatin was left unchanged at 1 g/1 g.

One subject had transient QT prolongation on SUL-DUR thought to be related to the study drug (Fridericia-corrected QT interval 462 ms). No specific safety signal for cardiac arrythmia was identified.

## 7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Durlobactam and sulbactam-durlobactam have not yet been approved or marketed in any country at this time.

## 7.4. FDA Approach to the Safety Review

Data from the single pivotal phase 3 study (ATTACK, study CS2514-2017-0004) is the focus of the safety review. The safety population includes subjects not eligible for the primary efficacy population. Data from a phase 2 study in subjects with cUTI are also analyzed but not pooled with the phase 3 study given differences in study design, treatment duration, and drug dosage in some subjects for safety assessments. In addition, the safety of SUL-DUR in subjects who received SUL-DUR under an expanded access program was reviewed. The safety data on DUR from six phase 1 studies in 123 healthy adult subjects receiving single doses ranging from 0.25 to

8 g and multiple doses ranging from 0.25 to 2 g administered intravenously every 6 hours for 8 days were also considered. Also, the extensive experience with ampicillin-SUL was considered in the evaluation of the safety of SUL-DUR.

Additional details on the safety analyses are presented in Section 17.

## 7.5. Adequacy of the Clinical Safety Database

The safety database consists of 158 subjects who received SUL-DUR at the proposed dose and duration including a phase 2 study in subjects with cUTI and a phase 3 study in subjects with HABP/VABP caused by *Acinetobacter baumannii-calcoaceticus* complex. The subjects in phase 2 and 3 trials also received background imipenem therapy. In addition, 12 subjects received SUL-DUR under the expanded access program. These subjects had *A. baumanii* infections with limited treatment options and did not otherwise qualify for participation in ongoing clinical studies.

Safety of DUR was also evaluated in six phase 1 studies in 123 healthy adult subjects receiving single doses ranging from 0.25 to 8 g and multiple doses ranging from 0.25 to 2 g administered intravenously q6h for 8 days.

Table 16 presents demographic characteristics of the safety population in the phase 3 trial. A majority of subjects in both arms were male (74%); about 53% in the SUL-DUR group and 45% in the colistin group were White. The mean age was 64 years in the SUL-DUR group and 67 years in the colistin group. The majority of subjects were enrolled from Europe. Some degree of renal impairment at baseline (creatinine clearance [CLcr] <90 mL/min) was present in 40% of subjects in the SUL-DUR and 44.2% of subjects in the placebo/colistin group. About 70% of subjects had an intensive care unit (ICU) stay.

**Table 16. Demographics of the Safety Population, Study CS2514-2017-0004**

| Characteristic | SUL-DUR N=91 | Colistin N=86 | SUL-DUR N=28 |
|---|---|---|---|
| Sex, n (%) | | | |
| Female | 24 (26.4) | 22 (25.6) | 7 (25.0) |
| Male | 67 (73.6) | 64 (74.4) | 21 (75.0) |
| Age, years | | | |
| Mean (SD) | 63.7 (15.1) | 66.5 (17.3) | 56.2 (16.3) |
| Median (min, max) | 65 (25, 91) | 68.5 (19, 98) | 59 (18, 80) |
| Age group, years, n (%) | | | |
| 18 to 64 years | 42 (46.2) | 37 (43.0) | 19 (67.9) |
| 65 to 75 years | 32 (35.2) | 18 (20.9) | 5 (17.9) |
| >75 years | 17 (18.7) | 31 (36.0) | 4 (14.3) |
| Age group ≥65, years, n (%) | | | |
| ≥65 | 49 (53.8) | 49 (57.0) | 9 (32.1) |
| Race, n (%) | | | |
| American Indian or Alaska Native | 5 (5.5) | 2 (2.3) | 0 |
| Asian | 33 (36.3) | 44 (51.2) | 4 (14.3) |
| Black or African American | 0 | 1 (1.2) | 0 |
| Other | 5 (5.5) | 0 | 0 |
| White | 48 (52.7) | 39 (45.3) | 24 (85.7) |

| Characteristic | SUL-DUR N=91 | Colistin N=86 | SUL-DUR N=28 |
|---|---|---|---|
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 15 (16.5) | 9 (10.5) | 1 (3.6) |
| Not Hispanic or Latino | 75 (82.4) | 77 (89.5) | 27 (96.4) |
| Not reported | 1 (1.1) | 0 | 0 |
| Country of participation, n (%) | | | |
| China | 21 (23.1) | 23 (26.7) | 3 (10.7) |
| Greece | 3 (3.3) | 2 (2.3) | 4 (14.3) |
| Hungary | 4 (4.4) | 2 (2.3) | 11 (39.3) |
| Israel | 6 (6.6) | 6 (7.0) | 3 (10.7) |
| Peru | 10 (11.0) | 2 (2.3) | 0 |
| Russia | 21 (23.1) | 14 (16.3) | 1 (3.6) |
| Taiwan | 10 (11.0) | 12 (14.0) | 0 |
| Others | 16 (17.6) | 25 (29.1) | 6 (21.4) |

Source: FDA Analysis
Abbreviations: DUR, durlobactam; max, maximum; min, minimum; N, number of subjects; SD, standard deviation; SUL, sulbactam

In the phase 3 study the median duration of SUL-DUR use was 8 days in Part A and 10.5 days in Part B.

The limitations of the safety assessments of SUL-DUR are related to a small size of the safety database with less than 200 subjects exposed to the proposed dose and duration. There was total 172 subjects who received SUL-DUR in the integrated phase 2 and 3 studies (53 subjects in phase 2, 91 subjects in part A, 28 subjects in part B). In general, a safety database for a drug addressing an unmet need under a flexible development program should include approximately 300 subjects at the dose and duration of therapy proposed for marketing (May 2022).

Of note, the study drugs were not masked for logistical reasons and the treating physician and other health care providers were not blinded in the study except for the outcome assessor. The safety population consisted of predominantly white and Asian subjects, mostly males (70%).

Disposition of the subjects in the safety population in Part A is presented in Table 17. The majority of subjects completed the phase 3 study. In both treatment groups, the most common reason for early study discontinuation was death and the most common reason for discontinuation of study drug was due to an AE. In the phase 2 study, 53 subjects were included in the sulbactam-durlobactam group. Two (3.8%) subjects in the SUL-DUR group discontinued the study drug because of AEs; one of these subjects also withdrew from the study early because of the AE.

**Table 17. Disposition of Subjects (Part A), Safety Population, Study CS2514-2017-0004**

| Reason for Treatment Discontinuation, n% | SUL-DUR N=91 | Colistin N=86 |
|---|---|---|
| Abnormal liver event | 0 | 1 (1) |
| Adverse event | 8 (9) | 10 (12) |
| Concurrent medical condition | 1 (1) | 0 |
| Death | 2 (2) | 4 (5) |
| No growth of ABC | 7 (8) | 4 (5) |
| Other | 5 (6) | 7 (8) |
| Renal toxicity | 0 | 2 (2) |
| Transferred to Part B | 1 (1) | 1 (1) |
| Withdrawal by subject | 0 | 2 (2) |

Source: FDA Analysis
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; N, number of subjects; n, number of subjects in category; SUL, su bactam

Table 18 provides the duration of exposure in the phase 3 study safety population.

**Table 18. Duration of Exposure, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Parameter | SUL-DUR N=91 n (%) | Colistin N=86 n (%) | SUL-DUR N=28 n (%) |
| Duration of treatment, days | | | |
| Mean (SD) | 8.5 (3.6) | 7.6 (4) | 9.7 (4.1) |
| Median (Q1, Q3) | 8 (7, 10.5) | 7 (5, 11) | 10.5 (7, 14) |
| Min, max | 1, 14 | 1, 14 | 1, 15 |
| Total exposure (person years) | 2 | 2 | 1 |
| Patients treated, by duration, n (%) | | | |
| <2 days | 3 (3.3) | 6 (7.0) | 1 (3.6) |
| ≥2 to <4 days | 6 (6.6) | 8 (9.3) | 1 (3.6) |
| ≥4 to <6 days | 7 (7.7) | 13 (15.1) | 4 (14.3) |
| ≥6 to <8 days | 27 (29.7) | 25 (29.1) | 3 (10.7) |
| ≥8 to <10 days | 11 (12.1) | 7 (8.1) | 4 (14.3) |
| ≥10 to <12 days | 18 (19.8) | 11 (12.8) | 3 (10.7) |
| ≥12 to <14 days | 3 (3.3) | 2 (2.3) | 4 (14.3) |
| ≥14 to <16 days | 16 (17.6) | 14 (16.3) | 8 (28.6) |
| ≥16 days | 0 | 0 | 0 |

Source: FDA Analysis.
Abbreviations: DUR, durlobactam; max, maximum; min, minimum; N, number of subjects; n, number of subjects in category; Q, quartile; SD, standard deviation; SUL, sulbactam

## 7.6. Safety Results

The overall incidence of treatment-emergent adverse events (TEAEs) was 87.9% in the SUL-DUR group and 94.2% in the colistin group, see Table 19. There were lower incidences of serious adverse events (39.6% versus 48.8%) and drug-related TEAEs (13.2% versus 30.2%) in the SUL-DUR group compared to colistin. There was one subject with a related TEAE which led to treatment discontinuation with SUL-DUR (anaphylaxis) and four subjects with drug-related TEAEs which led to treatment discontinuation with colistin (rash, seizure, acute kidney injury (n=2)). Moderate and severe TEAEs were less frequent in the SUL-DUR group compared to colistin.

In Part B, nine (32.1%) subjects had a serious adverse event (SAE) and of them, one subject had a drug-related SAE. The drug-related TEAEs experienced by subjects included increased transaminases, proteinuria, nausea, and neutropenia.

**Table 19. Overview of Adverse Events, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Event Category | SUL-DUR N=91 n (%) | Colistin N=86 n (%) | SUL-DUR N=28 n (%) |
| TEAEs | 80 (88) | 81 (94) | 24 (86) |
| Treatment related TEAE | 12 (13) | 26 (30) | 3 (11) |
| SAEs | 36 (40) | 42 (49) | 9 (32) |
| SAEs with fatal outcome | 24 (26) | 30 (35) | 4 (14) |
| Treatment related SAEs | 1 (11) | 2 (2) | 1 (4) |
| TEAE leading to permanent discontinuation of study drug | 10 (11) | 14 (16) | 4 (14) |
| Severe | 39 (43) | 44 (51) | 9 (32) |
| Moderate | 15 (17) | 21 (24) | 5 (18) |
| Mild | 26 (29) | 16 (19) | 10 (36) |

Source: FDA Analysis
Note: Treatment-emergent adverse events defined as an AE that starts, or a preexisting condition that worsens, on or after the start (based on date and time) of the first dose of study drug.
Note: Duration is 7 days, with extension up to 14 days where clinically indicated.
Note: Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Note: Severity as assessed by the investigator.
Abbreviations: AE, adverse event; DUR, durlobactam; N, number of patients in treatment group; n, number of patients with at least one event; SAE, serious adverse event; SUL, sulbactam; TEAE, treatment-emergent adverse events

**Safety in Subjects on Continuous Renal Replacement Therapy**

In the phase 3 study, 10 subjects received continuous renal replacement therapy. Of them, 7 (across Part A and Part B) received SUL-DUR at 1.5 g SUL/1.5 g DUR every 6 hours while on continuous renal replacement therapy and their dosing regimen was adjusted as their renal function changed over the course of treatment. No drug-related TEAEs were noted in this group of subjects.

Additional Considerations for Safety Assessments

Sulbactam has been approved in combination with ampicillin since 1986. The labeled dose of sulbactam in combination with ampicillin is up to 4 g over 24 hours as compared to up to 6 g over 24 hours for sulbactam in combination with durlobactam. Of note, in the treatment of *A. baumannii* infections sulbactam has been used up to 9 g over 24 hours (Betrosian et al. 2007; Assimakopoulos et al. 2019; Liu et al. 2021).

### 7.6.1. Deaths

No deaths were reported in the phase 1 or phase 2 studies.

In the randomized Part A of the study, there was a lower incidence of deaths in the SUL-DUR group [21% (19/91)] versus the colistin group [29% (25/86)] within 28 days of therapy. Both groups had an equal number of deaths (five in each arm) that occurred after 28 days. Overall 24

(26%) and 30 (35%) deaths were reported in Part A in the SUL-DUR and colistin groups, respectively.

The most commonly reported TEAEs leading to death through Day 28 were septic shock and sepsis in the SUL-DUR group, and septic shock, sepsis, pneumonia, and *Acinetobacter* sepsis in the colistin group. No deaths were assessed as related to study drug in the SUL-DUR group. Out of the deaths beyond 28 days, there was one subject each in the SUL-DUR and colistin group who had a failure of therapy for the index infection.

There were four deaths (14%) in the nonrandomized Part B of the study, with one death due to multiorgan failure beyond 28 days. Subject (b) (6) in Part B of the study died on treatment from either the index infection or COVID-19. The majority of the deaths, 22 in the SUL-DUR group and 25 in the colistin group occurred by Day 28. On treatment deaths, were numerically low compared to all deaths, see Table 20.

**Table 20. Timing of Deaths in Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Deaths | SUL-DUR (N=91) | Colistin (N=86) | SUL-DUR (N=28) |
| All deaths | 24 (26.4%) | 30 (34.9%) | 4(14%) |
| On-treatment deaths | 5 (5.5%) | 4 (4.7%) | 1(3.6%) |

Source: FDA Analysis
Abbreviations: DUR, durlobactam; N, number of subjects; SUL, sulbactam

Table 21 summarizes the causes of death.

**Table 21. Deaths, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Preferred Term | SUL-DUR N=91 n (%) | Colistin N=86 n (%) | SUL-DUR N=28 n (%) |
| Any AE leading to death | 24 (26.4) | 30 (35) | 4 (14) |
| Respiratory failure | 2 (2.2) | 0 | 0 |
| Acute myocardial infarction | 1 (1.1) | 0 | 0 |
| Alcohol poisoning | 1 (1.1) | 0 | 0 |
| Arteriosclerosis coronary artery | 1 (1.1) | 0 | 0 |
| Encephalitis | 1 (1.1) | 0 | 0 |
| Gastrointestinal hemorrhage | 1 (1.1) | 0 | 0 |
| Hemorrhage intracranial | 1 (1.1) | 0 | 0 |
| Intra-abdominal hemorrhage | 1 (1.1) | 0 | 0 |
| Peripheral artery thrombosis | 1 (1.1) | 0 | 0 |
| Shock | 1 (1.1) | 0 | 0 |
| Shock hemorrhagic | 1 (1.1) | 0 | 0 |
| Thrombosis mesenteric vessel | 1 (1.1) | 0 | 0 |
| Brain oedema | 2 (2.2) | 1 (1) | 0 |
| Pleural effusion | 0 | 0 | 1 (4) |
| Ventricular tachycardia | 0 | 0 | 1 (4) |
| Cerebral hemorrhage | 1 (1) | 1 (1) | 0 |
| Malignant neoplasm progression | 1 (1) | 1 (1) | 0 |
| Sepsis | 2 (2) | 2 (2) | 0 |
| Septic shock | 5 (6) | 5 (6) | 0 |

| | Part A | | Part B |
|---|---|---|---|
| Acute respiratory failure | 0 | 1 (1) | 0 |
| Bacterial sepsis | 0 | 1 (1) | 0 |
| Cerebrovascular accident | 0 | 1 (1) | 0 |
| Disease progression | 0 | 1 (1) | 0 |
| Intestinal ischemia | 0 | 1 (1) | 0 |
| Ischemic stroke | 0 | 1 (1) | 0 |
| Lung infection | 0 | 1 (1) | 0 |
| Pneumonia pseudomonal | 0 | 1 (1) | 0 |
| Pseudomonas infection | 0 | 1 (1) | 0 |
| Weaning failure | 0 | 1 (1) | 0 |
| Acute respiratory distress syndrome | 1 (1) | 2 (2) | 0 |
| Cardiac arrest | 1 (1) | 2 (2) | 0 |
| Pulmonary embolism | 0 | 2 (2) | 0 |
| Multiple organ dysfunction syndrome | 1 (1) | 4 (5) | 2 (7) |
| Pneumonia | 0 | 4 (5) | 0 |

Source: FDA Analysis
Note: Treatment-emergent adverse events defined as an AE that starts, or a preexisting condition that worsens, on or after the start (based on date and time) of the first dose of study drug.
Note: Duration is 7 days, with extension up to 14 days where clinically indicated.
Note: For patient-level data, see the table "List of Adverse Events Leading to Death…"
Abbreviations: AE, adverse event; DUR, durlobactam; N, number of patients in treatment arm; n, number of patients with adverse event; SUL, sulbactam

A detailed review of each of the deaths was conducted with a focus on demographic and baseline factors, potential for lack of efficacy, specific pathogens, TEAE imbalances, and the timing of events. Subjects who died were considered failures. The mortality rate for subjects on SUL-DUR was lower than for subjects on colistin. Deaths appeared to be related to the underlying comorbidities, complications in critically ill subjects or progression of the presenting pneumonia without apparent biologic plausibility or causal assignment to SUL-DUR treatment. The overall mortality rate observed in this study was similar to the mortality rates of 23% to 25% observed in other HABP/VABP trials (May 2014). In a systematic review of over 2500 patients with *Acinetobacter* infections from 16 observational studies, the overall mortality rate was 33%. Infections due to resistant strains were associated with a higher risk of mortality as compared to those due to susceptible strains (Lemos et al. 2014).

### 7.6.2. Serious Treatment-Emergent Adverse Events

Most of the SAEs were related to septic shock. The incidence of SAEs that were considered by the investigators to be related to study drug was lower in the SUL-DUR group (14%) as compared to colistin group (24%). The incidence of all SAEs was also lower in the SUL-DUR group (40%) than in colistin group (49%). SAEs that were higher (>1% difference) in the SUL-DUR group versus the comparator group were related to hepatobiliary, vascular, respiratory, thoracic and mediastinal disorders, Table 22.

One subject in the SUL-DUR group had a drug-related SAE (anaphylactic reaction). There were two subjects with drug-related SAEs in the colistin group.

In Part B, nine (32.1%) subjects had an SAE, and of them, one subject had a drug-related SAE. Four (14.3%) subjects experienced SAEs that led to death.

**Table 22. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| **System Organ Class<br>Preferred Term** | **SUL-DUR<br>N=91<br>n (%)** | **Colistin<br>N=86<br>n (%)** | **SUL-DUR<br>N=28<br>n (%)** |
| Any SAE | 36 (40) | 42 (49) | 9 (32) |
| Blood and lymphatic system disorders (SOC) | 0 | 3 (3.5) | 1 (4) |
| Neutropenia | 0 | 0 | 1 (4) |
| Agranulocytosis | 0 | 1 (1) | 0 |
| Anemia | 0 | 2 (2) | 0 |
| Cardiac disorders (SOC) | 5 (6) | 5 (6) | 2 (7) |
| Acute myocardial infarction | 1 (1) | 0 | 0 |
| Arteriosclerosis coronary artery | 1 (1) | 0 | 0 |
| Atrial fibrillation | 1 (1) | 0 | 0 |
| Bradycardia | 1 (1) | 0 | 0 |
| Ventricular tachycardia | 0 | 0 | 1 (4) |
| Cardio-respiratory arrest | 0 | 1 (1) | 0 |
| Cardiac arrest | 2 (2.2) | 4 (5) | 1 (4) |
| Congenital, familial and genetic disorders (SOC) | 2 (2) | 0 | 0 |
| Tracheoesophageal fistula | 2 (2) | 0 | 0 |
| Gastrointestinal disorders (SOC) | 5 (6) | 4 (5) | 2 (7) |
| Colitis ulcerative | 1 (1.1) | 0 | 0 |
| Duodenal ulcer perforation | 1 (1) | 0 | 0 |
| Intra-abdominal hemorrhage | 1 (1) | 0 | 0 |
| Thrombosis mesenteric vessel | 1 (1) | 0 | 0 |
| Gastrointestinal hemorrhage | 2 (2) | 1 (1) | 0 |
| Ascites | 0 | 0 | 1 (4) |
| Diverticulum intestinal hemorrhagic | 0 | 0 | 1 (4) |
| Gastrointestinal perforation | 0 | 1 (1) | 0 |
| Intestinal ischemia | 0 | 1 (1) | 0 |
| Intestinal obstruction | 0 | 1 (1) | 0 |
| General disorders and administration site conditions (SOC) | 1 (1.1) | 5 (6) | 2 (7) |
| Disease progression | 0 | 1 (1) | 0 |
| Multiple organ dysfunction syndrome | 1 (1) | 4 (5) | 2 (7) |
| Hepatobiliary disorders (SOC) | 4 (4) | 0 | 1 (4) |
| Drug-induced liver injury | 1 (1) | 0 | 0 |
| Hepatic function abnormal | 1 (1) | 0 | 1 (4) |
| Ischemic hepatitis | 1 (1) | 0 | 0 |
| Primary biliary cholangitis | 1 (1) | 0 | 0 |
| Infections and infestations (SOC) | 13 (14) | 21 (24) | 2 (7) |
| Encephalitis | 1 (1.1) | 0 | 0 |
| Klebsiella sepsis | 1 (1.1) | 0 | 0 |
| Peritonitis | 1 (1) | 0 | 0 |
| Pneumonia klebsiella | 1 (1) | 0 | 0 |
| Staphylococcal bacteremia | 1 (1) | 0 | 1 (4) |
| Liver abscess | 0 | 0 | 1 (4) |
| *Acinetobacter* infection | 1 (1) | 1 (1) | 0 |
| Pneumonia bacterial | 1 (1) | 1 (1) | 0 |
| Pneumonia pseudomonal | 1 (1) | 1 (1.2) | 0 |
| Septic shock | 7 (8) | 7 (8) | 0 |
| Bacterial sepsis | 0 | 1 (1) | 0 |
| Cholecystitis infective | 0 | 1 (1) | 0 |
| Clostridium difficile colitis | 0 | 1 (1) | 0 |

| | Part A | | Part B |
|---|---|---|---|
| Corona virus infection | 0 | 1 (1) | 0 |
| Lung infection | 0 | 1 (1) | 0 |
| Mastoiditis | 0 | 1 (1) | 0 |
| Meningitis bacterial | 0 | 1 (1) | 0 |
| Pseudomembranous colitis | 0 | 1 (1) | 0 |
| Pseudomonas infection | 0 | 1 (1) | 0 |
| Sepsis | 2 (2) | 3 (4) | 0 |
| Pneumonia | 1 (1) | 4 (5) | 0 |
| Injury, poisoning and procedural complications (SOC) | 3 (3) | 2 (2) | 0 |
| Alcohol poisoning | 1 (1) | 0 | 0 |
| Craniocerebral injury | 1 (1) | 0 | 0 |
| Post procedural hemorrhage | 1 (1) | 0 | 0 |
| Chemical peritonitis | 0 | 1 (1) | 0 |
| Tracheostomy malfunction | 0 | 1 (1) | 0 |
| Weaning failure | 0 | 1 (1) | 0 |
| Investigations (SOC) | 1 (1.1) | 0 | 0 |
| Liver function test abnormal | 1 (1.1) | 0 | 0 |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC) | 2 (2.2) | 1 (1) | 0 |
| Metastases to central nervous system | 1 (1) | 0 | 0 |
| Metastases to lung | 1 (1) | 0 | 0 |
| Malignant neoplasm progression | 1 (1) | 1 (1) | 0 |
| Nervous system disorders (SOC) | 3 (3) | 6 (7) | 0 |
| Hemorrhage intracranial | 1 (1) | 0 | 0 |
| Brain oedema | 2 (2) | 1 (1) | 0 |
| Cerebral hemorrhage | 1 (1) | 1 (1) | 0 |
| Cerebrovascular accident | 0 | 1 (1) | 0 |
| Ischemic stroke | 0 | 1 (1) | 0 |
| Seizure | 0 | 3 (4) | 0 |
| Renal and urinary disorders (SOC) | 1 (1) | 2 (2) | 0 |
| Acute kidney injury | 1 (1) | 2 (2) | 0 |
| Respiratory, thoracic and mediastinal disorders (SOC) | 8 (9) | 6 (7) | 2 (7) |
| Bronchial obstruction | 1 (1) | 0 | 0 |
| Hypercapnia | 1 (1) | 0 | 0 |
| Pleural effusion | 1 (1) | 0 | 1 (4) |
| Pneumonia aspiration | 1 (1) | 0 | 0 |
| Tracheomalacia | 1 (1) | 0 | 0 |
| Respiratory failure | 2 (2) | 1 (1) | 1 (4) |
| Acute respiratory distress syndrome | 2 (2) | 2 (2) | 0 |
| Acute respiratory failure | 0 | 1 (1) | 0 |
| Pulmonary embolism | 1 (1) | 2 (2) | 0 |
| Vascular disorders (SOC) | 3 (3) | 1 (1) | 1 (4) |
| Peripheral artery thrombosis | 1 (1) | 0 | 0 |
| Shock | 1 (1) | 0 | 0 |
| Shock hemorrhagic | 1 (1) | 0 | 1 (4) |
| Deep vein thrombosis | 0 | 1 (1) | 0 |

Source: FDA Analysis.
Note: Treatment-emergent adverse events defined as an AE that starts, or a preexisting condition that worsens, on or after the start (based on date and time) of the first dose of study drug.
Note: Serious adverse events defined as any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Note: Duration is 7 days, with extension up to 14 days where clinically indicated.
Abbreviations: AE, adverse event; DUR, durlobactam; N, number of patients in treatment arm; n, number of patients with adverse event; SAE, severe adverse event; SOC, system organ class; SUL, su bactam

FDA reviewed all the narratives submitted for the SAEs. The following subjects in the SUL-DUR group had SAEs that the reviewer assessed as possibly related to the study drug or a failure of the study drug.

A 62-year-old male, with history of traumatic brain injury, autonomic nervous system dysfunction and cervical spinal cord injury was diagnosed with *Acinetobacter baumannii-calcoaceticus* HABP and received SUL-DUR and imipenem for 11 days in Part A. On study Day 12, bronchoalveolar lavage culture revealed *Klebsiella oxytoca* and imaging showed improving bilateral small pleural effusions and bronchopneumonia. Endotracheal aspirate culture revealed *Acinetobacter* spp. and *Klebsiella oxytoca*, the subject experienced recurrent fever the following day. Meropenem, ampicillin sodium/sulbactam sodium, minocycline hydrochloride, and polymyxin B were started. The event resolved on day 22. This event of recurrent pneumonia can be related to failure of study drug.

A 65-year-old male, with history of post COVID-19 organizing pneumonia, hypoalbuminemia, depression, ventilator-associated pneumonia due to *Klebsiella*, was diagnosed with *Acinetobacter baumannii-calcoaceticus* bacteremia and was enrolled in Part B of the phase 3 study. On Study Day 6, the subject was found to have leukopenia and neutropenia. There was no fever or other signs of infection. The study medication and imipenem/cilastatin were withdrawn due to the event. On Study Day 8, the peripheral blood smear revealed severe neutropenia. All antibacterials were discontinued and granulocyte-colony stimulating factor was administered. On Study Day 10, low grade fever was noted with bronchial secretion cultures growing *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Treatment included amikacin, vancomycin, colistin, piperacillin-tazobactam, and micafungin sodium. On Study Day 11, the patient was treated with intravenous human immunoglobulin. Neutropenia was considered resolved on day 12. The unblinded investigator and Applicant considered the event of neutropenia severe and attributed it to SUL-DUR and imipenem/cilastatin.

A 72-year-old male was diagnosed with *Acinetobacter baumannii-calcoaceticus* HABP and randomized to SUL-DUR and imipenem/cilastatin in Part A. The subject was treated for 8 days, but on day 17 had recurrent *Acinetobacter* pneumonia along with Klebsiella bacteremia which was treated with cefoperazone. The event resolved. This reviewer assesses this event as likely failure of study drug.

A 51-year-old female was diagnosed with *Acinetobacter baumannii-calcoaceticus* VABP and received sulbactam-durlobactam + imipenem/cilastatin in Part B. Predose ALT 33 mcg/L (normal range [NR] 7 to 40 mcg/L), AST 21 mcg/L (NR 13 to 35 mcg/L), and total bilirubin was 54.6 mmol/L (NR 3.4 to 20.3 mmol/L). On Study Day 3, ALT was 126 mcg/l, AST was 231 mcg/l, and bilirubin was 41.3 mmol/L. The abnormal liver tests were reported as an SAE. SUL-DUR and imipenem/cilastatin were withdrawn. The unblinded investigator considered the event mild in severity and not related to study medication or imipenem/cilastatin and confirmed a history of liver insufficiency as another possible cause of the event. The Applicant considered the liver test elevation possibly related to study medication or imipenem/cilastatin. This reviewer assesses the event as likely to be related to imipenem or SUL-DUR.

Table 23 shows the incidence of SAEs by sex, age, ethnicity and race. No specific trend of safety signals was noted in any of the subgroups. In Part A, the incidence of SAEs in the colistin group

was higher in the age groups of >65 years and >75 years compared to the SUL-DUR group. Additionally, there was a higher incidence of SAEs in these age groups in Part B than in Part A, although, as noted previously, there was not comparator arm in Part B. The incidence of SAEs in the colistin group was higher than in the SUL-DUR group in Whites. Overall, the number of SAEs was too small to draw any meaningful conclusions.

**Table 23. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Characteristic | SUL-DUR N=91 $n/N_s$ (%) | Colistin N=86 $n/N_s$ (%) | SUL-DUR N=28 $n/N_s$ (%) |
| Sex, n (%) | | | |
| Female | 7/24 (30) | 9/22 (41) | 3/7 (43) |
| Male | 29/67 (43) | 33/64 (52) | 6/21 (29) |
| Age group, years, n (%) | | | |
| 18 to 64 years | 11/42 (26) | 12/37 (32) | 4/19 (21) |
| 65 to 75 years | 18/32 (56) | 9/18 (50) | 3/5 (60) |
| >75 years | 7/17 (41) | 21/31 (68) | 2/4 (50) |
| Age group ≥65, years, n (%) | | | |
| ≥65 | 25/49 (51) | 30/49 (61) | 5/9 (56) |
| Race, n (%) | | | |
| American Indian or Alaska Native | 0/5 (0) | 1/2 (50) | 0/0 (NA) |
| Asian | 14/33 (42) | 16/44 (36) | 1/4 (25) |
| Black or African American | 0/0 (NA) | 1/1 (100) | 0/0 (NA) |
| Other | 2/5 (40) | 0/0 (NA) | 0/0 (NA) |
| White | 20/48 (42) | 24/39 (62) | 8/24 (33) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 3/15 (20) | 6/9 (67) | 1/1 (100) |
| Not Hispanic or Latino | 32/75 (43) | 36/77 (47) | 8/27 (30) |
| Not Reported | 1/1 (100) | 0/0 (NA) | 0/0 (NA) |

Source: FDA Analysis.
Abbreviations: DUR, durlobactam; N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; Ns, total number of patients for each specific subgroup and were assigned to that specific arm; SUL, su bactam

## 7.6.3. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation

In Part A, the incidence of TEAEs that led to treatment discontinuation was lower in the SUL-DUR group (11%) compared to the colistin group (16.3%), Table 24. The most common types of TEAEs that led to treatment discontinuation in the SUL-DUR group were infections and infestations, and vascular disorders. In the colistin group, the most common types of TEAEs that led to treatment discontinuation were seizures and acute kidney injury.

In Part B, 14% of subjects experienced TEAEs that led to treatment discontinuation.

In Part A, among TEAEs considered related to study drug and leading to treatment discontinuation there was one subject in the SUL-DUR group with anaphylaxis and four subjects in the colistin group with rash (n=1), seizure (n=1), and acute kidney injury (n=2). All subjects recovered except the two subjects with acute kidney injury. Additionally, there was one subject

with neutropenia in Part B that was considered related to study drug and led to treatment discontinuation.

The SUL-DUR subject with anaphylaxis experienced the AEs of anaphylactic shock and allergy/hypersensitivity on Study Day 9 and was treated with methylprednisolone. The study medications were withdrawn. Anaphylactic shock resolved the same day.

Refer to Section 7.6.4 for a narrative for the subject in Part B who experienced an AE of neutropenia.

**Table 24. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| **System Organ Class (SOC)**<br>**Preferred Term** | **SUL-DUR**<br>**N=91**<br>**n (%)** | **Colistin**<br>**N=86**<br>**n (%)** | **SUL-DUR**<br>**N=28**<br>**n (%)** |
| Any AE leading to discontinuation | 10 (11) | 14 (16) | 4 (14) |
| Blood and lymphatic system disorders (SOC) | 0 | 1 (1) | 1 (4) |
| Neutropenia | 0 | 0 | 1 (4) |
| Agranulocytosis | 0 | 1 (1) | 0 |
| Cardiac disorders (SOC) | 1 (1) | 0 | 0 |
| Acute myocardial infarction | 1 (1) | 0 | 0 |
| Gastrointestinal disorders (SOC) | 1 (1) | 0 | 0 |
| Gastrointestinal hemorrhage | 1 (1) | 0 | 0 |
| Hepatobiliary disorders (SOC) | 1 (1) | 0 | 1 (4) |
| Hepatic function abnormal | 1 (1) | 0 | 1 (4) |
| Immune system disorders (SOC) | 1 (1) | 0 | 0 |
| Anaphylactic shock | 1 (1) | 0 | 0 |
| Infections and infestations (SOC) | 2 (2) | 3 (4) | 0 |
| Pneumonia bacterial | 1 (1) | 0 | 0 |
| Pneumonia pseudomonal | 1 (1) | 0 | 0 |
| Septic shock | 0 | 1 (1) | 0 |
| Stenotrophomonas sepsis | 0 | 1 (1) | 0 |
| Tuberculosis | 0 | 1 (1) | 0 |
| Injury, poisoning and procedural complications (SOC) | 1 (1) | 0 | 0 |
| Procedural hemorrhage | 1 (1) | 0 | 0 |
| Investigations (SOC) | 1 (1) | 0 | 0 |
| Electrocardiogram QT prolonged | 1 (1) | 0 | 0 |
| Nervous system disorders (SOC) | 1 (1) | 5 (6) | 0 |
| Brain oedema | 1 (1) | 0 | 0 |
| Cerebral hemorrhage | 0 | 1 (1) | 0 |
| Seizure | 0 | 4 (5) | 0 |
| Psychiatric disorders (SOC) | 0 | 0 | 1 (4) |
| Tic | 0 | 0 | 1 (4) |
| Renal and urinary disorders (SOC) | 0 | 3 (4) | 0 |
| Acute kidney injury | 0 | 3 (4) | 0 |
| Respiratory, thoracic and mediastinal disorders (SOC) | 0 | 1 (1) | 1 (4) |
| Pleural effusion | 0 | 0 | 1 (4) |
| Acute respiratory distress syndrome | 0 | 1 (1) | 0 |
| Skin and subcutaneous tissue disorders (SOC) | 1 (1) | 2 (2) | 0 |
| Rash | 1 (1) | 1 (1) | 0 |
| Dermatitis contact | 0 | 1 (1) | 0 |

| System Organ Class (SOC)<br>Preferred Term | Part A<br>SUL-DUR<br>N=91<br>n (%) | <br>Colistin<br>N=86<br>n (%) | Part B<br>SUL-DUR<br>N=28<br>n (%) |
|---|---|---|---|
| Vascular disorders (SOC) | 2 (2) | 0 | 0 |
| Shock | 1 (1) | 0 | 0 |
| Shock hemorrhagic | 1 (1) | 0 | 0 |

Source: FDA Analysis
Note: Treatment-emergent adverse events defined as an AE that starts, or a preexisting condition that worsens, on or after the start (based on date and time) of the first dose of study drug.
Note: Duration is 7 days, with extension up to 14 days where clinically indicated.
Abbreviations: AE, adverse event; DUR, durlobactam; N, number of patients in treatment arm; n, number of patients with adverse event; QT, time between the start of the QRS complex and the end of the T wave; SOC, system order class; SUL, su bactam

## 7.6.4. Treatment-Emergent Adverse Events

The overall incidence of TEAEs was 88% in the sulbactam-durlobactam arm and 94% in the colistin arm. The common relevant adverse events occurring in more than 5% of subjects receiving SUL-DUR are outlined in Table 25.

The TEAEs occurring with higher frequency in the SUL-DUR than in the comparator group were diarrhea (17% versus 11%), hypokalemia (12% versus 11%), and thrombocytopenia (6% versus 4%). Acute kidney injury was noted to be higher in the colistin group (36%) compared to the SUL-DUR group (6%). The most common TEAEs in both treatment arms were abnormal liver tests.

**Table 25. Selected Adverse Events Occurring at >5% Frequency, Safety Population, Study CS2514-2017-0004**

| Preferred Term | Part A<br>SUL-DUR<br>N=91<br>n (%) | <br>Colistin<br>N=86<br>n (%) | Part B<br>SUL-DUR<br>N=28<br>n (%) |
|---|---|---|---|
| Any AE | 80 (88) | 81 (94) | 24 (86) |
| Liver function test abnormal | 17 (19) | 18 (21) | 7(25) |
| Diarrhea | 15 (17) | 9 (11) | 2 (7) |
| Anemia | 12 (13) | 12 (14) | 3(11) |
| Hypokalemia | 11 (12) | 9 (11) | 0 |
| Pyrexia | 9 (10) | 8 (9) | 1 (4) |
| Septic shock | 9 (10) | 8 (9) | 0 |
| Arrythmias | 8 (9) | 8 (9) | 1(4) |
| Acute kidney injury | 5 (6) | 31 (36) | 5(18) |
| Thrombocytopenia | 5 (6) | 3 (4) | 0 |
| Constipation | 5 (6) | 5 (6) | 0 |

Source: FDA Analysis
Note: The following terms were combined: Proteinuria and protein in urine. Liver function test abnormal, hepatic function abnormal, increased transaminases, ALT increased and AST increased. Renal impairment, blood creatinine increased, toxic nephropathy, renal failure and acute kidney injury.
Abbreviations: AE, adverse event; ALT, alanine transaminase; AST; Aspartate aminotransferase; DUR, durlobactam; N, number of patients in treatment arm; n, number of patients with adverse event; SUL, sulbactam

There were lower incidences of drug-related TEAEs (12.1% versus 30.2%) in the SUL-DUR group compared to the colistin group. The most common drug-related treatment emergent adverse event in subjects who received SUL-DUR in Part A was diarrhea at 4.4%. There was one

subject each with related TEAEs of anaphylactic shock, transient prolonged QT interval, generalized tonic-clonic seizure and phlebitis on SUL-DUR (Part A). The TEAEs that were considered related to study drug in Part B were transaminases increased, proteinuria, nausea, and neutropenia (one [4%] patient each).

### 7.6.5. Laboratory Findings

Table 26 presents selected chemistry and hematology values. The imbalances in hypernatremia, hypokalemia, hyperglycemia, changes in bicarbonate, low hemoglobin and eosinophilia were higher in the SUL-DUR group than in the colistin group; however, the small safety database limits evaluation of laboratory value imbalances and many subjects were critically ill, hypovolemic and receiving various fluid replacement therapies which could affect electrolyte parameters. A higher proportion of SUL-DUR subjects were observed to have eosinophilia, in the range of 1500-3000 cells/ul. Of these subjects, one subject had a parasitic infection which was being treated with albendazole. All subjects were receiving another beta-lactam, i.e., imipenem, and two other subjects received other concomitant antibacterials, e.g., vancomycin.

**Table 26. Patients With Selected Last on-Treatment Chemistry and Hematology Values Level 2 Criteria by Treatment Arm, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Parameter | SUL-DUR N=91 n (%) | Colistin N=86 n (%) | SUL-DUR N=28 n (%) |
| Sodium, high (mEq/L) >155 | 8/88 (9) | 1/76 (1) | 0/27 (0) |
| Potassium, low (mEq/L) <3.4 | 12/86 (14) | 8/74 (11) | 0/15 (0) |
| Chloride, high (mEq/L) >112 | 17/88 (19) | 7/76 (9) | 3/27 (11) |
| Bicarbonate, low (mEq/L) <18 | 4/89 (5) | 1/76 (1) | 0/27 (0) |
| Bicarbonate, high (mEq/L) >30 | 18/89 (20) | 12/76 (16) | 7/27 (26) |
| Glucose, random, high (mg/dL) ≥200 | 15/89 (17) | 8/76 (11) | 7/27 (26) |
| Hemoglobin, low (g/dL) >1.5 g/dL dec. from baseline | 13/79 (17) | 10/66 (15) | 7/21 (33) |
| Eosinophils, high (cells/uL) >1500 | 4/88 (6) | 1/76 (1) | 0/27 (0) |

Source: FDA Analysis
Note: Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.
Abbreviations: DUR, durlobactam; N, number of patients in treatment arm; n, number of subjects in category; SUL, sulbactam

Table 27 depicts kidney and liver chemistry values. There were more subjects in the colistin group with elevation in creatinine >2x baseline (16% versus 2%) and eGFR decline of ≥50% (13% versus 1%).

**Table 27. Patients With Last on-Treatment Chemistry Value ≥ Level 2 Criteria by Treatment Arm, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Parameter | SUL-DUR N=91 $n/N_w$ (%) | Colistin N=86 $n/N_w$ (%) | SUL-DUR N=28 $n/N_w$ (%) |
| Kidney function | | | |
| Creatinine, high (mg/dL) ≥2X baseline | 2/82 (2) | 11/70 (16) | 2/22 (9) |
| eGFR, low (mL/min/1.73 $m^2$) ≥50% decrease | 1/79 (1) | 9/70 (13) | 0/22 (0) |
| CLcr, low (mL/min) ≥50% decrease | 1/51 (2) | 8/32 (25) | 1/16 (6) |

| | Part A | | Part B |
|---|---|---|---|
| Liver biochemistry | | | |
| Alkaline phosphatase, high (U/L) >2X ULN | 6/89 (7) | 6/76 (8) | 3/27 (11) |
| Alanine aminotransferase, high (U/L) >5X ULN | 1/89 (1) | 2/76 (3) | 0/27 (0) |
| Aspartate aminotransferase, high (U/L) >5X ULN | 2/89 (2) | 2/76 (3) | 1/26 (4) |
| Bilirubin, total, high (mg/dL) >2X ULN | 2/89 (2) | 1/76 (1) | 3/27 (11) |

Source: FDA Analysis
Note: Last value on treatment defined as last measured value.
Note: Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.
Note: Duration is 7 days, with extension up to 14 days where clinically indicated.
Abbreviations: CLcr; creatinine clearance; DUR, durlobactam; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; $N_w$, number of patients with data; SUL, sulbactam; ULN, upper limit of normal

Table 28 and Table 29 provide additional laboratory value changes for subjects in the phase 3 trials. Except for laboratory values reflecting changes in renal function, there are no notable imbalances between the treatment groups.

**Table 28. Subjects With Last on-Treatment Chemistry Value ≥ Level 2 Criteria by Treatment Arm, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| **Parameter** | **SUL-DUR N=91 n/$N_w$ (%)** | **Colistin N=86 n/$N_w$ (%)** | **SUL-DUR N=28 n/$N_w$ (%)** |
| General chemistry | | | |
| Sodium, low (mEq/L) <130 | 1/88 (1) | 10/76 (13) | 5/27 (18.5) |
| Sodium, high (mEq/L) >155 | 8/88 (9) | 1/76 (1) | 0/27 (0) |
| Potassium, low (mEq/L) <3.4 | 12/86 (14) | 8/74 (11) | 0/15 (0) |
| Potassium, high (mEq/L) >6 | 2/86 (2) | 1/74 (1) | 0/15 (0) |
| Chloride, low (mEq/L) <88 | 0/88 (0) | 1/76 (1) | 0/27 (0) |
| Chloride, high (mEq/L) >112 | 17/88 (19) | 7/76 (9) | 3/27 (11.1) |
| Bicarbonate, low (mEq/L) <18 | 4/89 (5) | 1/76 (1) | 0/27 (0) |
| Bicarbonate, high (mEq/L) >30 | 18/89 (20) | 12/76 (16) | 7/27 (26) |
| Calcium, low (mg/dL) <8 | 25/89 (28) | 21/76 (28) | 8/27 (30) |
| Calcium, high (mg/dL) >11 | 1/89 (1) | 0/76 (0) | 0/27 (0) |
| Phosphate, low (mg/dL) <2 | 3/89 (3) | 4/76 (5) | 0/27 (0) |
| Amylase, high (U/L) >1.5× ULN | 2/87 (2) | 1/75 (1) | 2/27 (7) |
| Lipase, high (U/L) >1.5× ULN | 9/88 (10) | 9/74 (12) | 6/27 (22) |
| Blood urea nitrogen, high (mg/dL) >27 | 27/78 (35) | 22/67 (33) | 5/26 (19) |
| Kidney function | | | |
| Creatinine, high (mg/dL) ≥2× baseline | 2/82 (2) | 11/70 (16) | 2/22 (9.1) |
| eGFR, low (mL/min/1.73 $m^2$) ≥50% decrease | 1/79 (1) | 9/70 (13) | 0/22 (0) |
| CLcr, low (mL/min) ≥50% decrease | 1/51 (2.0) | 8/32 (25.0) | 1/16 (6.2) |
| Liver biochemistry | | | |
| AP, high (U/L) >2× ULN | 6/89 (7) | 6/76 (8) | 3/27 (11) |
| Alanine aminotransferase, high (U/L) >5× ULN | 1/89 (1) | 2/76 (3) | 0/27 (0) |
| Aspartate aminotransferase, high (U/L) >5× ULN | 2/89 (2) | 2/76 (3) | 1/26 (4) |
| Bilirubin, total, high (mg/dL) >2× ULN | 2/89 (2) | 1/76 (1) | 3/27 (11) |

Source: FDA Analysis.
Note: Last value on treatment defined as last measured value.
Note: Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.
Abbreviations: AP, alkaline phosphatase; CLcr; creatinine clearance; DUR, durlobactam; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data; SUL, sulbactam; ULN, upper limit of normal

**Table 29. Last on-Treatment Hematology Value ≥ Level 2 Criteria by Treatment Group, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Parameter | SUL-DUR N=91 $n/N_w$ (%) | Colistin N=86 $n/N_w$ (%) | SUL-DUR N=28 $n/N_w$ (%) |
| Complete blood count | | | |
| WBC, low (cells/µL) <3000 | 1/88 (1) | 0/76 (0) | 1/27 (4) |
| WBC, high (cells/µL) >13,000 | 22/88 (25) | 22/76 (29) | 5/27 (195) |
| Hemoglobin, low (g/dL) >1.5 g/dL dec. from baseline | 13/79 (17) | 10/66 (15) | 7/21 (33) |
| Hemoglobin, high (g/dL) >2 g/dL inc. from baseline | 5/79 (6) | 3/66 (5) | 0/21 (0) |
| Platelets, low (cells/µL) <125,000 | 10/87 (12) | 9/76 (12) | 4/26 (15) |
| WBC Differential | | | |
| Lymphocytes, low (cells/µL) <750 | 21/88 (24) | 14/76 (18) | 6/27 (22) |
| Neutrophils, low (cells/µL) <1000 | 0/88 (0) | 0/76 (0) | 1/27 (4) |
| Eosinophils, high (cells/µL) >1500 | 4/88 (5) | 1/76 (1) | 0/27 (0) |

Source: FDA Analysis.
Note: Last value on treatment defined as the last measured value.
Note: Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.
Note: Duration is 7 days, with extension up to 14 days where clinically indicated.
Abbreviations: DUR, durlobactam; N, number of patients in treatment group; n, number of patients meeting criteria; Nw, number of patients with data; SUL, sulbactam; WBC, white blood cell

## 7.6.6. Assessment of Drug-Induced Liver Injury

In the phase 3 study, the incidence of TEAEs based on the hepatobiliary disorders were similar (11%) for subjects in the SUL-DUR and colistin groups, Table 30. The AEs in the SUL-DUR group were mild or moderate in severity, one was serious, and all resolved spontaneously.

The Agency's analysis of drug-induced liver injury identified preferred terms related to liver injury in two (2%) subjects treated with SUL-DUR and four (4%) subjects treated with colistin.

The Applicant reported three subjects in the SUL-DUR group (two subjects in part A and 1 in Part B), and one subject in the colistin group meeting Hy's Law laboratory criteria; however, these subjects had alternative plausible explanations for liver test elevation including: primary biliary cholangitis, acute ischemic hepatitis and progressive baseline liver insufficiency. Consequently, the Agency's analysis indicates that there were no Hy's law cases in the phase 3 study.

There were also no Hy's law cases reported in the phase 2 study. One subject in the SUL-DUR group had mild elevation of liver tests which resolved. In the phase 1 study, one healthy volunteer who received multiple doses of SUL-DUR had mild transient elevation of hepatic enzymes.

Neither SUL nor DUR has significant hepatic metabolism and liver injury assessment did not reveal any specific safety signal in this small safety database. Hepatic dysfunction, including hepatitis and cholestatic jaundice have been associated with the use of ampicillin-sulbactam, but have not been particularly attributed to sulbactam. In vitro data do not indicate that durlobactam is metabolized by CYP450.

**Table 30. Hepatobiliary Disorders Related Adverse Events, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Adverse Events | SUL-DUR N=91 n (%) | Colistin N=86 n (%) | SUL-DUR N=28 n (%) |
| AE grouping related to hepatobiliary disorders | 10 (11) | 9 (11) | 1 (4) |
| Alanine aminotransferase increased | 3 (3) | 2 (2) | 1 (4) |
| Aspartate aminotransferase increased | 3 (3) | 2 (2) | 1 (4) |
| Bilirubin conjugated increased | 2 (2) | 0 | 0 |
| Drug-induced liver injury | 1 (1) | 1 (1) | 0 |
| Hepatic cirrhosis | 1 (1) | 0 | 0 |
| Hepatitis acute | 0 | 1 (1) | 0 |
| Liver injury | 2 (2) | 4 (5) | 0 |
| Maximum severity | | | |
| Death | 0 | 0 | 0 |
| Life-threatening | 0 | 0 | 0 |
| Severe | 0 | 1 (1) | 0 |
| Moderate | 3 (3) | 3 (4) | 1 (4) |
| Mild | 7 (8) | 5 (6) | 0 |
| Serious | 1 (1) | 0 | 0 |
| Deaths | 0 | 0 | 0 |
| Resulting in discontinuation | 0 | 0 | 0 |
| Relatedness | 1 (1) | 0 | 0 |

Source: FDA Analysis
Note: Treatment-emergent adverse events defined as an AE that starts, or a preexisting condition that worsens, on or after the start (based on date and time) of the first dose of study drug.
Note: Duration is 7 days, with extension up to 14 days where clinically indicated.
Abbreviations: AE, adverse event; DUR, durlobactam; N, number of patients in treatment arm; n, number of patients with adverse event; SUL, sulbactam

### 7.6.7. Vital Signs

Mean changes from baseline to the end of treatment and to the end of post-treatment in vital sign values were small, with no clinically important differences observed among the treatment groups, Table 31. Median and interquartile ranges of pulse rate and respiratory rates over time were comparable between treatment arms.

**Table 31. Percentage of Patients Meeting Specific Hypotension Levels Postbaseline, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Blood Pressure (mm Hg) | SUL-DUR N=91 n/Nw (%) | Colistin N=86 n/Nw (%) | SUL-DUR N=28 n/Nw (%) |
| SBP <90 | 12/91 (13.2) | 15/86 (17.4) | 1/28 (3.6) |
| DBP <60 | 46/91 (50.5) | 50/86 (58.1) | 21/28 (75.0) |

Source: FDA Analysis
Abbreviations: DBP, diastolic blood pressure; DUR, durlobactam; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data; SBP, systolic blood pressure; SUL, sulbactam

### 7.6.8. Subgroups

Table 32 shows the incidence of common AEs by demographic subgroups of sex, age, ethnicity and race. No specific trends of safety signals were noted in any of the subgroups. The incidence of AEs in the colistin group was higher in age groups >65 years compared to the SUL-DUR group in Part A but the number of subjects was too small to draw any meaningful conclusions.

**Table 32. Adverse Events by Demographic Subgroup, Safety Population, Study CS2514-2017-0004**

| | Part A | | Part B |
|---|---|---|---|
| Characteristic | SUL-DUR N=91 n/Ns (%) | Colistin N=86 n/Ns (%) | SUL-DUR N=28 n/Ns (%) |
| Sex, n (%) | | | |
| Female | 20/24 (83) | 21/22 (96) | 7/7 (100) |
| Male | 61/67 (91) | 60/64 (94) | 17/21 (81) |
| Age group, years, n (%) | | | |
| 18 to 64 years | 37/42 (88) | 33/37 (89) | 15/19 (79) |
| 65 to 75 years | 30/32 (94) | 18/18 (100) | 5/5 (100) |
| >75 years | 14/17 (82) | 30/31 (97) | 4/4 (100) |
| Age group ≥65, years, n (%) | | | |
| ≥65 | 44/49 (90) | 48/49 (98) | 9/9 (100) |
| Race, n (%) | | | |
| American Indian or Alaska Native | 5/5 (100) | 2/2 (100) | 0/0 (NA) |
| Asian | 31/33 (94) | 43/44 (98) | 4/4 (100) |
| Black or African American | 0/0 (NA) | 1/1 (100) | 0/0 (NA) |
| Other | 5/5 (100) | 0/0 (NA) | 0/0 (NA) |
| White | 40/48 (83) | 35/39 (90) | 20/24 (83) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 14/15 (93) | 7/9 (78) | 1/1 (100) |
| Not Hispanic or Latino | 66/75 (88) | 74/77 (96) | 23/27 (85) |
| Not reported | 1/1 (100) | 0/0 (NA) | 0/0 (NA) |
| Is in United States, n (%) | | | |
| United States | 1/1 (100) | 0/0 (NA) | 0/0 (NA) |
| Non-United States | 80/90 (89) | 81/86 (94) | 24/28 (86) |

Source: FDA Analysis
Abbreviations: DUR, durlobactam; N, number of patients in treatment arm; n, number of patients with adverse event; $N_s$, total number of patients for each specific subgroup and were assigned to that specific arm; SUL, su bactam

**Safety Data From Expanded-Access Patients**

Twelve patients received SUL-DUR under the expanded access program in the United States and under the Italian Medicines Agency compassionate-use program. Before treatment with SUL-DUR, the patients generally failed multiple salvage regimens with combinations of antibacterials. The treatment duration with SUL-DUR ranged from 1 to 42 days. Refer to Section 17 for additional detail.

## 7.7. Key Safety Review Issues

### 7.7.1. Limited Size of the Safety Database

No unexpected safety signals were identified in the SUL-DUR development program. However, the limitations of the safety assessments of SUL-DUR are related to the small size of the safety database, which comprises less than 200 subjects exposed to the proposed dose and duration of therapy.

In the randomized part of the phase 3 study, there were 24 (26%) and 30 (35%) deaths in the SUL-DUR and colistin groups, respectively. Mortality outcomes were related to underlying comorbid conditions, complications in critically ill patients or progression of the presenting pneumonia without apparent biologic plausibility or causal assignment to SUL-DUR treatment. The overall mortality rate observed in this study was similar to that observed in other HABP/VABP trials. The overall incidences of TEAEs, SAEs, and drug-related TEAEs were lower in the SUL-DUR group than in the colistin group. A large proportion of subjects in both groups experienced severe TEAEs, but moderate and severe TEAEs were less frequent in the SUL-DUR group compared to colistin. The most common TEAEs experienced by subjects in the SUL-DUR group were diarrhea and hypokalemia. The phase 2 study did not reveal any concerning safety signals and was consistent with safety findings in the pivotal phase 3 study.

In a thorough QT study, a supratherapeutic dose of durlobactam (4 g) did not prolong the QT interval.

Sulbactam has been approved in combination with ampicillin since 1986. The ampicillin-SUL prescribing information includes warnings for hypersensitivity reactions, hepatotoxicity including hepatitis and cholestatic jaundice, severe cutaneous adverse reactions, and *Clostridium difficile*-associated diarrhea. The contribution of each component to the development of these adverse reactions is not certain.

Overall, the safety profile for SUL-DUR appears consistent with other β-lactam/β-lactamase inhibitor drug products. Given the significant unmet need for treatment options for HABP/VABP due to ABC (including CRABC), the limited safety database was deemed acceptable to support the approval of SUL-DUR.

# 8. Therapeutic Individualization

## 8.1. Intrinsic Factors

### 8.1.1. Renal Function

SUL and DUR are primarily renally eliminated. Renal function status is identified as the only intrinsic factor warranting dose adjustment.

**Patients With Renal Impairment**

A clinical study (study CS2514-2017-0002) was conducted to compare the PK of SUL and DUR in subjects with renal impairment to that of subjects with normal renal function following the administration of a single IV infusion of 1.0 g SUL and 1.0 g DUR to subjects with normal renal function (CLcr ≥90 mL/min), mild renal impairment (estimated glomerular filtration rate [eGFR] ≥60 to <90 mL/min/1.73 $m^2$), and moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 $m^2$) and a single IV infusion of SUL 0.5 g / DUR 0.5 g to subjects with severe renal impairment (eGFR <30 mL/min/1.73 $m^2$) including subjects with end-stage renal disease on hemodialysis (refer to Section 14.2). The results indicated that the dose-normalized $AUC_{0-\infty}$ for both SUL and DUR was approximately two- and four-fold higher in subjects with moderate renal impairment and severe renal impairment, respectively, than in those with normal renal function (Table 33). Therefore, dose adjustment is needed in patients with renal impairment.

Patients Receiving Intermittent Hemodialysis

Intermittent hemodialysis effectively removed sulbactam and durlobactam from plasma, with approximately 33% for durlobactam and 40% for sulbactam of the dose excreted in dialysate. Therefore, in subjects on hemodialysis, SUL-DUR should be administered following the completion of hemodialysis according to the recommended dose regimens by renal function.

**Table 33. Dose Normalized Fold AUC Increase in Subjects With Renal Impairment Compared to Subjects With CLcr ≥90 mL/min**

| Estimated eGFR (mL/min/1.73 $m^2$) | Sulbactam | Durlobactam |
|---|---|---|
| ≥60 to <90 | 1.4 | 1.4 |
| ≥30 to <60 | 2.0 | 1.9 |
| <30 | 4.3 | 3.7 |

Source: Applicant's draft label for NDA 216974.
Abbreviations: AUC, area under the curve; CLcr; creatinine clearance; eGFR, estimated glomerular filtration rate

Patients Receiving Continuous Renal Replacement Therapy

In the phase 3 study, seven patients received SUL-DUR and underwent Continuous Renal Replacement Therapy (CRRT). As stated in the protocol, these patients received 1.5 g sulbactam/1.5 g durlobactam every 6 hours while on CRRT and their dosing regimen was adjusted as their renal function changed over the course of treatment. The important CRRT parameters (e.g., effluent flow rate, point of dilution, and blood flow rate) were not recorded for these subjects. Given the limited data from a small number of subjects, the Applicant did not propose a dosage in the labeling for patients receiving CRRT. Instead, the Applicant proposed to monitor renal function regularly and adjust the dosage of SUL-DUR accordingly as renal function may change during the course of therapy. The review team agrees with this proposal from the Applicant.

Patients With Augmented Renal Function

Seriously ill patients who receive intravenous fluid resuscitation may have augmented renal function (CLcr ≥130 mL/min). The mean clearance of sulbactam and durlobactam was found to be increased in patients with CLcr of 130 mL/min or greater (12.2 L/h for SUL and 12.0 L/h

DUR) as compared to patients with CLcr of 90 to 129 mL/min (9.98 L/h for SUL and 9.40 L/h for DUR). Hence, dose adjustment is needed in patients with augmented renal function.

**Evaluation on the Applicant's Proposed Renal Function-Based Dosage Adjustments**

During the review of this NDA, the review team identified a potential risk of medication error associated with the Applicant's initially proposed renal function-based dosage adjustments. Following notification of the Agency's concern with dosing errors, the Applicant submitted proposals to revise the renal function-based dosage adjustments described in the prescribing information. FDA's evaluation of the initially proposed and revised renal function-based dosage adjustments is described below.

Evaluation on the Applicant's Initially Proposed Dosage Adjustments

In the phase 3 study (study CS2514-2017-0004), dose regimens of SUL-DUR in patients with altered renal function were adjusted according to Table 7, Section 6.1. Results from the phase 3 study revealed that patients with severe renal impairment (CLcr <30 mL/min) had substantially higher geometric mean exposures for both drugs than patients with CLcr ≥60 mL/min even though patients with CLcr <30 mL/min received sulbactam-durlobactam using an extended dosing interval of every q8h or q12h. The increase in exposures was more pronounced on Days 2 and 3, which is consistent with prolonged half-life and lower clearance in patients with severe renal impairment. Hence, the Applicant modified the dosage adjustments in patients with renal impairment and provided their initial proposal of renal function-based dose regimens for labeling at the time of the NDA submission, as shown in Table 34.

**Table 34. Applicant's Initially Proposed Dosage of SUL-DUR in Adults**

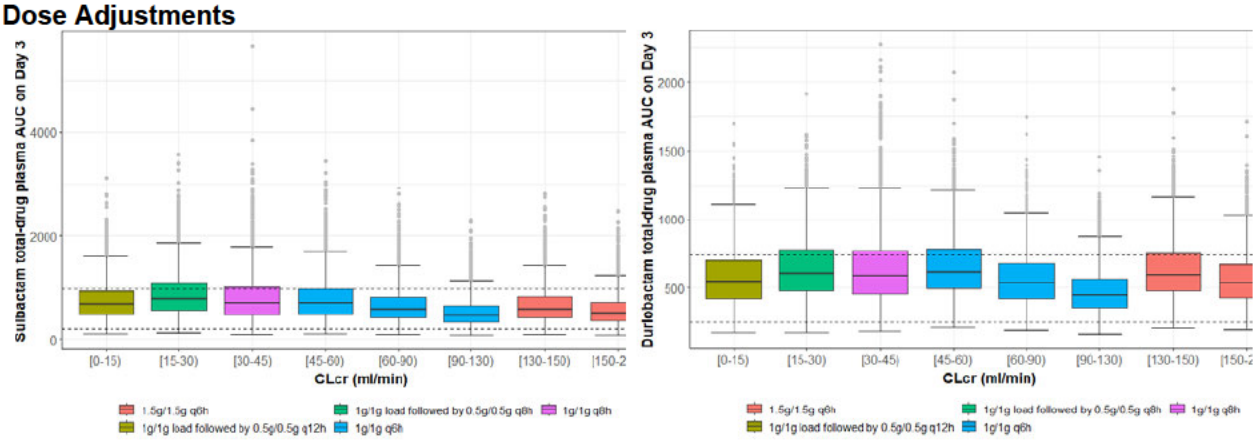
| Estimated CLcr (mL/min) | Proposed Dosage of SUL-DUR | Frequency | Infusion Time |
|---|---|---|---|
| ≥130 | 1.5 g/1.5 g | Every 6 hours | 3 hours |
| 45-129 | 1 g/1 g | Every 6 hours | 3 hours |
| 30-44 | 1 g/1 g | Every 8 hours | 3 hours |
| 15-29 | Loading dose of 1 g/1 g followed by 0.5 g/0.5 g | Every 8 hours | 3 hours |
| <15[1] | Loading dose of 1 g/1 g followed by 0.5 g/0.5 g | Every 12 hours | 3 hours |

Source: Table 39 of Applicant's module 2.7.2 Summary of Clinical Pharmacology for NDA 216974.
[1] For patients on hemodialysis, the dose should be administered after the dialysis session has ended.
Abbreviations: CLcr, creatinine clearance (as estimated by the Cockcroft-Gault equation); DUR, durlobactam; SUL, su bactam

*Exposure Estimates in Patients Receiving the Initially Proposed Dosage Adjustments*

Using the population PK model developed with pooled PK data from phase 1, phase 2, and phase 3 studies, SUL and DUR exposures were estimated at the initially proposed dose adjustments (Table 34) in the simulated patients representing each of eight renal function categories covering CLcr from ≥0 to ≤200 mL/min (refer to Section 14.5). Figure 2 shows the SUL and DUR total-drug plasma AUCs at steady state (Day 3) among simulated patients across renal function categories. The results show that the predicted plasma AUC of SUL and DUR at the steady state were generally comparable across renal function categories and were within the range of exposures from subjects with normal renal function at the initially proposed dose regimens.

**Figure 2. SUL (Left) and DUR (Right) Total-Drug Plasma Distributions of AUC at Steady State (Day 3) in Simulated Patients Across Renal Function Groups at the Applicant's Initially Proposed Dose Adjustments**

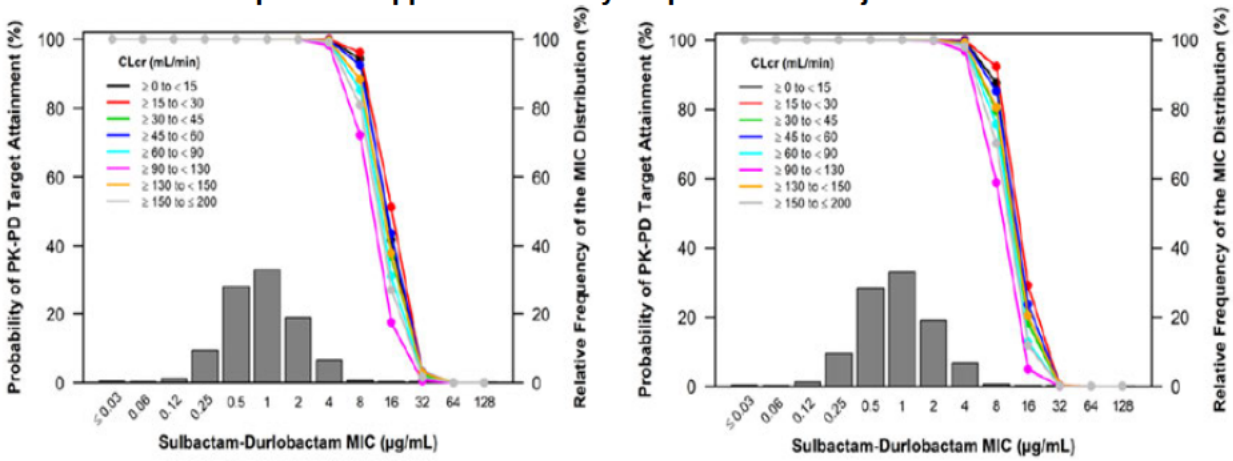



Source: Analyses by pharmacometrics review team in the FDA.
Note: Horizontal dashed lines represent the 90% prediction interval of the CLcr ≥90 to <130 mL/min group, which is defined as the 5th and 95th percentiles for SUL or DUR total-drug plasma AUC.
Abbreviations: AUC, area under the curve; CLcr, creatinine clearance (as estimated by the Cockcroft-Gault equation); DUR, durlobactam; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours; SUL, sulbactam

*PTA Analyses at the Initially Proposed Dosage Adjustments*

Using the PK/PD targets of SUL (%*f*T > MIC of 50%) and DUR (*f*AUC:MIC ratio of 10) associated with a 1-$\log_{10}$ colony-forming units (CFU) reduction, PTA analyses based on free-drug plasma concentration or total-drug concentration in ELF was performed at the initially proposed dose regimens (Table 34) in the simulated subjects across various renal function categories and global surveillance MIC distribution. As shown in Figure 3, the initially proposed dose regimens resulted in ≥90% PTA at MICs ≤4 mg/L across all renal function categories.

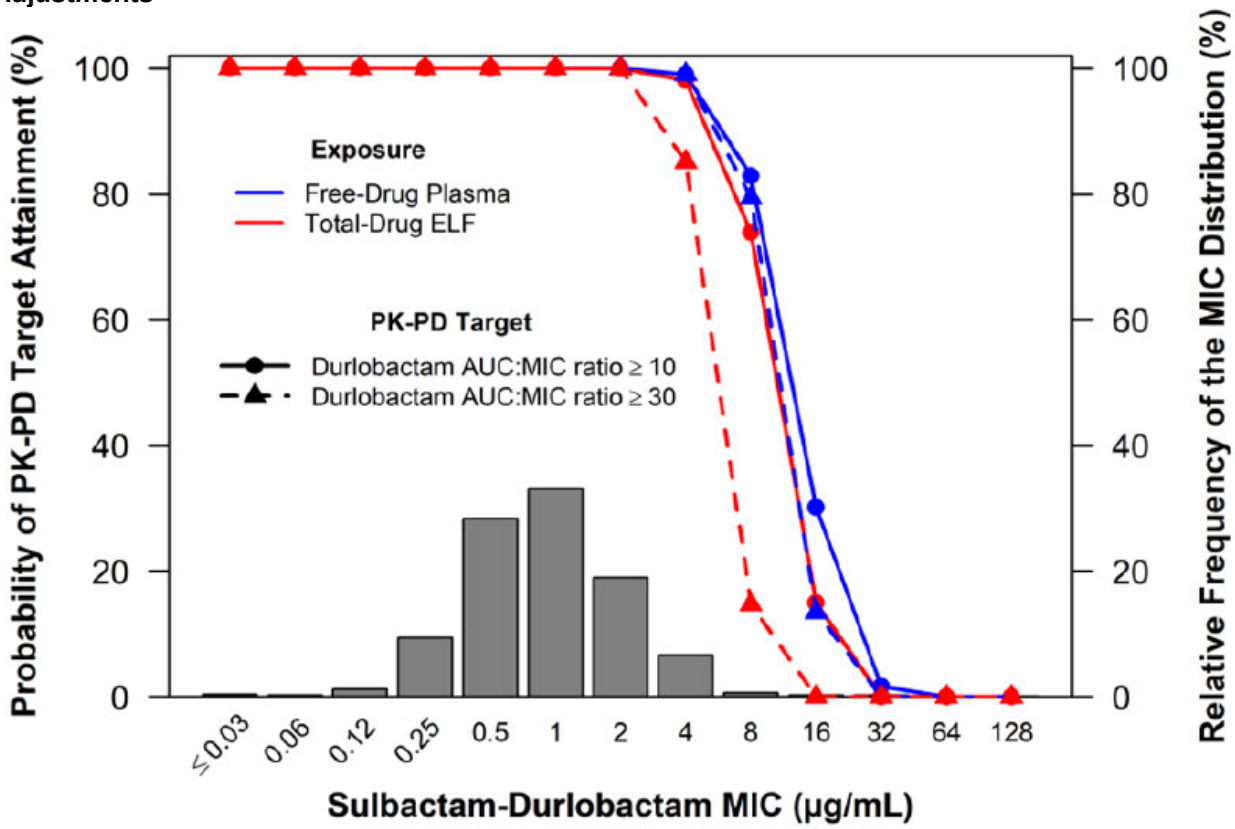
**Figure 3. Percentage Probabilities of PK/PD Target Attainment by MIC on Day 1 Based on Free Drug Plasma Exposures (Left) and Total-Drug ELF Exposures (Right) in Simulated Patients Across Renal Function Groups at the Applicant's Initially Proposed Dose Adjustments**




Source: Figure 60 and Figure 61 of Applicant's module 2.7.2 Summary of Clinical Pharmacology for NDA 216974.
Note: PTA analysis was based on PK/PD targets of sulbactam (50%*f*T > MIC) and durlobactam (*f*AUC:MIC ratio of 10) which are associated with a 1-$\log_{10}$ CFU reduction.
Abbreviations: %*f*T > MIC; percent of time free drug remains above the minimum inhibitory concentration; *f*AUC:MIC, relationship between area under the free concentration–time curve and minimum inhibitory concentration ratio; CFU, colony forming units; CLcr, creatinine clearance; ELF, epithelium lining fluid; MIC, maximum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; PTA, probability of target attainment

PTA analyses were also conducted in simulated patients who were generated to resemble the distributions of demographic variables from the phase 3 clinical study patient population with ABC infections (refer to Section 14.5). PTA analyses were performed at the initially proposed renal function-based dose regimens for unbound plasma concentrations or total drug concentrations in ELF. As shown in Figure 4, the PTA results indicate that the Applicant's initially proposed doses can generate drug concentrations in plasma or ELF to achieve the PK/PD targets associated with 1-log kill in at least 90% of simulated clinical patients at MIC up to 4 µg/mL.

**Figure 4. Percent Probabilities of PK/PD Target Attainment by MIC on Day 1 Among Simulated Patients Resembling the Clinical Study Population at the Applicant's Initially Proposed Dose Adjustments**




Source: Figure 62 of Applicant's module 2.7.2 Summary of Clinical Pharmacology for NDA 216974.
Abbreviations: AUC, area under the curve; ELF, epithelium lining fluid; MIC minimum inh bitory concentration; PD, pharmacodynamics; PK, pharmacokinetics

In summary, the predicted SUL and DUR exposures and PTA analyses across each of the renal function groups support the Applicant's initially proposed dosage adjustments as presented in Table 34 for patients with reduced or augmented renal functions.

Evaluation on the Applicant's Proposed Revisions on Renal Function-Based Dosage Adjustments

SUL-DUR for injection is supplied as a kit containing 3 single-dose vials each containing sterile powder for reconstitution: two vials contain 0.5 g durlobactam in each vial and one vial contains

1 g sulbactam. One single dosing kit fits well to the 1 g SUL/1 g DUR dose. For the Applicant's initially proposed dose adjustment of 0.5 g SUL/0.5 g DUR for patients with CLcr <45 mL/min, one single dosing kit will provide more drug product than the dose needed hence result in remaining contents of the vial. For the Applicant's initially proposed dose adjustment of 1.5 g SUL/1.5 g DUR for patients with CLcr ≥130 mL/min, one single dosing kit is not adequate, hence two dosing kits are required but provide more drug product than the dose needed resulting in remaining contents of the vial. The remaining drug product in the dosing kit may pose the potential risk for inappropriate disposal or future use. Therefore, the use of 0.5 g SUL/0.5 g DUR and 1.5 g SUL/1.5 g DUR doses raises the concern of potential medication errors during the process of dosing preparation, and/or drug administration. To avoid potential errors associated with the doses of 0.5 g SUL/0.5 g DUR and 1.5 g SUL/1.5 g DUR, the Applicant revised the dose adjustments and standardized the dose to 1 g SUL/1g DUR across all renal function categories with the adjustment of the dosing frequency, as shown in Table 35.

**Table 35. Applicant's Proposed Revisions on Dosage of SUL-DUR in Adults**

| Estimated CLcr (mL/min)[1] | Recommended Dose of Sulbactam and Durlobactam (g) | Frequency | Infusion Time |
|---|---|---|---|
| Greater than or Equal to 130 | Sulbactam 1 g and durlobactam 1g | Every 4 hours | 3 hours |
| 45 to 129 | Sulbactam1 g and durlobactam1 g | Every 6 hours | 3 hours |
| 30 to 44 | Sulbactam 1 g and durlobactam 1 g | Every 8 hours | 3 hours |
| 15 to 29 | Sulbactam 1 g and sulbactam 1 g | Every 12 hours | 3 hours |
| Less than 15[2] | Sulbactam 1 g and durlobactam 1 g | For patients initiating XACDURO:<br>Every 12 hours for the first 3 doses (0, 12, and 24 hours), followed by every 24 hours after the third dose<br><br>For patients who have been on the XACDURO treatment and their CLcr declines to less than 15 mL/min:<br>Every 24 hours | 3 hours |

Source: Adapted from Table 3 of Applicant's response to the FDA Information Request for NDA 216974 dated on March 14, 2023.
[1] CLCR = creatinine clearance estimated by Cockcroft-Gault equation
[2] For patients on hemodialysis, the dose should be administered after the dialysis session has ended.
Abbreviations: CLcr, creatinine clearance; DUR, durlobactam; SUL, sulbactam; XACDURO, sulbactam and durlobactam

Since there is no change in the dose regimen (1 g SUL/1g DUR) proposed to patients with normal renal function (CLcr ≥90 to <130 mL/min), and this dose regimen has been shown to be adequate for efficacy and safety (See Section 6 and 7), our review of the revised dose adjustment focused on whether the predicted drug exposures at the revised dose adjustments are comparable to those at the dose for patients with normal renal function.

*Evaluation on the Revised Dose Adjustment for Patients With CLcr ≥0 to <15 mL/min*

To avoid using the 0.5 g sulbactam/0.5 g durlobactam dose, the Applicant proposed the following dose regimens for patients with CLcr ≥0 to <15 mL/min.

- For patients who receive sulbactam-durlobactam treatment the first time: 1.0 g sulbactam/1.0 g durlobactam q12h on Day 1 followed by 1.0 g sulbactam/1.0 g durlobactam q24h in patients with CLcr ≥0 to <15 mL/min.
- For patients who are already being treated with sulbactam-durlobactam and need a dose adjustment because the patient's CLcr declines to <15 mL/min during the treatment: 1.0 g sulbactam/1.0 g durlobactam q24h.

Of note, the 1.0 g sulbactam/1.0 g durlobactam q12h regimen was the regimen used in the phase 3 study.

PK analyses showed a small trend for decreased exposures in patients with high body weight (see Section 8.1.2). Thus, the 1.0 g sulbactam/1.0 g durlobactam q12h dosing interval on Day 1 is added to quickly achieve steady state drug exposure in patients across a body weight range of 35 kg to 150 kg. As shown in Table 36, the dosing regimen of 1.0 g sulbactam/1.0 g durlobactam q12h on Day 1 followed by 1.0 g sulbactam/1.0 g durlobactam q24h yielded drug concentrations that achieved PTA >90% across all body weight categories on Day 1 and Day 3 in both plasma and ELF. For patients who have been receiving sulbactam-durlobactam treatment and their CLcr decreases to ≥0 to ≤15 mL/min during the treatment, they would need dose adjustment to accommodate the change in CLcr, since the SUL and DUR exposures would have achieved steady state before the dose adjustment. Hence, a 1.0 g sulbactam/1.0 g durlobactam q24h dose regimen without a loading dose is proposed when the patients' CLcr is decreased to and maintained at ≥0 to ≤15 mL/min during therapy.

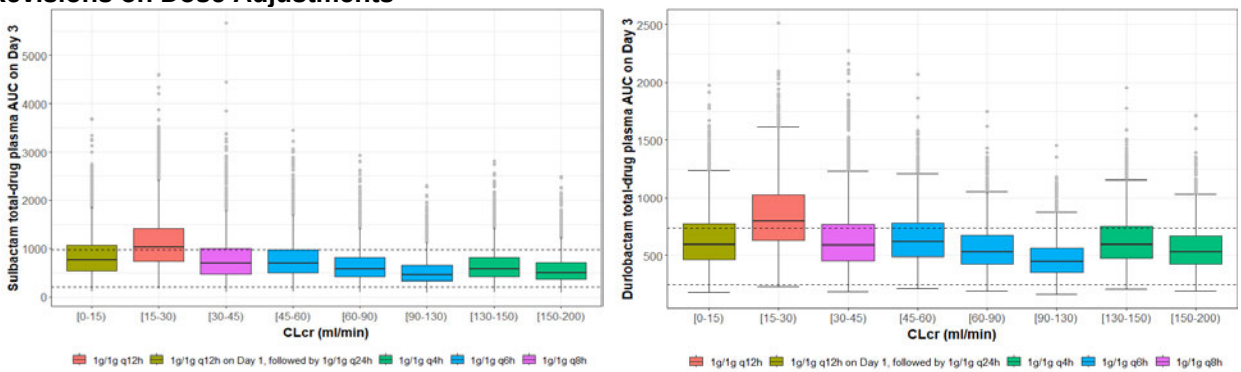
Figure 5 shows the predicted SUL and DUR total-drug plasma AUCs at steady state (Day 3) at the revised dose adjustments across renal function categories. The Day 3 AUCs predicted at the revised dose regimen for patients with CLcr ≥0 to ≤15 mL/min are slightly higher than those with normal renal function but are lower than the Day 3 AUCs in the patients who received a higher dose in the phase 3 study (1.0 g sulbactam/1.0 g durlobactam q12h). Even though the number of subjects evaluated in the phase 3 study is limited, the patients in the phase 3 study were deemed to have acceptable AE profiles including patients with altered renal function. Hence, it is considered that the revised dose adjustments proposed by the Applicant would result in similar AE profiles and thus would be acceptable (refer to Section 7.6).

**Table 36. Percent Probabilities of PK/PD Target Attainment on Days 1 and 3 Among Simulated Patients With Creatinine Clearance of ≥0 to ≤15 mL/min by Weight Groups After Administration of 1 g Sulbactam/1 g Durlobactam q12h, Followed by 1 g Sulbactam/1 g Durlobactam q24h**

| Exposure | MIC (μg/mL)[b] | Day | Percent probabilities of PK-PD target attainment by weight (kg) | | | |
|---|---|---|---|---|---|---|
| | | | ≥ 35 to < 50 | ≥ 50 to < 90 | ≥ 90 to < 120 | ≥ 120 to ≤ 150 |
| Free-drug plasma | 4 | 1 | 100 | 100 | 100 | 100 |
| | | 3 | 100 | 99.8 | 98.2 | 96.2 |
| Total-drug ELF | 4 | 1 | 100 | 100 | 99.7 | 99.0 |
| | | 3 | 100 | 99.6 | 97.2 | 94.3 |

Source: Table 2 of Applicant's response to the FDA Information Request for NDA 216974 dated on March 14, 2023.
[a] Based on the sulbactam free-drug plasma and total-drug ELF %T > MIC target ≥50 and durlobactam free-drug plasma and total-drug ELF AUC:MIC ratio target ≥10.
[b] Represents the sulbactam-durlobactam MIC value.
Note: Shaded cells indicate probabilities of PK/PD target attainment ≥90%.
Abbreviations: AUC, area under curve; ELF, epithelium lining fluid; PD, pharmacodynamics; PK, pharmacokinetics; MIC, maximum inh bitory concentration; q12h, every 12 hours, q24h, every 24 hours; %T > MIC; percent of time free drug remains above the minimum inhibitory concentration

**Figure 5. SUL (Left) and DUR (Right) Total-Drug Plasma Distributions of AUC at Steady State (Day 3) in Simulated Patients Across Renal Function Groups at the Applicant's Proposed Revisions on Dose Adjustments**




Source: Analyses by pharmacometrics review team in the FDA.
Note: Horizontal dashed lines represent the 90% prediction interval of the CLcr ≥90 to <130 mL/min group, which is defined as the 5th and 95th percentiles for SUL or DUR total-drug plasma AUC.
Abbreviations: AUC, area under the curve; CLcr, creatinine clearance; DUR, durlobactam; q4h, every 4 hours, q6h, every 6 hours; q8h, every 8 hours, q12h, every 12 hours; q24h, every 24 hours; SUL, sulbactam

Overall, the simulations, PTA analyses and safety considerations support the revised dosing regimen of 1.0 g sulbactam/1.0 g durlobactam q12h on Day 1 (only for patients who are receiving SUL-DUR for the first time) followed by 1.0 g sulbactam/1.0 g durlobactam q24h for patients with CLcr ≥0 to ≤15 mL/min.

*Evaluation of the Revised Dose Adjustment for Patients With CLcr ≥15 to <30 mL/min*

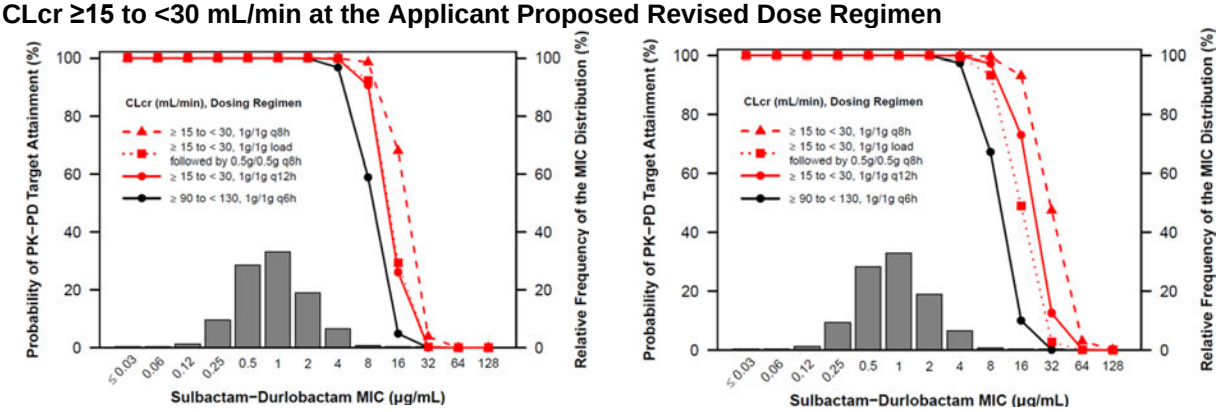
To avoid using the 0.5 g sulbactam/0.5 g durlobactam dose, the Applicant proposed a new regimen of 1.0 g sulbactam/1.0 g durlobactam administered q12h. Of note, the 1.0 g sulbactam/1.0 g durlobactam q8h regimen was the regimen evaluated in the phase 3 study for patients with CLcr ≥15 to <30 mL/min.

Figure 6 shows the results of %PTA by MIC on Day 1 based on both free-drug plasma concentration and total drug concentration in ELF to achieve sulbactam PK/PD target of 50% *f*T > MIC and durlobactam PK/PD target of $AUC_{0-24}$/MIC of 10 (which corresponds to 1-log10

CFU reduction). The proposed new dosing regimen of 1.0 g sulbactam/1.0 g durlobactam administered q12h yielded PTA ≥90% at an MIC of 4 µg/mL in patients with CLcr ≥15 to <30 mL/min based on free plasma concentration or total drug concentration in ELF.

The Day 3 AUCs predicted at the revised dose regimen for patients with CLcr ≥15 to <30 mL/min were higher than those with normal renal function (Figure 6) but were lower than those from the patients who received a higher dose regimen in the phase 3 study (1.0 g sulbactam/1.0 g durlobactam q8h). Even though the number of subjects evaluated in the phase 3 study is limited, the patients in the phase 3 study were deemed to have acceptable AE profiles including patients with altered renal function. Hence, it is considered that the revised dose adjustments proposed by the Applicant would result in similar AE profiles and thus would be acceptable (refer to Section 7.6).

**Figure 6. Percentage Probabilities of PK/PD Target Attainment by MIC on Day 1 Based on Free Drug Plasma Exposures (Left) and Total-Drug ELF Exposures (Right) in Simulated Patients With CLcr ≥15 to <30 mL/min at the Applicant Proposed Revised Dose Regimen**




Source: Figure 16 of Applicant's response to the FDA Information Request for NDA 216974 dated on March 14, 2023.
Note: PTA analysis was based on PK/PD targets of sulbactam (50%*f*T > MIC) and durlobactam (*f*AUC:MIC ratio of 10) which are associated with a 1-$\log_{10}$ CFU reduction.
Abbreviations: *f*AUC:MIC, relationship between area under the free concentration–time curve and minimum inhibitory concentration ratio; CFU, colony forming units; CLcr, creatinine clearance; ELF, epithelium lining fluid; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; PTA, probability of target attainment; q6h, every 6 hours, q8hrs, every 8 hours; q12h, every 12 hours; *f*T > MIC; percent of time free drug remains above the minimum inh bitory concentration

Overall, the simulations, PTA analyses and safety considerations support the revised dosing regimen of 1.0 g sulbactam/1.0 g durlobactam q12h for patients with CLcr ≥15 to <30 mL/min.

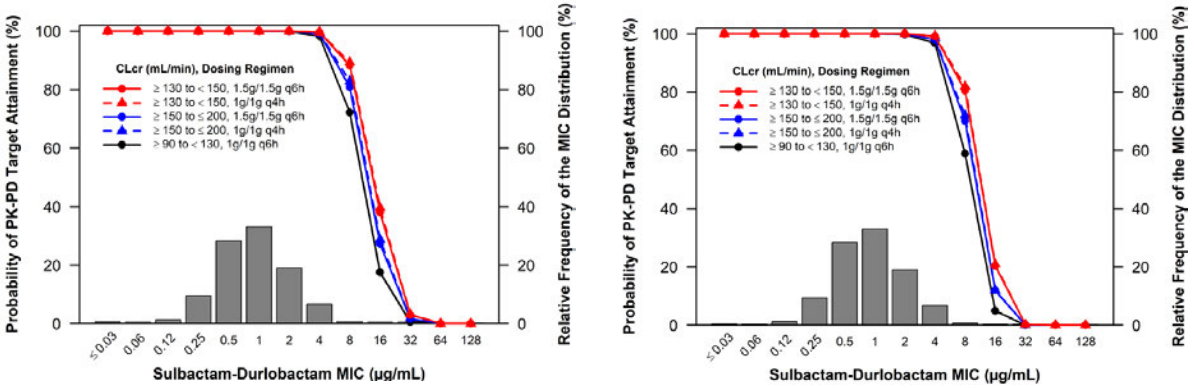
*Evaluation of the Revised Dose Adjustment for Patients With CLcr ≥130 mL/min*

To avoid using the 1.5 g sulbactam/1.5 g durlobactam dose, the Applicant proposed a new dose regimen of 1.0 g sulbactam/1.0 g durlobactam administered every 4 hours (q4h) for patients with CLcr ≥130 mL/min.

Figure 7 shows the results of %PTA by MIC on Day 1 based on both free-drug plasma concentration and total drug concentration in ELF to achieve a sulbactam PK/PD target of 50% *f*T > MIC and a durlobactam PK/PD target of $AUC_{0-24}$/MIC of 10 (which corresponds to 1-log10 CFU reduction). The proposed new dose regimen of 1.0 g sulbactam/1.0 g durlobactam q4h yielded a PTA ≥90% at an MIC of 4 µg/mL in subjects with CLcr ≥130 mL/min based on free plasma concentration or total drug concentration in ELF.

As shown in Figure 6, this dosing regimen results in AUCs at steady state that are comparable to AUCs in patients with normal renal function.

**Figure 7. Percentage Probabilities of PK/PD Target Attainment by MIC on Day 1 Based on Free Drug Plasma Exposures (Left) and Total-Drug ELF Exposures (Right) in Simulated Patients With CLcr ≥130 mL/min at the Applicant Proposed Revised Dose Regimen**




Source: Figure 5 of Applicant's response to the FDA Information Request for NDA 216974 dated on February 25, 2023.
Abbreviations: CLcr, creatinine clearance; ELF, epithelium lining fluid; MIC, maximum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; q4h, every 4 hours, q6h, every 6 hours

The simulations and PTA analyses support the revised dosing regimen of 1.0 g sulbactam/1.0 g durlobactam q4h for patients with CLcr ≥130 mL/min.

**Recommendations on Renal Function-Based Dose Adjustments**

Overall, the Applicant's proposed revisions on the dose adjustments are acceptable. We recommend that the dose regimens presented in Table 35 be included into the labeling.

### 8.1.2. Body Weight

Body weight (BW) was identified as a statistically significant predictor of the variability in clearance and central volume distribution for sulbactam and durlobactam (refer to Section 14.5). Geometric Mean (%CV) values of $AUC_{0-24}$ and the maximum plasma concentration ($C_{max}$) on Days 1 through 3 are provided in Table 37 for patients from the phase 2 and 3 studies, stratified by body weight category. $AUC_{0-24}$ and $C_{max}$ increased as body weight decreased for both drugs. Compared to the exposures from patients with BW of 51 to 90 kg, $AUC_{0-24}$ and $C_{max}$ values on Days 2 and 3 are approximately 2-fold higher for both drugs in patients with BW of 35 to 50 kg. While the number of evaluable patients with BW ≤50 kg from the phase 3 study was limited to draw any conclusion, results of safety analyses suggest that the incidence of SAEs and treatment discontinuations due to AEs following SUL-DUR treatment was similar between patients with BW ≤50 kg and patients with BW >50 kg (see Section 17). Therefore, the higher exposures observed in subjects with low body weight (BW ≤50 kg) are not expected to raise specific safety concerns.

Compared to the exposures from patients with BW between 51 and 90 kg, approximately 25% reduction in $AUC_{0-24}$ on Day 1 was observed in patients with BW >90 kg. The Applicant conducted PTA analyses in the simulated subjects at various body weight bands (35 to 50 kg, 51 to 90 kg, 91 to 120 kg, and 121 to 150 kg) and across various degrees of renal function based on

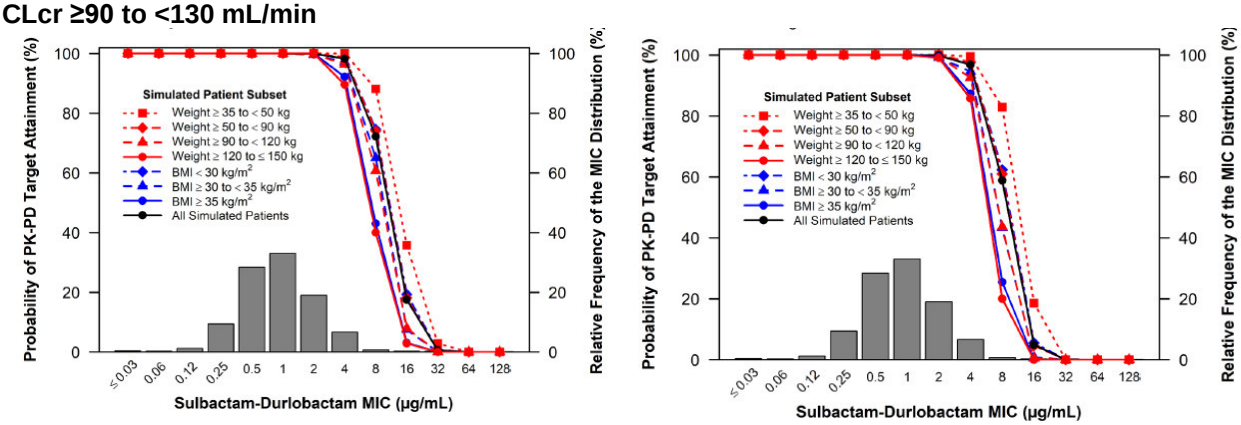
the Applicant's initially proposed dosing regimens listed in Table 34. In general, the PK/PD targets of SUL (%*f*T > MIC of 50%) and DUR (*f*AUC:MIC ratio of 10) associated with a 1-log10 CFU reduction are achieved in ≥90% of simulated patients at MICs up to 4 µg/mL at steady-state (Day 3), including those in the highest weight category (≥120 kg to ≤150 kg), either based on unbound plasma concentration or total-drug concentration in ELF. Of note, MIC of 4 µg/mL covers the MIC levels of greater than 98% of isolates from global surveillance studies and the phase 3 study. Similar PTA results were observed in the simulated patients with a body mass index <30 kg/m$^2$, 30 to <35 kg/m$^2$, or ≥35 kg/m$^2$ at the Applicant's initially proposed dose regimens listed in Table 34. Figure 8 shows the representative %PTA results from simulated subjects with normal renal function (CLcr ≥90 to <130 mL/min). In addition, the Applicant's revised renal function-based dose regimens are deemed acceptable to provide adequate drug exposures across body weight bands (see Section 8.1.1). Therefore, the Applicant's proposal of no dose adjustment based on body weight appears acceptable.

**Table 37. Geometric Mean (%CV) $AUC_{0-24}$ and $C_{max}$ for Sulbactam and Durlobactam in Patients Enrolled in the Phase 2 and 3 Studies by Body Weight Categories**

| | Sulbactam | | | Durlobactam | | |
|---|---|---|---|---|---|---|
| Parameter | 35 – 50 kg (n = 10) | 51 – 90 kg (n = 121) | 91 – 150 kg (n = 31) | 35 – 50 kg (n = 10) | 51 – 90 kg (n = 121) | 91 – 150 kg (n = 31) |
| $AUC_{0-24}$, Day 1 (h•µg/mL) | 797 (39.4%) | 474 (54.2%) | 369 (45.5%) | 739 (21.3%) | 459 (37.9%) | 382 (30.6%) |
| $AUC_{0-24}$, Day 2 (h•µg/mL) | 938 (47.9%) | 520 (69.9%) | 419 (57.3%) | 856 (23.5%) | 500 (59.0%) | 438 (35.7%) |
| $AUC_{0-24}$, Day 3 (h•µg/mL) | 958 (50.9%) | 457 (109%) | 426 (60.0%) | 870 (27.3%) | 429 (115%) | 444 (36.1%) |
| $C_{max}$, Day 1 (µg/mL) | 52.5 (39.3%) | 32.6 (50.4%) | 25.5 (45.3%) | 48.0 (21.4%) | 30.8 (36.2%) | 25.5 (33.0%) |
| $C_{max}$, Day 2 (µg/mL) | 54.6 (42.7%) | 32.9 (56.4%) | 26.4 (47.9%) | 49.4 (23.8%) | 30.8 (46.0%) | 26.4 (31.4%) |
| $C_{max}$, Day 3 (µg/mL) | 55.1 (43.4%) | 30.2 (88.6%) | 26.5 (50.8%) | 49.7 (24.8%) | 27.5 (95.6%) | 26.3 (31.5%) |

Source: Adapted from Table 28 from Applicant's Module 2.7.2 Summary of Clinical Pharmacology
Abbreviations: $AUC_{0-24}$, area under the curve from 0 to 24 hours; $C_{max}$, maximum plasma concentration; CV, coefficient of variation; n, number of subjects in category

**Figure 8. Percentage Probabilities of PK/PD Target Attainment by MIC on Day 1 Based on Free Drug Plasma Exposures (Left) and Total-Drug ELF Exposures (Right) in Simulated Subjects With CLcr ≥90 to <130 mL/min**




Source: Figure 11 and Figure 12 of Applicant's response to the FDA Information Request for NDA 216974 dated on February 2, 2023
Abbreviations: BMI, body mass index; CLcr, creatinine clearance; ELF, epithelium lining fluid; MIC, maximum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics

### 8.1.3. Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of sulbactam and durlobactam have not been evaluated. Hepatic impairment is not expected to alter the elimination of XACDURO as neither sulbactam nor durlobactam undergo substantial hepatic metabolism and excretion. Dosage adjustments are not necessary in patients with impaired hepatic function.

### 8.1.4. Other Intrinsic Factors

Results of population PK covariate analyses based on pooled data from phase 1, phase 2, and phase 3 studies indicate that age (18 to 91 years old), country of origin (China versus other), race (White 65%, Black 13%, Asian 16.7%, American Indian/Alaska Native 1.86%, Other 3.46%), and sex (male 63%, female 37%) were not statistically significant covariates that affect the PK of sulbactam and durlobactam (refer to Section 14.5).

## 8.2. Extrinsic Factors

### 8.2.1. Pharmacokinetics based Drug-Drug Interaction

Results from phase 1 study demonstrated that no drug-drug interactions were observed among durlobactam, sulbactam, imipenem, and cilastatin in healthy subjects (refer to Section 14.2 In Vivo Studies). Both sulbactam and durlobactam undergo minimal hepatic metabolism. No formal in vitro studies with cytochrome P450 enzymes (CYPs) and sulbactam were conducted.

Durlobactam is not metabolized by CYPs. In vitro studies showed that durlobactam did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 and did not induce CYP1A2, CYP2B6, or CYP3A4 at therapeutic plasma

concentrations. Hence, durlobactam is unlikely to result in clinically relevant CYP-mediated DDIs.

In vitro data showed that sulbactam did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, BSEP, OAT1, OAT3, MATE1, or MATE2-K at therapeutic plasma concentrations. In vitro data also indicated that durlobactam did not inhibit P-gp, BCRP, OATP1B1, OAT1, OAT3, or OCT2 at therapeutic plasma concentrations.

In vitro data suggest that sulbactam and durlobactam are both substrates of OAT1. However, only sulbactam is predicted to have active secretion as a significant portion of total clearance; therefore, inhibition of OAT1 may increase sulbactam plasma concentrations. No clinical studies have been conducted with SUL-DUR and OAT1 inhibitors. However, since the in vitro data suggest the potential risk of drug-drug interaction between OAT1 inhibitor and sulbactam and the inhibitory effect of OAT1 inhibitors has been observed for other β-lactam drugs, concomitant administration of OAT1 inhibitors such as probenecid with SUL-DUR is not recommended.

## 8.3. Plans for Pediatric Drug Development

The Applicant submitted a pediatric study plan along with a request for a deferral of pediatric studies in all age groups until efficacy and safety have been demonstrated in the adult population. The Applicant's request was discussed with the Pediatric Review Committee (PeRC) on March 28, 2023, and the PeRC concurred with granting a deferral for the pediatric studies.

A postmarketing requirement to conduct a multi-dose study to assess the pharmacokinetics, safety and tolerability of sulbactam-durlobactam in children from birth to less than 18 years who are receiving systemic antibiotic therapy for suspected or confirmed infection will be requested upon approval.

Also, a repeat dose juvenile toxicity study is ongoing to inform dosing in patients from birth to less than1 year of age. A postmarketing commitment for the study completion and final report submission dates will be issued upon approval.

## 8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Table 38 and Table 39 discuss the nonclinical data that will be conveyed in SUL-DUR's labeling related to pregnancy, lactation, and effects on fertility/reproductive potential.

**Table 38. Nonclinical Data Supporting Labeling on Pregnancy and Lactation**

| Labeling Section | Nonclinical Data |
|---|---|
| 8.1 Pregnancy | Daily administration of durlobactam at 400, 800, or 1600 mg/kg/day (administered as four doses per day) via subcutaneous injection to pregnant mice from GD 6 through 15 resulted in durlobactam-related, (b) (4) the maximum recommended human dose based on AUC comparisons. |
| 8.2 Lactation | There are no data on the presence of (b) (4) durlobactam (b) (4) in animal milk. |
| 13.1 Carcinogenesis, mutagenesis, impairment of fertility | Carcinogenicity studies have not been conducted with XACDURO. Durlobactam was negative in (b) (4) genetic toxicology studies, including the *Salmonella typhimurium* bacterial reverse mutation assay, in vivo and in vitro micronucleus assays, and the in vivo Pig-A assay in rats. No adverse effects on fertility, reproductive performance, fetal viability, growth, or postnatal development were observed in male and female rats, and female mice for durlobactam at intravenous doses up to 1000 mg/kg/day (approximately 4 times the MRHD based on AUC comparisons) and subcutaneous doses up to 1600 mg/kg/day, (equivalent to 4 times the MRHD based on AUC comparisons), respectively. |

Source: Reviewer generated table.
Abbreviations: AUC, area under curve; GD, gestation day; MRHD, maximum recommended human dose, XACDURO, sulbactam and durlobactam

**Table 39. Reproductive Toxicity Safety Margins for Durlobactam**

| Study | NOAEL (mg/kg) | Nonclinical Exposure | Safety Margin[1] |
|---|---|---|---|
| Fertility rat | 1000 | 1600 | 3 |
| EFD rat | 1000 | 1600 | 3 |
| EFD mouse | 400 | 470 | 1 |
| PPND rat | 1000 | 1600 | 3 |

Source: Reviewer generated table.
[1] Exposure multiples were based on population pharmacokinetics analysis where the clinical dose of durlobactam resulted in systemic exposures of $AUC_{(0\text{-}24h)}$ =466 microgram*hour/mL.
Abbreviations: $AUC_{(0\text{-}24h)}$, area under the curve from 0 to 24 hours; EFD, embryofetal development; NOAEL, no observed adverse effect level; PPND, peri and postnatal development

# 9. Product Quality

### Approval With a Postmarketing Requirement

The Office of Pharmaceutical Quality review team has assessed NDA 216974 with respect to chemistry, manufacturing, and controls (CMC). The proposed drug product contains two sterile solid components, sulbactam for injection and durlobactam for injection, filled into separate single-dose glass vials, which need to be reconstituted and further diluted for intravenous infusion. The sulbactam-durlobactam drug product for commercial use will be provided in a carton of three co-packaged vials, one vial of sulbactam for injection (containing 1g of sulbactam) and two vials of durlobactam for injection (each containing 0.5g of durlobactam). The majority of CMC information provided in the NDA to assure and demonstrate the identity, strength, purity, and quality of the proposed drug product, sulbactam for injection and durlobactam for injection, was found to be adequate. In addition, all manufacturing facilities

listed in the NDA were found adequate. However, the currently proposed impurity controls for the durlobactam component (drug substance and drug product) are not aligned with the recommendations of ICH guidances and additional postmarketing studies will be needed to address the impurity control issues. In addition, since the proposed drug product is an injectable powder for reconstitution, it needs to comply with applicable guidances and regulations to ensure that the excess solid in a vial is sufficient to allow for withdrawal and administration of the net container content of the drug product. As agreed by the Applicant, these issues will be further addressed through additional post approval studies (PMR and PMC, respectively) included in Section 24, below. For further details refer to OPQ Review of this NDA in DARRTS.

### 9.1. Device or Combination Product Considerations

Not applicable.

## 10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The Office of Scientific Investigations (OSI) performed inspections at three study sites that participated in study CS2514-2017-0004. OSI's assessment was that the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the proposed indication. Please refer to the review by Cheryl Grandinetti, PharmD, for additional information. The Applicant certified that there were no investigators with disclosable financial interests or arrangements. Please refer to the financial disclosure form in Section 25.

## 11. Advisory Committee Summary

A meeting of the Antimicrobial Drugs Advisory Committee was convened on April 17, 2023, to discuss NDA 216974 for SUL-DUR. The committee was asked to vote on whether the overall benefit-risk assessment is favorable for the use of SUL-DUR for treatment of patients with HABP/VABP caused by susceptible strains of ABC organisms. There were 12 "yes" votes, 0 "no" votes, and 0 abstentions.

The committee agreed that the study demonstrated compelling results for the efficacy of sulbactam-durlobactam in reducing mortality in HABP/VABP caused by ABC but highlighted the limitations of a small safety database and recommended that augmented postmarketing surveillance be conducted to collect more safety data.

Consequently, a postmarketing requirement to conduct a single-arm, open-label, prospective trial of the safety of sulbactam-durlobactam in patients with *Acinetobacter baumannii-calcoaceticus* complex infections will be requested upon approval.

# III. Additional Analyses and Information

## 12. Summary of Regulatory History

The Applicant, Entasis Therapeutics, Inc., submitted a pre-investigational new drug (PIND 131330) type B meeting request on July 6, 2016, to discuss the development of Sulbactam-Durlobactam (ETX 2514) Powder for Injection for the treatment of multi-drug resistant (MDR) *Acinetobacter baumanii* infections.

A PIND meeting was held on September 26, 2016. Multiple aspects of the drug development program for Sulbactam-ETX 2514 Powder for Injection were discussed, including a phase 1 pharmacokinetic and tolerability study, projected dosing, and drug exposure necessary to provide an adequate safety database. Additionally, pivotal study design options were proposed by the Division of Anti-Infectives (Division) for consideration by the Applicant.

On March 8, 2017, a subsequent meeting was held to further discuss the clinical development strategy for Sulbactam-ETX 2514 Powder for Injection. Topics of discussion included comparator drug treatment effect, noninferiority (NI) margin, and the proposed primary analysis population.

On June 22, 2017, the Applicant submitted their initial IND for Sulbactam-ETX 2514 Powder for Injection, and the IND was deemed safe to proceed.

On July 21, 2017, and July 28, 2017, the Applicant submitted requests for Qualified Infectious Disease Product designation and Fast Track designation, respectively. On September 1, 2017, the Division granted the product both Qualified Infectious Disease Product and Fast Track designations for the treatment of hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP) and bloodstream infections due to *Acinetobacter baumannii (A. baumannii*).

A phase 2, double-blind, randomized, placebo-controlled study evaluating sulbactam and durlobactam (SUL-DUR) in the treatment of complicated urinary tract infections was conducted from January to May 2018. All patients received background therapy with imipenem-cilastatin.

After discussions with the Division, the Applicant decided to focus the SUL-DUR development program on the treatment of carbapenem-resistant *A. baumannii* infections. In June 2018, the Applicant submitted a protocol for a phase 3 noninferiority study evaluating the safety and efficacy of SUL-DUR in patients with *A. baumannii* by comparing SUL-DUR to colistin.

On November 5, 2018, an End-of-Phase 2 meeting was held wherein a streamlined development strategy was discussed. The Applicant planned to conduct a single phase 3 study in patients with HABP/VABP and bloodstream infections caused by *A. baumannii*. An NI margin of 19% was agreed to be used in the study. A phase 3 study titled, “A Randomized, Active-Controlled Study to Evaluate the Efficacy and Safety of Intravenous Sulbactam-ETX2514 in the Treatment of Patients With Infections Caused by *Acinetobacter baumannii-calcoaceticus* Complex” was started in September 2019. The primary efficacy analysis plan included patients with carbapenem-resistant infections.

On June 4, 2019, the Office of Medication Error Prevention and Risk Management conditionally approved the Applicant's proprietary name, XACDURO.

To address the statutory requirements under the Pediatric Research Equity Act, the Applicant submitted their initial Pediatric Study Plan (iPSP) on December 13, 2018. The Division did not agree with the Applicant's extrapolation of safety data to the pediatric population and did not agree with the Applicant's plan to request a waiver in neonates up to 12 months of age, as *Acinetobacter baumannii-calcoaceticus* infections do occur in neonatal intensive care settings. The Applicant was issued an "Initial Pediatric Study Plan – Written Response" letter on March 17, 2019.

The Applicant submitted a revised iPSP on June 21, 2019, indicating that they were no longer seeking any waivers, and they planned to study Sulbactam-ETX 2514 Powder for Injection in children 0 to <17 years of age. The Division and the Pediatric Review Committee (PeRC) agreed with the plan to request a deferral of pediatric studies from birth to less than 17 years of age until efficacy and safety have been demonstrated in the adult population. On July 18, 2019, the Applicant was issued an "Agreed iPSP" letter.

An End-of-Phase 2 Chemistry, Manufacturing, and Controls (CMC) meeting was planned for November 21, 2019; however, following review of the FDA Preliminary Meeting Responses, the meeting was cancelled.

In June 2020, the Applicant requested a meeting to discuss the possibility of performing the final analysis in the ongoing phase 3 study using an alternative alpha level, citing challenges with enrollment related to the coronavirus disease of 2019 (COVID-19) pandemic as well as higher-than-anticipated rates of colistin resistance, which precluded the inclusion of some of the enrolled subjects in the primary efficacy analysis. At a meeting in August 2020, the Division noted they did not agree with the use of an alternative alpha level but suggested an expansion of the NI margin from 19% to 20% while retaining a two-sided alpha of 0.05, which was accepted by the Applicant. The protocol was subsequently amended, and the phase 3 study was completed in July 2021.

The Applicant amended their Agreed iPSP on May 18, 2021, requesting an extension of the timeline for pediatric development due to adult enrollment issues because of the COVID-19 pandemic and high rates of colistin resistance. The Applicant was issued an "Amended Agreed Initial Pediatric Study Plan"- letter on August 18, 2021.

The Applicant was granted two meetings to discuss the product quality and manufacturing/CMC aspects of their development program. These meetings were held on June 23, 2021, and March 24, 2022.

A Pre-NDA meeting was held on March 25, 2022.

On September 29, 2022, Entasis Therapeutics, Inc. submitted NDA 216974 for SUL-DUR as an injection for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex in adults. SUL-DUR is a copackaged product containing sulbactam (SUL), a beta-lactam antibacterial and beta-lactamase inhibitor, and durlobactam (DUR), a beta-lactamase

inhibitor. NDA 216974 was submitted as a 505(b)(2) program, received priority review, and has a PDUFA goal date of May 29, 2023.

# 13. Pharmacology Toxicology

## 13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

### 13.1.1. Pharmacology

#### 13.1.1.1. Primary Pharmacology

Sulbactam exhibits its antibacterial activity through the inhibition of penicillin binding protein (PBP) 3, a transpeptidase required for the final step of peptidoglycan formation, which is essential for the synthesis of the bacterial cell wall. Durlobactam, which is also referred to as ETX2514 throughout this review, is a β-lactamase inhibitor which may covalently bind to the catalytic serine residue of that enzyme. Durlobactam fully restored sulbactam's activity against Class A-, C-, and D-expressing strains in a β-lactamase isogenic panel in *A. baumannii (*see Section 20.1).

#### 13.1.1.2. Secondary Pharmacology

The secondary pharmacology of durlobactam was evaluated via in vitro radioligand binding, as well as enzyme and functional assays, covering 192 distinct molecular targets including receptors, ion channels, transporters, and enzymes. Durlobactam was shown to inhibit chymotrypsin (the half maximal inhibitory concentration of 122 μM) and showed binding to the agonist site of the cannabinoid CB1 receptor with a half maximal effective concentration of 410 μM. At a concentration of 1 mM, durlobactam resulted in a 30% inhibition in the cathepsin S assay.

**Table 40. Effect of Durlobactam in In Vitro Radioligand Binding, Enzyme, and Functional Assays**

| Target | Binding Ki or Enzyme $IC_{50}$ (μM) | Functional $IC_{50}$ or $EC_{50}$ (μM) | Mode of Action |
|---|---|---|---|
| Chymotrypsin | 122 | No data available | Inhibitor |
| Cannabinoid $CB_1$ receptor | >1000<br>(28% inhibition at 1mM) | 410 | Agonist |
| Cathepsin S | >1000<br>30% inhibition at 1mM | No data available | No data available |

Source: Reviewer generated table.
Abbreviations: $EC_{50}$, half maximal effective concentration; $IC_{50}$, half maximal inhibitory concentration; Ki, inhibitory constant

## 13.1.1.3. Safety Pharmacology

**Table 41. Central Nervous System**

| Study Features and Methods | Details |
|---|---|
| Study number | PC2514-2018-0002 |
| Study title | Central Nervous System Safety Pharmacology Evaluation of ETX2514 Following Intravenous Infusion Administration to Male Rats |
| Species/strain | Rats, Sprague Dawley |
| Number/sex/dose group | 8, male |
| Doses | 500, 1000, 2000 mg/kg |
| Route of administration | Intravenous (2-hour infusion) |
| Dosing frequency | Single dose |
| Findings | No drug-related findings. |

Source: Reviewer generated table
Abbreviations: ETX2514, durlobactam

**Table 42. Cardiovascular**

| Study Features and Methods | Details |
|---|---|
| Applicant study number | SN-002514-2015-08 |
| Study title | Cardiovascular Safety Pharmacology Evaluation of ETX2514 Administered by Intravenous Infusion to Male Telemetry-Instrumented Conscious Dogs |
| Species/strain | Dog, beagle |
| Number/sex/dose group | 4 |
| Doses | 0, 500, 1000, 2000 mg/kg |
| Route of administration | 4 dogs were infused at over a period of 2 hours (+2 minutes) on Days 1, 5, 8, and 12. |
| Dosing frequency | Once every 4 days |
| Findings | No durlobactam-related effects. |

Source: Reviewer generated table.
Abbreviations: ETX2514, durlobactam

**Table 43. Cardiovascular Screening In Vitro**

| Study Features and Methods | Details |
|---|---|
| Study number | SN-002514-2017-0012 |
| Study title | ETX2514: Selectivity Screening in Cardiac Ion Channel Electrophysiological Assays In Vitro |
| Test system | Eight human recombinant cardiac ion channels in stably transfected CHO cells (human Cav1.2/βα2δ, hHCN4, hKv1.5, hKv4.3/hKChIP2.2, hKv7.1/hKCNE1, hKv11.1 (hERG), hNav1.5) and HEK293 cells (hCav3.2) |
| Replicates | Data from up to four cells expressing a given channel were analyzed to derive scaled percent inhibition data for durlobactam. |
| Doses | Up to 1000 µM |
| Route of exposure | In vitro. |
| Findings | Durlobactam did not cause >50% mean inhibitory effect in any of these systems. |

Source: Reviewer generated table
Abbreviations: CHO, Chinese hamster ovary cells; ETX2514, durlobactam; hERG, human ether-à-go-go-related gene

**Table 44. Respiratory**

| Study Features and Methods | Details |
|---|---|
| Applicant study number | SN-002514-2015-08 |
| Study title | Respiratory Safety Pharmacology Evaluation Using Head-Out Plethysmography of ETX2514 Following Intravenous Administration to Male Rats |
| Species/strain | Rat, Sprague Dawley |
| Number/sex/dose group | 8, male |
| Doses | 0, 500, 1000, 2000 mg/kg |
| Route of administration | Intravenous infusion on each dosing day at 5 mL/kg/hour. |
| Dosing frequency | Single dose |
| Findings | No drug-related findings. |

Source: Reviewer generated table
Abbreviations: ETX2514, durlobactam

### 13.1.1.3.1. Pharmacokinetics

The absorption, distribution, metabolism, and excretion profile of durlobactam and related compounds were studied in vitro and in vivo in mice, rats, rabbits, and dogs. The information was obtained to validate nonclinical safety studies that provide human risk assessment assistance prior to, and during, clinical trials.

## Absorption

The intravenous pharmacokinetics (PK) of durlobactam were generally dose proportional with increasing dose. Exposure in males and females was comparable. The observed half-life of durlobactam in rats and dogs was brief at 0.23 and 0.80 hours, respectively, and there was minimal accumulation with multiple dosing. In studies involving co-administration of sulbactam with durlobactam or each agent alone, minimal differences in PK were observed when administered alone or in combination to rats, suggesting no significant drug-drug interactions.

**Table 45. Intravenous Pharmacokinetics of Durlobactam in Rats and Dogs After a Single Dose**

| Species | Rat | Dog |
|---|---|---|
| Study # | PC2514-2016-0027 | PC2514-2016-0026 |
| Dose (mg/kg) | 3 | 0.4 |
| $C_{max}$ (ng/mL) | 4125 | 1500 |
| $T_{max}$ (h) | 0.25 | 0.26 |
| $Vd_{ss}$ (L/kg) | 0.5 | 0.28 |
| CL (mL/min/kg) | 45 | 5.1 |
| Renal CL (mL/min/kg) | 23 | 3.6 |
| $T_{½}$ (h) | 0.23 | 0.8 |
| $AUC_{(0\text{-last})}$ (ng*h/mL) | 1129 | 1390 |

Source: Reviewer generated table from Study PC2514-2016-0027: ETX2514: In Vivo Pharmacokinetics of ETX2514 in Male Han Wistar Rats and Study PC2514-2016-0026: ETX2514: In Vivo Pharmacokinetics of ETX2514 in Beagle Dogs
Abbreviations: $AUC_{(0\text{-last})}$, area under the curve from dosing to the time of the last measured concentration; CL, clearance; $C_{max}$, maximum plasma concentration; ETX2514, durlobactam; $T_{max}$, time to maximum plasma concentration; $T_{½}$, half-life, $Vd_{ss}$, volume of distribution at steady state

**Table 46. ADME/PK TK Data From General Toxicology Studies**

| Study Features and Methods | Details |
|---|---|
| Study title | ETX2514 and Sulbactam: 28 Day Intravenous (Infusion) Administration Toxicity Study in the Rat Followed by a 4-Week Recovery Period. Study PC2514-2017-0018 |
| Dose | Sulbactam $AUC_{(0\text{-}24h)}$ 458 µg*h/mL (Day 28, in high dose combination 600 mg/kg sulbactam/600 mg/kg durlobactam)<br><br>Durlobactam $AUC_{(0\text{-}24h)}$ 481 µg*h/mL (Day 28, in high dose combination 600 mg/kg sulbactam/600 mg/kg durlobactam) |
| Accumulation | None |
| Dose proportionality: | Dose proportional |

Source: Reviewer generated table
Abbreviations: ADME, absorption, distribution, metabolism, and excretion; $AUC_{(0\text{-}24h)}$, area under the curve from 0 to 24 hours; ETX2514, durlobactam; PK, pharmacokinetics; TK, toxicokinetics

**Table 47. Durlobactam Toxicokinetics Parameters in Rat Plasma After 1 and 28 Days of Dosing With Durlobactam or Sulbactam-Durlobactam**

| Day | Dose Group | Durlobactam Dose (mg/kg) | Sulbactam Dose (mg/kg) | $AUC_{(0\text{-}26h)}$ µg*h/mL |
|---|---|---|---|---|
| 1 | 2 | 600 | 0 | 441 |
| | 3 | 300 | 300 | 247 |
| | 4 | 600 | 600 | 530 |
| 28 | 2 | 600 | 0 | 439 |
| | 3 | 300 | 300 | 223 |
| | 4 | 600 | 600 | 481 |

Source: Reviewer generated table from Study report # PC2514-2017-0018: ETX2514 and Sulbactam: 28 Day Intravenous (Infusion) Administration Toxicity Study in the Rat Followed by a 4-Week Recovery Period. Study PC2514-2017-0018
Abbreviations: $AUC_{(0\text{-}26h)}$, area under the curve from 0 to 26 hours; ETX2514, durlobactam

**Table 48. Durlobactam Toxicokinetics Parameters in Dog Plasma After 1 and 28 Days of Dosing With Durlobactam**

| Day | Dose Group | Durlobactam Dose (mg/kg) | $C_{max}$ | $AUC_{(0\text{-}26h)}$ |
|---|---|---|---|---|
| 1 | 2 | 500 | 674 | 1560 |
| | 3 | 1000 | 1390 | 3280 |
| | 4 | 2000 | 2650 | 6480 |
| 28 | 2 | 500 | 684 | 1680 |
| | 3 | 1000 | 1240 | 2955 |
| | 4 | 2000 | 2490 | 6105 |

Source: Reviewer generated table from Study report # PC2514-2020-0001. A 28-Day Study of ETX2514 by Intravenous Infusion in Beagle Dogs with a 28-Day Recovery Period. Study PC2514-2020-0001
Abbreviations: $AUC_{(0\text{-}26h)}$, area under the curve from 0 to 26 hours; $C_{max}$, maximum plasma concentration; ETX2514, durlobactam

**Table 49. Sulbactam Toxicokinetic Parameters in Rat Plasma After 7 and 28 Days of Dosing With Sulbactam Alone or Sulbactam-Durlobactam**

| Species (Duration) Report Number | Dose (mg/kg/day) | Sex | Steady State Exposures | | |
|---|---|---|---|---|---|
| | | | $C_{max}$ (µg/mL) | AUC (µg*h/mL) | Animal to Human AUC Ratio [a, b] |
| Rat (7-Day) PC2514-2017-0016 | 100 | M/F | 36.6/49.9 | 79.8/101 | 0.19 |
| | 100/100 | M/F | 42.0/41.1 | 93.2/98.7 | 0.21 |
| | 200 | M/F | 86.2/51.9 | 201/128 | 0.35 |
| | 200/200 | M/F | 114/96.4 | 246/234 | 0.52 |
| | 400 | M/F | 135/160 | 319/285 | 0.65 |
| | 400/400 | M/F | 192/183 | 459/406 | 0.93 |
| Rat (28-Day) PC2514-2017-0018 | 300/300 | M/F | 117/123 | 179/222 | 0.43 |
| | 600/600 | M/F | 195/293 | 338/582 | 0.99 |

**Abbreviations:** AUC = area under the concentration time curve; $C_{max}$ = maximum plasma concentration; F = female; M = male.
[a] Geometric mean Phase 3 patient $AUC_{0\text{-}24h}$ = 466 µg*h/mL.
[b] Mean of males and females used to calculate ratio.

Source: Applicant's table

## Distribution

Quantitative, whole-body autoradiography studies following administration of intravenous (IV) [$^{14}$ C]-durlobactam to rats showed that the highest concentrations were observed in those tissues associated with renal excretion of the dose, such as the bladder and the kidneys. Tissue concentrations declined rapidly, and by 168 hours postdose, radioactivity was measurable only in the liver, kidney cortex, skin, urinary bladder contents, and blood. Concentrations in the brain and spinal cord were low throughout with tissue/blood ratios of <0.1, indicating that test material-related radioactivity had not penetrated the blood-brain barrier. Protein binding of durlobactam was very low with the percentage of unbound durlobactam ranging from 78.3% to 100% across mouse, rat, guinea pig, dog, and humans, with no evidence of saturation or concentration dependence. Sulbactam protein binding was also low, with the percentage unbound ranging from 62% in humans to 95% in mice.

## Metabolism

Hydrolysis of the diazabicyclooctenone core and subsequent decarboxylation in the plasma represented a significant metabolic pathway. In vitro rat and human plasma incubations demonstrated ring hydrolysis and multiple downstream metabolites, which included loss of the sulfate. Durlobactam was metabolically stable in rat, dog, and human hepatocytes, as well as rat and dog microsomes. Fortification of microsomes with cytosol resulted in 'ring opened' metabolites and subsequent bioconjugated compounds.

**Table 50. Comparative Systemic Exposures of Durlobactam and Metabolites/Degradants in Rats and Humans**

| Species | Durlobactam (M277) | ETX-021627 (M172) | ETX-014799 (M251) | ETX-021272 (M294) | ETX-021605 (M448) | ETX-202496 (M323) | ETX-011204 (M277) |
|---|---|---|---|---|---|---|---|
| | $AUC_{0\text{-}24}$, µM*h | | | | | | |
| Rat[a] (PC2514-2022-0014) | 3567 | 281 | 54.2 | 9.01 | 7.73 | 4.66 | 3.64 |
| Human (CS2514-2016-0001)[b,d] | 1740 | 200 | 40.8 | 1.86 | 0.468 | 0.472 | 21.6 |
| Fold exposure in rat[c] | 2.05 | 1.41 | 1.33 | 4.84 | 16.5 | 9.87 | 0.17 |

Source: Applicant generated table.
Abbreviations: $AUC_{(0\text{-}24h)}$, area under the curve from 0 to 24 hours

## Excretion

**Table 51. Excretion: Recovery of Radioactivity From Male Nonpigmented Rats Following a Single 2 Hour Intravenous Infusion Administration of [14C] ETX-2514 At 250 mg/kg**

| Sample | Collection period | 4M | 5M | 6M | 31M | Mean | SD |
|---|---|---|---|---|---|---|---|
| Urine | Predose | BLQ | BLQ | BLQ | BLQ | BLQ | - |
| | 0 - 6 h | 73.31 | 39.72 | 27.68 | 47.07 | 46.95 | 19.31 |
| | 6 h - 24 h | 10.46 | 9.87 | 60.02 | 12.06 | 23.10 | 24.63 |
| | 24 h - 48 h | 0.50 | 0.96 | 1.88 | 0.43 | 0.94 | 0.67 |
| | 48 h - 72 h | 0.10 | 0.09 | 0.27 | 0.09 | 0.14 | 0.09 |
| | 72 h - 96 h | 0.07 | 0.08 | 0.12 | 0.04 | 0.08 | 0.03 |
| | 96 h - 120 h | 0.04 | 0.04 | 0.06 | 0.02 | 0.04 | 0.02 |
| | 120 h - 144 h | 0.03 | 0.03 | 0.04 | 0.04 | 0.04 | 0.01 |
| | 144 h - 168 h | 0.02 | 0.02 | 0.02 | 0.06 | 0.03 | 0.02 |
| | Subtotal | 84.53 | 50.81 | 90.09 | 59.81 | 71.31 | 18.97 |
| Faeces | Predose | BLQ | BLQ | BLQ | BLQ | BLQ | - |
| | 0 - 24 h | 2.00 | 2.63 | 1.33 | 4.06 | 2.51 | 1.16 |
| | 24 h - 48 h | 0.98 | 1.10 | 1.00 | 1.48 | 1.14 | 0.23 |
| | 48 h - 72 h | 0.29 | 0.33 | 0.26 | 0.31 | 0.30 | 0.03 |
| | 72 h - 96 h | 0.09 | 0.09 | 0.10 | 0.05 | 0.08 | 0.02 |
| | 96 h - 120 h | 0.04 | 0.03 | 0.05 | 0.07 | 0.05 | 0.02 |
| | 120 h - 144 h | 0.03 | 0.02 | 0.02 | 0.03 | 0.03 | 0.01 |
| | 144 h - 168 h | BLQ | BLQ | BLQ | 0.04 | 0.02 | 0.02 |
| | Subtotal | 3.43 | 4.20 | 2.76 | 6.04 | 4.11 | 1.42 |
| Expired Air [A] | Predose-72h | 0.02 | 0.01 | 0.02 | NA | 0.02 | 0.01 |
| Cage Wash | 0 - 24 h | 7.99 | 5.36 | 2.52 | 4.02 | 4.97 | 2.32 |
| | 24 h - 48 h | 0.21 | 0.23 | 0.16 | 0.05 | 0.16 | 0.08 |
| | 48 h - 72 h | 0.04 | 0.06 | 0.08 | 0.02 | 0.05 | 0.03 |
| | 72 h - 96 h | 0.02 | 0.03 | 0.03 | 0.02 | 0.03 | 0.01 |
| | 96 h - 120 h | 0.01 | 0.01 | 0.01 | 0.02 | 0.01 | 0.01 |
| | 120 h - 144 h | 0.01 | 0.01 | 0.01 | 0.04 | 0.02 | 0.02 |
| | 144 h - 168 h | BLQ | BLQ | BLQ | 0.22 | 0.06 | 0.11 |
| | Subtotal | 8.28 | 5.70 | 2.81 | 4.39 | 5.30 | 2.31 |
| Carcass | 168 h | 0.51 | 0.45 | 0.46 | 1.19 | 0.65 | 0.36 |
| Total Recovery | | 96.77 | 61.17 [B] | 96.14 | 71.43 [B] | 81.38 | 17.91 |

NA Not applicable. Not sampled
A Sample collection stopped after 72 hours post dose administration as <1% of administered dose was detected in two consecutive sampling intervals.
B Low mass balance. Potentially due to low recovery of total urinary excretion sample as faeces, cage washings and carcass similar across all animals (see Table 4 for 4M and 6M mass balance only)
BLQ Below limit of quantification. Equivalent to zero in calculations.

Source: Applicant's table
Abbreviations: ETX2514, durlobactam; SD, standard deviation

Radioactivity was eliminated very quickly via the renal route with concentrations also observed in the gastrointestinal tract, suggesting some biliary excretion. The elimination half-life was less

than 1 hour in both rats and dogs. In one rat study, 87.3% of the dose was excreted in the urine, 3.10% in the feces, 5.55% in the cage wash, 0.49% in the carcass, and 0.02% expired in the air. Over 52% of the excreted dose in urine was intact durlobactam. In vitro studies confirmed durlobactam and sulbactam are substrates for the kidney transporter organic anion transporter 1 (OAT)1.

### 13.1.1.4. General Toxicology

**Study Title/Number: A 28-Day Study of ETX2514 by Intravenous Infusion in Beagle Dogs With a 28-Day Recovery Period. Study PC2514-2020-0001**

Key Study Findings

- Adverse effects included watery stool; vomiting and salivation (increased at all durlobactam doses); mucoid, discolored feces (increased at 1000 and 2000 mg/kg); reduced epididymides, testes, and prostate weight (at all doses, by as much as 37%); and reduced alkaline phosphatase (reduced by 13 to 44% at all doses)
- At the end of the recovery period, prostate weights were elevated by 75% to 125%. The reduction in testes weights persisted (-26% at the high dose) at the end of the recovery period.
- A no observed adverse effect level (NOAEL) could not be determined because of prostate findings at the lowest dose, but changes reversed by the end of dosing except for prostate and testes weights.

Conducting Laboratory and Location: (b) (4)

Good laboratory practice (GLP) compliance: Yes

QA statement: Yes

**Table 52. Study Information for a 28-Day Study of ETX2514 by Intravenous Infusion in Beagle Dogs With a 28-Day Recovery Period, Study PC2514-2020-0001**

| Study Features and Methods | Details |
|---|---|
| Dose and frequency of dosing | 0, 500, 1000, 2000 mg/kg |
| Route of administration | Intravenous, via the saphenous or cephalic vein using a percutaneously placed catheter |
| Formulation/vehicle | Sterile water for injection adjusted to pH 5 to 7 |
| Species/strain | Dog, beagle. Canis familiaris |
| Number/sex/group | 3/sex/dose (main study group) |
| Age | 5 months old |
| Satellite groups/ unique design | Recovery animals (2/sex/dose) retained undosed for a 28-day recovery period to assess the evolution of delayed toxicities and the reversibility of any adverse findings |
| Deviation from study protocol affecting interpretation of results | No |

Source: Reviewer generated table
Abbreviations: ETX2514, durlobactam

**Table 53. Observations and Results for a 28-Day Study of ETX2514 by Intravenous Infusion in Beagle Dogs With a 28-Day Recovery Period, Study PC2514-2020-0001**

| Parameters | Major Findings |
|---|---|
| Mortality | There were no drug-related deaths |
| Clinical signs | **Table 54. Clinical Signs (Number of Instances) in Dogs Dosed With Durlobactam** |

| Dose (mg/kg) | 0 | 500 | 1000 | 2000 |
|---|---|---|---|---|
| Discolored feces | 12 | 16 | 33 | 73 |
| Mucoid feces | 21 | 21 | 40 | 78 |
| Watery feces | 2 | 7 | 8 | 15 |
| Emesis/vomitus | 1 | 4 | 1 | 28 |
| Salivation | 12 | 26 | 27 | 142 |

Body weights

**Table 55. Body Weight in Dogs Dosed With Durlobactam (Mean % Changes Compared to Control)**

| Dose (mg/kg) | 0 | 500 | 1000 | 2000 |
|---|---|---|---|---|
| Male | - | -5 | -13 | -10 |
| Female | - | -3 | -4 | -12 |

Ophthalmoscopy: No drug-related changes

ECG: No drug-related changes

Hematology

**Table 56. Hematology in Dogs Dosed With Durlobactam**

| DUR Dose (mg/kg) | 0 (Controls) | 500 | 1000 | 2000 |
|---|---|---|---|---|
| | | % Change compared to controls | | |
| Erythrocytes | 6.3 $10^6$ cells/microliter | - | - | -21% |
| Hemoglobin (g/dL) | 14 (g/dL) | - | - | -14% |
| Hematocrit (%) | 43 (%) | - | | -11% |

Source: Reviewer generated table
- no changes observed compared to control
Abbreviations: DUR, durlobactam

Clinical chemistry

**Table 57. Clinical Chemistry in Dogs Dosed With Durlobactam**

| Dose (mg/kg) | 0 | 500 | 1000 | 2000 |
|---|---|---|---|---|
| Alkaline phosphatase (U/L) | 102 | 89 | 74[1] | 57[1] |

Source: Reviewer generated table
[1] Statistically significant from controls in females at 1000 mg/kg and in both sexes at 2000 mg/kg

Urinalysis: No drug-related changes

Gross pathology: No drug-related changes

| Parameters | Major Findings |
|---|---|
| Organ weights | **Table 58. Organ Weight Changes (%) at End of Dosing in Dogs Dosed With Durlobactam** |

| Dose (mg/kg) | 0 (Controls) | 500 | 1000 | 2000 |
|---|---|---|---|---|
| | Relative organ WT/BW (%) | % Change compared to controls | | |
| Epididymides | 0.026 | -10% | -11% | -21% |
| Testes | 0.09 | -12% | -21% | -36% |
| Kidney | 0.55 | +13% | +12% | +17% |
| Prostate | 0.03 | -37% | -17% | -23% |

Abbreviations: BW, body weight; WT, weight

**Table 59. Organ Weight Changes (%) at End of Recovery in Dogs Dosed With Durlobactam**

| Dose (mg/kg) | 0 (Controls) | 500 | 1000 | 2000 |
|---|---|---|---|---|
| | Relative organ WT/BW (%) | % Change compared to controls | | |
| Prostate | 0.03 | +75% | +111% | +125% |
| Testes | 0.1 | - | - | - |

Abbreviations: BW, body weight; WT, weight

| | |
|---|---|
| Histopathology | There were no drug-related histopathology findings |
| Adequate battery | Yes |

Source: Reviewer generated table.
Abbreviations: ETX2514, durlobactam

*Reviewer's Comments: In study PC2514-2017-0018, using lower doses (300/300 and 600/600 mg/kg sulbactam-durlobactam, see below) did not affect testes weights at any time points, and prostate weights were only marginally reduced at the end of dosing. Prostate weights were comparable to controls at the end of the reversibility period.*

**Study Title/Number: ETX2514 and Sulbactam: 28 Day Intravenous (Infusion) Administration Toxicity Study in the Rat Followed by a 4 Week Recovery Period, Study PC2514-2017-0018**

Key Study Findings

- No NOAEL was determined since effects (enlarged liver, kidneys, and spleen) were observed at both of the combination doses tested.
- Effects in the liver, kidney, and spleen were reversible over the 4-week recovery period, although liver findings (minimal increase in liver weight, hepatocellular hypertrophy, and glycogen accumulation) persisted in a few animals to the end of the reversibility period.
- Unlike findings in study PC2514-2020-0001 at 1000 mg/kg and above in dogs, testes weights were not affected at any time points, and prostate weights were only marginally reduced at the end of dosing in this study. Prostate weights were comparable to controls at the end of the reversibility period.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

QA statement: Yes

**Table 60. Study Information for ETX2514 and Sulbactam: 28 Day Intravenous (Infusion) Administration Toxicity Study in the Rat Followed by a 4-Week Recovery Period, Study PC2514-2017-0018**

| Study Features and Methods | Details |
|---|---|
| Dose and frequency of dosing | 0, 600 mg/kg durlobactam, 300/300 mg/kg (sulbactam-durlobactam), 600/600 mg/kg (sulbactam-durlobactam) |
| Route of administration | Intravenous |
| Formulation/vehicle | 0.9% sodium chloride |
| Species/strain | Rat |
| Number/sex/group | 15 |
| Age | 13-16 weeks old |
| Satellite groups/ unique design | An assessment of delayed onset toxicity and / or reversibility of toxicity was made during a 4-week recovery period (5 animals/sex/group) |
| Deviation from study protocol affecting interpretation of results | No |

Source: Reviewer generated table
Abbreviations: ETX2514, durlobactam

**Table 61. Observations and Results: Changes From Control**

| Parameters | Major Findings |
|---|---|
| Mortality | No drug-related findings |
| Clinical signs | No drug-related clinical signs |
| Body weights | No toxicologically significant changes in body weight |
| Ophthalmoscopy | No toxicologically significant ophthalmoscopy changes |
| Hematology | |

**Table 62. Hematology Findings in Rats Dosed With Durlobactam (600 mg/kg) or Sulbactam-Durlobactam (300/300 or 600/600 mg/kg) for 28 Days**

| | 0 (Control) | | 600[1] | | 300/300[2] | | 600/600[3] | |
|---|---|---|---|---|---|---|---|---|
| **Parameters** | **M** | **F** | **M** | **F** | **M** | **F** | **M** | **F** |
| Hemoglobin (g/dL) | 15 | - | +6% | - | -13% | - | -20% | - |
| RBC counts 10 12/L | 9 | - | - | - | -23% | - | -23% | - |
| Reticulocyte (%) | 3 | - | - | - | +67% | - | +67%* | - |
| Packed cell volume | 49 | - | +2% | - | -14%* | - | -18% | - |
| White cell count | 10.7 | - | -1% | - | +33%* | - | +40%* | - |
| Neutrophil $10^9$/L | 2.6 | | -27%* | | +69%* | | +120%* | - |
| Monocytes $10^9$/L | 0.2 | | - | | +200%* | | +150%* | - |

Source: Reviewer generated table
[1] 600 mg/kg durlobactam
[2] 300 mg/kg durlobactam plus 300 mg/kg sulbactam
[3] 600 mg/kg durlobactam plus 600 mg/kg sulbactam
Abbreviations: F, female; M, male; RBC, red blood cell

Sulbactam-durlobactam (600/600 mg/kg) was associated with marginal increases in platelet count in male rats at the end of the recovery period.

**Table 63. Platelet Count (X$10^3$/µl) in Rats Dosed With Durlobactam (600 mg/kg) or Sulbactam-Durlobactam (300/300 or 600/600 mg/kg) for 28 Days at the End of Dosing and the Recovery Period**

| | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| **SUL/DUR Dose** | **0** | **600[1]** | **300/300[2]** | **600/600[3]** | **0** | **600[1]** | **300/300[2]** | **600/600[3]** |
| End of dosing | 1111 | 892 | 967 | 1081 | 1003 | 988 | 1091 | 1044 |
| End of recovery | 1049 | 1067 | 1034 | 1185 | 1199 | 1075 | 1041 | 1135 |

Source: Reviewer generated table.
[1] 600 mg/kg durlobactam
[2] 300 mg/kg durlobactam plus 300 mg/kg sulbactam
[3] 600 mg/kg durlobactam plus 600 mg/kg sulbactam
Abbreviations: DUR, durlobactam; SUL, sulbactam

| Parameters | Major Findings |
|---|---|

Clinical chemistry

**Table 64. Clinical Chemistry Findings in Rats Dosed With Durlobactam (600 mg/kg) or Sulbactam-Durlobactam (300/300 or 600/600 mg/kg) for 28 Days**

| | 0 (control) | | 600[1] | | 300/300[2] | | 600/600[3] | |
|---|---|---|---|---|---|---|---|---|
| **Parameters** | **M** | **F** | **M** | **F** | **M** | **F** | **M** | **F** |
| AST (U/L) | 83 | 101 | - | - | +30%* | -8% | +128%* | +76% |
| ALP (U/L) | 86 | - | +3% | - | +47%* | - | +62%* | - |

Source: Reviewer generated table
[1] 600 mg/kg durlobactam
[2] 300 mg/kg durlobactam plus 300 mg/kg sulbactam
[3] 600 mg/kg durlobactam plus 600 mg/kg sulbactam
Abbreviations: AP, a kaline phosphatase; AST; Aspartate aminotransferase; F, female; M, male

Urinalysis

**Table 65. Urinalysis Findings in Rats Dosed With Durlobactam (600 mg/kg) or Sulbactam-Durlobactam (300/300 or 600/600 mg/kg) for 28 Days**

| | 0 (control) | | 600[1] | | 300/300[2] | | 600/600[3] | |
|---|---|---|---|---|---|---|---|---|
| **Parameters** | **M** | **F** | **M** | **F** | **M** | **F** | **M** | **F** |
| Urinary volume (mL) | 28 | - | - | | -18% | - | -36%* | |

[1] 600 mg/kg durlobactam
[2] 300 mg/kg durlobactam plus 300 mg/kg sulbactam
[3] 600 mg/kg durlobactam plus 600 mg/kg sulbactam
Abbreviations: F, female; M, male

Gross pathology

**Table 66. Gross Pathology Findings in Rats Dosed With Durlobactam (600 mg/kg) or Sulbactam-Durlobactam (300/300 or 600/600 mg/kg) for 28 Days**

| | 0 (control) | | 600[1] | | 300/300[2] | | 600/600[3] | |
|---|---|---|---|---|---|---|---|---|
| **Parameters** | **M** | **F** | **M** | **F** | **M** | **F** | **M** | **F** |
| Large liver | 0 | 1 | 0 | 1 | 3 | 1 | 7 | 4 |
| Large kidney | 0 | 0 | 1 | 1 | 2 | 0 | 2 | 1 |
| Large spleen | 0 | 8 | 1 | 10 | 9 | 10 | 11 | 12 |

[1] 600 mg/kg durlobactam
[2] 300 mg/kg durlobactam plus 300 mg/kg sulbactam
[3] 600 mg/kg durlobactam plus 600 mg/kg sulbactam
Abbreviations: F, female; M, male

| Parameters | Major Findings |
|---|---|
| Organ weights | |

**Table 67. Effect of 28 Daily Intravenous Doses of Durlobactam and Sulbactam-Durlobactam on Rat Organ Weight**

| | 0 (control) | | 600[1] | | 300/300[2] | | 600/600[3] | |
|---|---|---|---|---|---|---|---|---|
| **Parameters** | **M** | **F** | **M** | **F** | **M** | **F** | **M** | **F** |
| Liver BW ratio | 2% | 3% | +3% | -2% | +42%[4] | -4% | +73%[4] | +16%[4] |
| Kidney BW ratio | 0.6% | 0.7% | +4% | +3% | +12%[4] | -1% | +22%[4] | +4% |
| Spleen BW ratio | 0.16% | 0.59% | +7% | -14% | +160%[4] | -17% | +164%[4] | -5% |
| Thyroid and parathyroid BW ratio | 0.004% | 0.005% | -3% | -1% | +2% | +6% | +31%[4] | +15% |

Source: Reviewer generated table.

For controls, group means are shown. For treated groups, percent difference from controls is shown.

[1] 600 mg/kg durlobactam
[2] 300 mg/kg durlobactam plus 300 mg/kg sulbactam
[3] 600 mg/kg durlobactam plus 600 mg/kg sulbactam
[4] Statistically significant.
Abbreviations: BW, body weight; F, female; M, male

| Parameters | Major Findings |
|---|---|
| Histopathology | |
| Adequate battery | Yes |

**Table 68. Histopathology Findings in Rats Dosed With Durlobactam (600 mg/kg) or Sulbactam-Durlobactam (300/300 or 600/600 mg/kg) for 28 Days**

| Parameters | 0 (control) | 600[1] | 300/300[2] | 600/600[3] |
|---|---|---|---|---|
| Liver, inflammatory cell infiltrate (minimal/slight) | 15 | 15 | 25 | 25 |
| Liver glycogen | 3 | 4 | 21 | 27 |
| Lung inflammation alveolar interstitial (minimal/slight) | 16 | 11 | 11 | 20 |
| Lung inflammation alveolar interstitial (moderate/marked) | 0 | 0 | 9 | 7 |
| Spleen hematopoiesis (minimal/slight) | 14 | 16 | 26 | 29 |
| Kidney tubule dilatation (minimal) | 2 | 1 | 4 | 4 |
| Kidney tubule basophilia (minimal/slight) | 12 | 17 | 16 | 22 |
| Thyroid follicular cell hypertrophy | | 0 | 0 | 2 |

Source: Reviewer generated table
[1] 600 mg/kg durlobactam
[2] 300 mg/kg durlobactam plus 300 mg/kg sulbactam
[3] 600 mg/kg durlobactam plus 600 mg/kg sulbactam

**Table 69. Histopathology Findings in Recovery Animals Dosed With Durlobactam (600 mg/kg) or Sulbactam-Durlobactam (300/300 or 600/600 mg/kg) for 28 Days Followed by 28 Days Recovery**

| Parameters | 0 (control) | 600[1] | 300/300[2] | 600/600[3] |
|---|---|---|---|---|
| Liver, diffuse hepatocellular hypertrophy, minimal | 0 | 0 | 0 | 4 |
| Glycogen hepatocyte (minimal) | 0 | 0 | 9 | 1 |

Source: Reviewer generated table
[1] 600 mg/kg durlobactam
[2] 300 mg/kg durlobactam plus 300 mg/kg sulbactam
[3] 600 mg/kg durlobactam plus 600 mg/kg sulbactam

Source: Reviewer generated table

*Reviewer's Comments: Most of the effects were reversible. Findings that persisted at the end of dosing were infrequent and/or minimal. At the end of recovery, liver weight was marginally increased (+25% in both 300/300 and 600/600 doses). Glycogen accumulation (as well as inflammatory changes) could contribute to the liver weight increase, which was the highest in males administered 600+600 mg/kg/day ETX2514 + Sulbactam. Glycogen accumulation could arise from increased glycogen synthesis or impaired glycogen catabolism.*

# 13.2. Individual Reviews of Studies Submitted With the New Drug Application

## 13.2.1. General Toxicology

**A 2-Week Once Daily Intravenous Infusion Impurity Qualification and Toxicokinetic Study With Sulbactam-Durlobactam in Sprague Dawley Rats**

Key Study Findings

- The toxicity profile of the conditioned 300/300 and 600/600 mg/kg sulbactam-durlobactam (solution prepared then stored at room temperature [15 to 30℃] for at least 24 hours prior to use) was similar to the toxicity profile obtained in other studies of sulbactam-durlobactam in rats at the same doses.
- Findings included minimally-increased platelets and liver weights as well as increased incidence of thrombus at the injection/cannulation site.
- The specified impurities in sulbactam-durlobactam preparations were not associated with new toxicities beyond those known for sulbactam-durlobactam.

**Table 70. Study Information for Study PC2514-2022-0014: A 2-Week Once Daily Intravenous Infusion Impurity Qualification and Toxicokinetic Study With Sulbactam-Durlobactam in Sprague Dawley Rats**

| Study Features and Methods | Details |
|---|---|
| Study no | PC2514-2022-0014 |
| Study report location | NDA 216974 SDN 006 |
| Conducting laboratory and location | (b) (4) |
| Date of study initiation | 4/26/2022 |
| GLP compliance | Yes |
| QA statement | Yes |
| Durlobactam, lot #, purity | Lot B20050044. purity 98% |
| Sulbactam lot #, purity | Lot 2011184. purity 99% |

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice, QA, quality assurance; #, number

**Table 71. Study Design in Study PC2514-2022-0014: A 2-Week Once Daily Intravenous Infusion Impurity Qualification and Toxicokinetic Study With Sulbactam-Durlobactam in Sprague Dawley Rats**

| Group | Durlobactam Dose mg/kg | Sulbactam Dose mg/kg | Animals/Sex/Dose Main Study | Animals/Sex/Dose Toxicokinetics |
|---|---|---|---|---|
| 1 (Control) | 0 | 0 | 10 | 3 |
| 2 (Low) | 300 | 300 | 10 | 6 |
| 3 (High) | 600 | 600 | 10 | 6 |

Source: Reviewer generated table

**Table 72. Study Features and Methods in Study PC2514-2022-0014: A 2-Week Once Daily Intravenous Infusion Impurity Qualification and Toxicokinetic Study With Sulbactam-Durlobactam in Sprague Dawley Rats**

| Study Features and Methods | Details |
|---|---|
| Frequency of dosing | Once daily |
| Route of administration | Intravenous |
| Dose volume | 5 mL/kg |
| Formulation/vehicle | 0.9% sodium chloride injection USP |
| Species/strain | Rat |
| Number/sex/group | 10 |
| Age | 8-9 weeks old |
| Weight | 271-348 g (males), 202-244 g (females) |
| Satellite groups | Toxicokinetics animals. 6/sex/dose |
| Unique study design | Samples of 60 and 120 mg/mL were collected at the time of mixing from formulations prepared for administration on Days 1 and 8 of the dosing phases. In addition, nondosing samples of Durlobactam in saline at concentrations of 60 and 120 mg/mL were prepared, conditioned, and sampled alongside the dose formulations from Days 1 and 8 of the dosing phase (for reference). Samples were stored at room temperature (15 to 30℃) for at least 24 hours. After at least 24 hours of room temperature storage, 7 x 1.5-mL samples were collected into cryovials from each 11-mL sample. The 1.5- mL sub-samples were stored in a freezer, set to maintain -10 to -30 ºC, until shipped to the lab for analysis. |

Source: Reviewer generated table
Abbreviations: USP, United States Pharmacopeia.

## Observations and Results

Stability

Samples collected on Days 1 and 8 ranged from 92.51% to 95.83% of target Sulbactam concentrations and 85.89% to 91.33% of target durlobactam concentrations. Sulbactam-Durlobactam stability samples collected from conditioned formulations had concentrations ranging from 86.41% to 95.76% of target for sulbactam and 69.93% to 81.74% of target for durlobactam.

Impurities

Total impurities ranged from (b) (4) w/w for freshly prepared dose formulation samples and (b) (4) w/w for conditioned (stability) samples. Specified impurities included

(b) (4)

**Table 73. Observations and Results for a 2-Week Once Daily Intravenous Infusion Impurity Qualification and Toxicokinetic Study With Sulbactam-Durlobactam in Sprague Dawley Rats**

| Parameters | Major Findings |
|---|---|
| Mortality | There were no drug-related deaths |
| Clinical signs | Discolored yellow urine was noted for all Sulbactam-Durlobactam-treated groups |
| Body weights | There were no drug-related changes in body weight |
| Feed consumption | There were no drug-related changes in feed consumption |
| Hematology | Sulbactam-durlobactam was associated with increased (+25-28%) platelet counts in females at the 300/300 and the 600/600 sulbactam-durlobactam doses. |

**Table 74. Sulbactam-Durlobactam Associate Increases in Platelet Count in Study PC2514-2022-0014**

| | | Male | | | Female | | |
|---|---|---|---|---|---|---|---|
| **Sulbactam-Durlobactam Dose** | | **0** | **300/300[1]** | **600/600[2]** | **0** | **300/300[1]** | **600/600[2]** |
| Platelets | X103/µL | 1096 | 1138 | 1135 | 1007 | 1256 | 1292 |
| | % Control | - | +4% | +4% | - | +25% | +28% |

Source: Reviewer generated table
[1] 300 mg/kg durlobactam plus 300 mg/kg sulbactam
[2] 600 mg/kg durlobactam plus 600 mg/kg sulbactam

| | |
|---|---|
| Clinical chemistry | There were no toxicologically significant drug-related effects in clinical chemistry parameters. |
| Urinalysis | There were no toxicologically significant drug-related effects in clinical urinalysis parameters. |
| Gross pathology | There were no drug-related effects in clinical chemistry parameters. |
| Organ weights | Liver weights were marginally increased (by 10-13%) in rats receiving the high dose combination (600 mg/kg durlobactam with 600 mg/kg sulbactam). |

**Table 75. Sulbactam-Durlobactam-Related Effects on Organ Weight Parameters in Study PC2514-2022-0014**

| | Sulbactam-Durlobactam | | | | | |
|---|---|---|---|---|---|---|
| Sex | Males | | | Females | | |
| Dose Level (mg/kg/day) | 0 | 300/300 | 600/600 | 0 | 300/300 | 600/600 |
| Liver | | | | | | |
| Absolute Weight (g) | 10.0824 | 102 | 109 | 6.9108 | 102 | 111* |
| Body Weight Ratio (%) | 2.7698 | 103 | 110* | 2.8737 | 103 | 113* |
| Brain Weight Ratio (%) | 494.8392 | 100 | 107 | 357.1781 | 101 | 109 |

* = Statistically significant difference (absolute or relative) compared with respective control mean value.
Note: Values for absolute weight and ratio of organ weights (relative to body or brain) for test article-treated groups expressed as percentage control mean value.

Source: Applicant table

| | |
|---|---|
| Histopathology<br>Adequate battery | Yes |
| Peer review | No |

| Parameters | Major Findings |
|---|---|
| Histological findings | Sulbactam-durlobactam was associated with increased incidence and/or severity of thrombus in test article-treated groups compared to control groups, mainly in females. This finding correlated with a clinical pathology finding of higher platelet count in females administered 600/600 mg/kg/day. Thrombi were generally located in the vascular lumen and/or superficially attached to (with little or no involvement of) the vascular wall, often fully occluding the vascular lumen and, in few cases, exhibited some recanalization. |

**Table 76. Incidence and Severity of Sulbactam-Durlobactam Related Microscopic Findings in Study PC2514-2022-0014**

| | | Sulbactam-Durlobactam | | | | | |
|---|---|---|---|---|---|---|---|
| | Sex | Males | | | Females | | |
| | Dose Level (mg/kg/day) | 0 | 300/300 | 600/600 | 0 | 300/300 | 600/600 |
| | Number Examined | 10 | 10 | 10 | 10 | 10 | 10 |
| Catheter Site Thrombus | | | | | | | |
| | Slight | 0 | 1 | 0 | 0 | 0 | 2 |
| | Marked | 0 | 0 | 1 | 1 | 2 | 4 |
| | Severe | 0 | 0 | 0 | 1 | 0 | 1 |
| Infusion Site Thrombus | | | | | | | |
| | Minimal | 1 | 0 | 0 | 0 | 0 | 0 |
| | Slight | 0 | 2 | 1 | 0 | 1 | 1 |
| | Moderate | 0 | 0 | 1 | 0 | 1 | 0 |
| | Marked | 0 | 2 | 0 | 0 | 0 | 2 |

Source: Applicant table

Source: Applicant table

### 13.2.1.1. In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

**Study Title/Number: ETX-2514: Bacterial Reverse Mutation Assay. Study SN-002514-2015-05**

Key Study Findings

- There were no increases in revertant colonies in strains treated with durlobactam with or without S9 in the dose range study, but all doses between 5 and 5000 µg/plate +/- S9 were toxic in all tester strains as indicated by reduced or absent revertant colonies and bacterial background lawns.
- The repeat assay using durlobactam concentrations between 1.6 and 5 µg showed no increases in revertant colonies in strains treated with durlobactam with or without S9.
- The study is not considered to be a valid assessment of the mutagenicity of durlobactam, since toxicity precluded testing of the strains at doses above 5 µg/plate.

GLP compliance: Yes

Test system: *Salmonella typhimurium* up to 5000 µg/plate +/- S9 (strains TA98, TA100, TA1535 and TA1537) and Escherichia coli strain WP2uvrA

Study Validity

Study is valid: No. Excessive toxicity precluded obtaining data above 5 µg/plate making the study uninterpretable.

Results

Cytotoxicity was observed in almost all strains at 50 µg/plate and higher. However, no positive increases in revertant colonies were observed with any of the tester strains treated with durlobactam in the presence or absence of S9. The fold increase in revertant numbers remained between 0.2 and 1.7 for all strains and conditions.

In the repeat mutagenicity assay without S9, durlobactam produced toxicity at 1.6 to 5 µg/plate with TA98 and WP2uvrA and at 5 µg/plate with TA100, as indicated by reduced colony counts. In the presence of S9, durlobactam produced toxicity at 1.6 to 5 µg/plate with TA100 and WP2uvrA and at 5 µg/plate with TA98 and TA1535. Excessive toxicity precluded obtaining data at concentrations above 5 µg/plate. The genotoxicity of durlobactam could not be determined from these data.

**Study Title/Number: ETX-2514: In Vitro Human Lymphocyte Micronucleus Assay. Study SN-002514-2015-06**

Key Study Findings

- Durlobactam was negative for inducing micronuclei in cultured human peripheral blood lymphocytes with or without metabolic activation.

GLP compliance: Yes

QA statement: Yes

Test system: Human peripheral blood lymphocytes; up to 325 µg/plate +/-S9]

Study Validity

Study is valid: Yes. The high dose produced approximately 50% cytotoxicity, but at least two additional nontoxic dose levels were tested.

**Table 77. Binucleated Cells With Micronuclei Results of In Vitro Human Lymphocyte Micronucleus Assay**

| Metabolic Activation | Treatment | Concentration µg/mL | Cytotoxicity (%) | Mean MNBN Cell Frequency (%) | Statistical Significance |
|---|---|---|---|---|---|
| Without activation (3-hour treatment) | Vehicle | - | - | 0.15 | - |
| | Durlobactam | 2.2 | 13 | 0.3 | NS |
| | | 13 | 29 | 0.35 | NS |
| | | 325 | 54 | 0.25 | NS |
| | Mitomycin C | 1 | 63 | 4.35* | p≤0.001 |

| Metabolic Activation | Treatment | Concentration µg/mL | Cytotoxicity (%) | Mean MNBN Cell Frequency (%) | Statistical Significance |
|---|---|---|---|---|---|
| Without activation (24-hour treatment) | Vehicle | - | - | 0.2 | - |
| | Durlobactam | 9.2 | 13 | 0.5 | NS |
| | | 78 | 27 | 0.5 | NS |
| | | 325 | 47 | 0.35 | NS |
| | Mitomycin C | 0.3 | 62 | 3.25* | p≤0.001 |
| With metabolic activation (3-hour treatment) | Vehicle | - | - | 0.2 | |
| | Durlobactam | 159 | 14 | 0.35 | NS |
| | | 228 | 9 | 0.2 | NS |
| | | 325 | 7 | 0.2 | NS |
| | Cyclophosphamide | 15 | 50 | 3.1* | p≤0.001 |

Source: Reviewer generated table
Note: Criteria for positive: Test article will be considered positive if (1) A statistically significant increase in the frequency of MNBN cells at one or more concentrations is observed (2) The increase of MNBN cells exceeds the normal range in both replicates (3) A concentration-related increase in the proportion of MNBN cells is observed.
Abbreviations: MNBN, binucleated cell with micronuclei; NS, not significant

## 13.2.1.2. In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

**Table 78. Study Information for Study 002514-2015-07 In Vivo Rat Bone Marrow Micronucleus Assay**

| Study Features and Methods | Details |
|---|---|
| Study number | SN-002514-2015-07 |
| Study report location | EDR NDA 216974 SDN 1 |
| Conducting laboratory and location | (b) (4) |
| Date of study initiation | 1/25/2016 |
| GLP compliance | Yes |
| QA statement | Yes |
| Drug lot no. | A02468-077A1 |
| Purity (%) | 96.2 |
| Doses in definitive study | 0, 500, 1000, 2000 mg/kg |
| Frequency of dosing | Single dose |
| Route of administration | Intravenous infusion |
| Dose volume | 5 mL/kg/h |
| Formulation/vehicle | Water for injection |
| Species/strain | Rat/Sprague Dawley |
| Number/sex/group | 6 males |
| Basis of dose selection | The high dose was based on toxicity data from Study 2514-2015-01: 7-Day Daily 2-Hour Intravenous Infusion Tolerability Study with ETX2514 in Rats, and is the limit dose for test articles having little to no toxicity. Since there were no significant differences between the sexes in toxicity or toxicokinetics, only males were used in the micronucleus assay. |
| Negative control | 0.9% sterile saline |
| Positive control | 60 mg/kg cyclophosphamide |

Source: Reviewer generated table
Abbreviations: ETX2514, durlobactam

Key Study Findings

- Durlobactam did not induce statistically significant increases in micronucleated PCEs at any test article dose up to 2000 mg/kg.
- Durlobactam was negative for inducing micronuclei in cultured human peripheral blood lymphocytes with, or without, metabolic activation.

Study Validity

The study was valid. Negative and positive controls were acceptable based on historical data. The vehicle control MN PCE data were comparable with the laboratory's historical vehicle control ranges. The high dose was the limit dose, 2000 mg/kg.

**Table 79. Micronucleus Assay Data for Male Sprague Dawley Rats Dosed With Durlobactam**

**Report Title:** In Vivo Rat Bone Marrow Micronucleus Assay — **Test Article: Durlobactam**

| | | | |
|---|---|---|---|
| **Test for Induction of:** Bone marrow micronuclei | | **Treatment Schedule:** Single dose | **Study No.** SN-002514-2015-07 (8331482) |
| **Species/Strain:** Rat / Hsd:SD | | **Sampling Time:** 24 and 48 hours after dosing | |
| **Age:** 9 weeks | | **Method of Administration:** IV infusion[a], oral gavage[b] | |
| **Cells Evaluated:** Polychromatic erythrocytes | | **No. of Cells Analyzed/Animal:** 4000 | **GLP Compliance:** Yes |
| **Vehicle/Formulation:** | **Test Article:** Sterile water for injection, USP | **Positive Control:** Deionized water | **Date of Dosing:** 08 February 2016 |
| **Special Features:** None. | | | |
| **Toxic/Cytotoxic Effects:** None. | | | |
| **Genotoxic Effects:** None. | | | |
| **Evidence of Exposure:** Durlobactam was administered parenterally at dose levels up to the limit dose (2000 mg.kg) with verified systemic exposures in prior GLP-compliant repeat-dose studies. | | | |

| Test Article | Dose (mg/kg) | No. of Animals | Harvest Time (Hours) | Mean % PCE | % MNPCE Mean ± SDv |
|---|---|---|---|---|---|
| Vehicle | - | 6M | 24 | 43.03 | 0.05 ± 0.02 |
| | - | 6M | 48 | 42.67 | 0.04 ± 0.01 |
| Durlobactam | 500 | 6M | 24 | 43.20 | 0.03 ± 0.03 |
| | 1000 | 6M | 24 | 41.77 | 0.05 ± 0.03 |
| | 2000 | 6M | 24 | 45.10 | 0.03 ± 0.02 |
| | 2000 | 6M | 48 | 44.13 | 0.04 ± 0.03 |
| Cyclophosphamide | 60 | 3M | 24 | 40.67 | 0.84 ± 0.22*** |

*** $p \leq 0.001$; GLP = Good Laboratory Practice; IV = Intravenous; M = Male; PCE = Polychromatic erythrocytes; MNPCE = Micronucleated PCEs; SDv = Standard deviation.
[a]Vehicle and test article were administered by IV infusion.
[b]Positive control was administered via oral gavage.

Source: Applicant's Table
Abbreviations: SD, Sprague Dawley

### 13.2.1.3. Genotoxicity Study of Impurities

Entasis has screened 27 durlobactam-related confirmed and proposed structures of impurities, degradants, and metabolites in silico. One proposed structure, (b) (4) produced a structural alert for potential mutagenicity per ICH M7. In order to further characterize the potential genotoxicity of (b) (4), study PC2514-2022-0018 evaluated the compound in an Ames assay.

Due to excessive cytotoxicity, this study was considered invalid. Cytotoxicity precluded the evaluation of doses above (b) (4) microgram/plate in most strains, and above (b) (4) micrograms /plate for *E. coli*.

The Applicant subsequently conducted a Pig-A assay (study PC2514-2022-0016: Evaluation of Pig-A Mutant Frequencies in Male Sprague Dawley Rats Administered a Conditioned

Formulation of Durlobactam Sodium). The Applicant took the position that a negative using conditioned durlobactam, which contained elevated levels of impurities, could serve to qualify the impurities present in the preparation. Although the Pig-A assay was negative, the Agency has consulted with internal experts and informed the Applicant that (b) (4) can only be qualified as nongenotoxic if the compound is tested individually using an assay such as the Pig-A or the hypoxanthine phosphoribosyl transferase assay. The Agency will request that this study be conducted as a postmarketing requirement.

**Table 80. Study Information for Mutagenicity Assessment of (b) (4) in a Bacterial Reverse Mutation Assay, Study PC2514-2022-0018**

| Study Features and Methods | Details |
|---|---|
| Study number | PC2514-2022-0018 |
| Study report location | EDR NDA 216974 SDN 1 |
| Conducting laboratory and location | (b) (4) |
| Date of study initiation | 6/22/2022 |
| GLP compliance | Yes |
| QA statement | Yes |
| Drug lot no. | N192-93-1 |
| Purity (%) | 91% |

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; QA, quality assurance

**Table 81. Bacterial Reverse Mutation Assay Dose Levels (µg/plate) for (b) (4) With and Without Metabolic Activation**

| Bacterial Strain[a, b] | Dose Level 1 | Dose Level 2 | Dose Level 3 | Dose Level 4 | Dose Level 5 | Dose Level 6 |
|---|---|---|---|---|---|---|
| *Salmonella Typhimurium* TA100 | 39.1 | 19.5 | 9.77 | 4.88 | 2.44 | 1.22 |
| *S. typhimurium* TA1535 | 39.1 | 19.5 | 9.77 | 4.88 | 2.44 | 1.22 |
| *S. typhimurium* TA97a | 39.1 | 19.5 | 9.77 | 4.88 | 2.44 | 1.22 |
| *S. typhimurium* TA98 | 39.1 | 19.5 | 9.77 | 4.88 | 2.44 | 1.22 |
| *Escherichia coli* WP2 | 1250 | 625 | 313 | 156 | 78.1 | NA |

Abbreviations: NA= Not Applicable
[a] Dose levels selected based on a range-finding study (b) (4) Study Number 54022.00102RF) dose levels rounded to three significant figures.
[b] Three replicate plates per test condition.
Source: Applicant's table

**Basis of Concentration Selection: Test Article Dose Levels, Along With Positive and Negative Controls, were Selected Based on a Range-Finding Study ((b) (4) Study Number 54022.00102RF)**

Key Study Findings

- All doses above (b) (4) µg/plate +/- S9 were toxic in all tester strains except for WP2 uvrA, where the cytotoxicity was apparent above (b) (4) µg/plate.
- (b) (4) exposure did not result in an increase in revertants compared to control at any dose.
- This study revealed no evidence of genotoxicity but was not considered valid since cytotoxicity precluded testing of many tester strains to doses above (b) (4) µg/plate.

**Study PC2514-2022-0016: Evaluation of Pig-a Mutant Frequencies in Male Sprague Dawley Rats Administered a Conditioned Formulation of Durlobactam Sodium**

Conducting Lab: (b) (4)

Key Study Findings

- Treatment with Durlobactam Sodium did not affect Pig-A mutant frequencies in RBC or reticulocytes on Day 15 or on Day 28.
- Durlobactam was negative in the Pig-A mutagenicity assay.
- The Applicant intended to use data from this study to evaluate the genotoxicity of compounds present in the sample. The Agency had previously communicated to the Applicant that the (b) (4) impurity should be evaluated individually in a Pig-A assay (or in vitro HPGRT assay) before it would be considered nongenotoxic.

(b) (4) This study evaluated the potential of conditioned Durlobactam Sodium and related degradants/impurities to induce Pig-A gene mutations in the bone marrow erythroid lineage precursor cells as measured in reticulocytes (PCE) and RBC in the blood of male, Sprague Dawley Rats. This batch of drug product contained relatively high amounts of impurities.

For 28 consecutive days, rats were administered conditioned Durlobactam Sodium (600 or 2000 mg/kg/day) or the vehicle control daily via a 2-hour intravenous infusion. Animals assigned to the positive control group were administered ENU daily for 3 days (Days 1 to 3) by oral gavage. A blood sample was collected from each animal on Day 15 via the indwelling catheter (Groups 1 to 3) or via retroorbital bleed (group 4 or animals with nonpatent catheters) and these samples were assessed for Pig-A mutant levels. All animals were humanely euthanized on Day 28, and blood collected for a second Pig-A assessment.

Animals dosed with the test article experienced dose-dependent reductions in final body weight and body weight gain. Animals receiving 2000 mg/kg/day had statistically reduced final body weight and body weight gain compared to those receiving the vehicle control (6% and 30% reductions respectively).

Under the conditions of the assay, the criteria for a valid test were met. Negative controls were consistent with historical control data; the positive control ENU induced a higher frequency of PCE and RBC with the Pig-A mutant phenotype at $p<0.05$, as compared to the negative control.

Results

Treatment with conditioned Durlobactam Sodium did not affect Pig-A mutant frequencies in RBC or reticulocytes on Day 15 or on Day 28.

**Table 82. Summary Pig-A-Mutant Frequencies in Durlobactam-Treated Rats**

| Dose Level (mg/kg/day) | % PCE | Mutant RBC per 106 RBC | Mutant RET per 106 RBC | % PCE^ | Mutant RBC per 106 RBC | Mutant RET per 106 RBC |
|---|---|---|---|---|---|---|
| | Day 15 | | | Day 28 | | |
| 0 | 4.11 ± 0.41 | 0.42 ± 0.26 | 0.16 ± 0.21 | 3.71 ± 0.60 | 0.49 ± 0.21 | 1.35 ± 2.19 |
| 600 | 3.62 ± 0.58 | 0.38 ± 0.09 | 0.74 ± 0.75 | 3.77 ± 0.16 | 0.39 ± 0.14 | 0.54 ± 0.89 |
| 2000 | 3.77 ± 0.61 | 0.43 ± 0.22 | 0.73 ± 0.80 | 5.08 ± 0.79* | 0.70 ± 0.30 | 0.59 ± 0.63 |
| ENU 20 | 3.00 ± 0.36* | 43.01 ± 8.92* | 259.04 ± 56.17* | 3.16 ± 0.39 | 126.93 ± 23.59* | 241.47 ± 47.01* |

Values are means ± standard deviation
* Statistically significant at $p < 0.05$ (t-test or Dunnett's Pairwise Comparison)
^ Increasing Linear Trend Test at $p < 0.05$
Abbreviations: PCE=polychromatic erythrocyte (also called reticulocyte), RBC=Red Blood Cell (also called erythrocyte), RET=Reticulocyte
Source: Applicant's table
Abbreviations: ENU 20; N-ethyl-N-nitrosourea

## 13.2.1.4. Reproductive and Developmental Toxicology

### 13.2.1.4.1. Fertility and Early Embryonic Development

**Study Title/Number: ETX2514: Intravenous (Infusion) Study of Male Fertility and Early Embryonic Development in the Rat, Study PC2514-2018-0003**

Key Study Findings

- There was no ETX2514-related effect on male reproductive organ weights, mating behavior, fertility, or embryonic survival.
- The NOAEL for male fertility was 1000 mg/kg/day (1220 µg*h/mL), about 3 times the clinical exposure based on the area under the concentration-time curve (AUC) comparisons.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

QA statement: Yes

**Table 83. Study Information for ETX2514: Intravenous (Infusion) Study of Male Fertility and Early Embryonic Development in the Rat, Study PC2514-2018-0003**

| Methods | Details |
|---|---|
| Dose and frequency of dosing | 100, 300, 1000 mg/kg/day |
| Route of administration | Intravenous infusion (2.5 mL/kg/h for 2 hours) |
| Formulation/vehicle | 0.9% sodium chloride injection, USP |
| Species/strain | Rat, Crl:CD(SD) |
| Number/sex/group | 20 |
| Satellite groups | None |
| Study design | Males were dosed for up to 21 days (2 weeks prior to pairing and during the pairing phase until confirmation of mating). Four groups of 20 female Crl:CD(SD) rats were used for mating and were not dosed. Females were sent for necropsy on Gestation Day 13. The progress and outcome of pregnancy were evaluated. |
| Deviation from study protocol affecting interpretation of results | No |

Source: Reviewer generated table
Abbreviations: CD(SD), caesarean-derived Sprague Dawley; ETX2514, durlobactam; GLP, good laboratory practice, USP, United States Pharmacopeia

## Observations and Results

**Table 84. Observations and Results from ETX2514: Intravenous (Infusion) Study of Male Fertility and Early Embryonic Development in the Rat, Study PC2514-2018-0003**

| Parameters | Major Findings |
|---|---|
| Mortality | There was no drug-related moribundity or mortality. 6, 4, 2 and 1 instances of death/moribundity occurred in the control, 100, 300 and 1000 mg/kg animals respectively. Deaths were associated with failure of the indwelling cannula and/or poor condition of the tail or clinical observations associated with the tail cuff used for cannulation. |
| Clinical signs | There were no drug-related clinical signs. Sores and or lesions on the tail, were associated with the tail cuff used to provide a port for the infusion and was recorded across all groups, including controls. |
| Body weights | Body weights were similar between controls and dosed animals despite sporadic, biologically, insignificant reductions in bodyweight gain at the higher doses. |
| Necropsy findings | There were no statistically and/or biologically significant drug-related effects on male reproductive organ weights, mating behavior, fertility, or embryonic survival at any dose. |

Source: Reviewer generated table
Abbreviations: ETX2514, durlobactam

The NOAEL for male fertility is considered 1000 mg/kg/day. At this dose the maximum plasma concentration ($C_{max}$) was 617,000 ng/mL and $AUC_{(0-T)}$ was 1,220,000 h*ng/mL.

### 13.2.1.4.2. Embryo-Fetal Development

**Study Title/Number: ETX2514: Intravenous (Infusion) Study of Fertility and Embryo-Fetal Development in the Rat, Study PC2514-2017-0019**

Key Study Findings

- At doses up to 3 times the maximum recommended dose based on AUC comparisons, there were no toxicologically significant drug-related effects of durlobactam in pups born to rats dosed for 2 weeks prior to pairing, during pairing, and up to gestation Day 17.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

QA statement: Yes

**Table 85. Study Information for ETX2514: Intravenous (Infusion) Study of Fertility and Embryo-Fetal Development in the Rat, Study PC2514-2017-0019**

| Methods | Details |
|---|---|
| Dose and frequency of dosing | |
| Route of administration | The test article was administered to female rats intravenously by infusion 2.5 mL/kg/hour for 2 hours daily for 2 weeks prior to pairing, during pairing, and up to GD 17, inclusive, via a motorized infusion pump into the vena cava via the femoral vein. For the remainder of the daily 24-hour period, animals were administered sterile saline 0.9% NaCl |
| Formulation/vehicle | Sterile 0.9% NaCl |
| Species/strain | Rat/ Crl:CD(SD) |
| Number/sex/group | 25 |
| Satellite groups | Blood samples for toxicokinetics (0.5 mL nominal) were taken from animals at predose and 1, 2-, 3-, 5-, and 7-hours post end of infusion on Pre-Pairing Day 1 and at predose and 0.5, 1.92, 3-, 5-, and 7-hours post start of infusion on GD 17. |

| Methods | Details |
|---|---|
| Study design | Females were dosed for up to 46 days (2 weeks prior to pairing, during the pairing phase, and up to Gestation Day 17. Four groups of 25 (undosed) male Crl:CD(SD) rats were used for mating.<br><br>**Table 86. Animal group assignments for ETX2514: Intravenous (Infusion) Study of Fertility and Embryo-Fetal Development in the Rat, Study PC2514-2017-0019**<br>Group Number / Dose (mg/kg) / N (Untreated Males) / N (Females)<br>1 / 0 / 25 / 25<br>2 / 100 / 25 / 25<br>3 / 300 / 25 / 25<br>4 / 1000 / 25 / 25<br>Source: Reviewer generated table |
| Deviation from study protocol affecting interpretation of results | No |

Source: Reviewer generated table
Abbreviations: CD(SD), caesarean-derived Sprague Dawley; ETX2514, durlobactam; GD, gestation day; NaCl, sodium chloride

## Observations and Results

**Table 87. Observations and Results for ETX2514: Intravenous (Infusion) Study of Fertility and Embryo-Fetal Development in the Rat, Study PC2514-2017-0019**

| Parameters | Major Findings |
|---|---|
| Mortality | No drug-related mortality occurred. |
| Clinical signs | There were no drug-related clinical findings. All groups showed observations related to the indwelling catheter and the tail cuff used to secure it. |
| Body weights | There were no biologically significant effects on mean maternal body weight during gestation. Between Pre-Pairing Days 1 and 4, mean food consumption was statistically significantly reduced for all ETX2514-treated groups, compared with controls. |
| Food consumption | For animals administered 100, 300, or 1000 mg/kg/day, mean maternal food consumption was marginally (+10-15%) increased, compared with that of controls, between GD 4 and 6 only. |
| Necropsy findings<br>Cesarean section data | There were no biologically significant drug-related necropsy findings including mean number of corpora lutea, the number live fetuses/female, the percentage of male fetuses, and mean fetal weights at cesarean section. |

| Parameters | Major Findings |
|---|---|
| Necropsy findings<br>Offspring | There were no drug-related increases in external, skeletal, or visceral malformations. |
| Toxicokinetics | **Table 88. Pharmacokinetics for ETX2514: Intravenous (Infusion) Study of Fertility and Embryo-Fetal Development in the Rat, Study PC2514-2017-0019** |

| Dose (mg/kg) | $AUC_{(0\text{-}24h)}$ Day 1 (µg*h/mL) | $AUC_{(0\text{-}24h)}$ Day 17 (µg*h/mL) |
|---|---|---|
| 100 | 29 | 150 |
| 300 | 50 | 498 |
| 1000 | 324 | 1600 |

Source: Reviewer generated table
Note: Clinical $AUC_{(0\text{-}24h)}$ values were around 466 µg*h/mL
Abbreviations: $AUC_{(0\text{-}24h),\ area}$ under the curve from 0 to 24 hours

Source: Reviewer generated table
Abbreviations: ETX2514, durlobactam; GD, gestation day

## Study Title/Number: Subcutaneous Injection Embryo-Fetal Development and Toxicokinetic Study With ETX2514 in Mice

Key Study Findings

- At doses equivalent to 2 to 4 times the human exposure (800 to 1600 mg/kg), variations, including delayed ossification and supernumerary ribs, were increased in mice.
- No other adverse effects on mean body weight, reproductive performance, or cesarean section parameters were observed for animals administered up to 1600 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

QA statement: Yes

**Table 89. Study Information for Subcutaneous Injection Embryo-Fetal Development and Toxicokinetic Study With ETX2514 in Mice**

| Methods | Details |
|---|---|
| Dose and frequency of dosing | 0, 400, 800 and 1600 mg/kg/day |
| Route of administration | Subcutaneous |
| Formulation/vehicle | Sterile water for injection |
| Species/strain | Mouse/Crl:CD-1 |
| Number/sex/group | 26 |
| Study design | Animals were administered a dose volume of 6.25 mL/kg four times daily by subcutaneous injection beginning on GD 6 and continuing through GD 15 |
| Satellite groups | Animals were administered a dose volume of 6.25 mL/kg four times daily by subcutaneous injection beginning on GD 6 and continuing through GD 18 for TK animals |
| Deviation from study protocol affecting interpretation of results | Yes/No |

Source: Reviewer generated table
Abbreviations: CD, caesarean-derived; ETX2514, durlobactam; GD, gestation day; TK, toxicokinetics

Observations and Results

**Table 90. Observations and Results for Subcutaneous Injection Embryo-Fetal Development and Toxicokinetic Study With ETX2514 in Mice**

| Parameters | Major Findings |
|---|---|
| Mortality | All animals survived to the scheduled sacrifice. |
| Clinical signs | No drug-related clinical signs were observed |
| Body weights | No biologically significant effect on bodyweight |
| Necropsy findings Cesarean section data | There were no drug-related differences in cesarean section data including implantation sites, pre- and postimplantation loss. |
| Necropsy findings Offspring | **Table 91. Necropsy findings in the offspring in Subcutaneous Injection Embryo-Fetal Development and Toxicokinetic Study With ETX2514 in Mice** |
| Toxicokinetics | **Table 92. Pharmacokinetics in Subcutaneous Injection Embryo-Fetal Development and Toxicokinetic Study With ETX2514 in Mice** |

**Table 91. Necropsy findings in the offspring in Subcutaneous Injection Embryo-Fetal Development and Toxicokinetic Study With ETX2514 in Mice**

| | % Litters Affected | | | |
|---|---|---|---|---|
| **Dose (mg/kg)** | **0** | **400** | **800** | **1600** |
| Unossified hindlimb-calcaneum | 11 | 29 | 43 | 59 |
| Asymmetric ossification-sternebra | 5 | 5 | 35 | 14 |
| Unossified sternebra | 0 | 0 | 0 | 9 |
| Supernumerary rib | 42 | 57 | 61 | 77 |

Source: Reviewer generated table

**Table 92. Pharmacokinetics in Subcutaneous Injection Embryo-Fetal Development and Toxicokinetic Study With ETX2514 in Mice**

| Dose (mg/kg/day) | $C_{max}$ (µg/mL) | $AUC_{0-24h}$ (µg*h/mL) | Exposure Multiple |
|---|---|---|---|
| 400 | 175 | 470 | 1 |
| 800 | 332 | 831 | 1.8 |
| 1600 | 724 | 1880 | 4 |

Source: Reviewer generated table
Abbreviations: $AUC_{0-24h}$, area under the curve from 0 to 24 hours; $C_{max,}$ maximum plasma concentration

Source: Reviewer generated table
Abbreviations: ETX2514, durlobactam

**Study Title/Number: A GLP Pre- and Post-Natal Development Study of ETX2514 by the Intravenous Route (2-Hour Infusion) in the Rat (Segment III), Study PC2514-2019-0004**

Key Study Findings

- Durlobactam dosing at 300 and 1000 mg/kg from gestation day 6 to lactation Day 20 resulted in the increased incidence of cecum distended with fluid in dams.
- There were no toxicologically significant adverse effects in offspring from rats dosed with durlobactam up to 1000 mg/kg.
- The 1000 mg/kg dose is equivalent to about 3 times the clinical exposure based on AUC comparisons.

Conducting laboratory: (b) (4)

GLP compliance: Yes

**Table 93. Study Information for GLP Pre- and Post-Natal Development Study of ETX2514 by the Intravenous Route (2-Hour Infusion) in the Rat (Segment III), Study PC2514-2019-0004**

| Method | Details |
|---|---|
| Dose and frequency of dosing | 0, 300 and 1000 mg/kg |
| Route of administration | Intravenous (2-hour infusion) |
| Formulation/vehicle | 0.9% NaCl |
| Species/strain | Rat, Sprague Dawley |
| Number/sex/group | 22 mated females |
| Study design | Drug was administered to mated female rats from GD 6 to lactation Day 20. A control group received saline at the same dose volume. The females were allowed to give birth and litter parameters were recorded up to date 21 postpartum. One male one female pup was selected from each litter form the F1 generation. The dams and nonselected pups were necropsied after day 21 postpartum. F1 offspring (20/sex/group) were maintained untreated and monitored for postweaning development behavioral tests and mating activity. Body weights were obtained from F1 males and females. The study was terminated with a necropsy of F1 males after the cesarean sections of the F1 females on day 13 post coitum. The pregnancy status, number of corpora lutea and numbers and types of uterine implantations were determined in the females. All F1 animals are subjected to microscopic examinations kidneys of all F1 animals were collected, weighed and examined microscopically. |
| Protocol deviations affecting results | No |

Source: Reviewer generated table
Abbreviations: ETX2514, durlobactam; GD, gestation day; GLP, good laboratory practice; NaCl, sodium chloride

## Observations and Results

**Table 94. Observations and Results for GLP Pre- and Post-Natal Development Study of ETX2514 by the Intravenous Route (2-Hour Infusion) in the Rat (Segment III), Study PC2514-2019-0004**

| Generation | Major Findings |
|---|---|
| F0 dams | **Table 95. Incidence of Cecum, Distended With Fluid in F0 Females**<br>**Control** / **300 mg/kg** / **1000 mg/kg**<br>1 / 16 / 22<br>Source: Reviewer generated table |
| F1 generation | No toxicologically significant drug-related embryofetal, perinatal or subsequent postnatal development, sexual maturation, performance on behavioral tests, mating performance, fertility or gestation effects. |
| F2 generation | No toxicologically significant drug-related findings |

Source: Reviewer generated table
Abbreviations: ETX2514, durlobactam; GLP, good laboratory practice

# 14. Clinical Pharmacology

## 14.1. In Vitro Studies

### 14.1.1. Preclinical Studies to Determine the PK/PD Targets of Sulbactam and Durlobactam

**Identification of PK/PD Index**

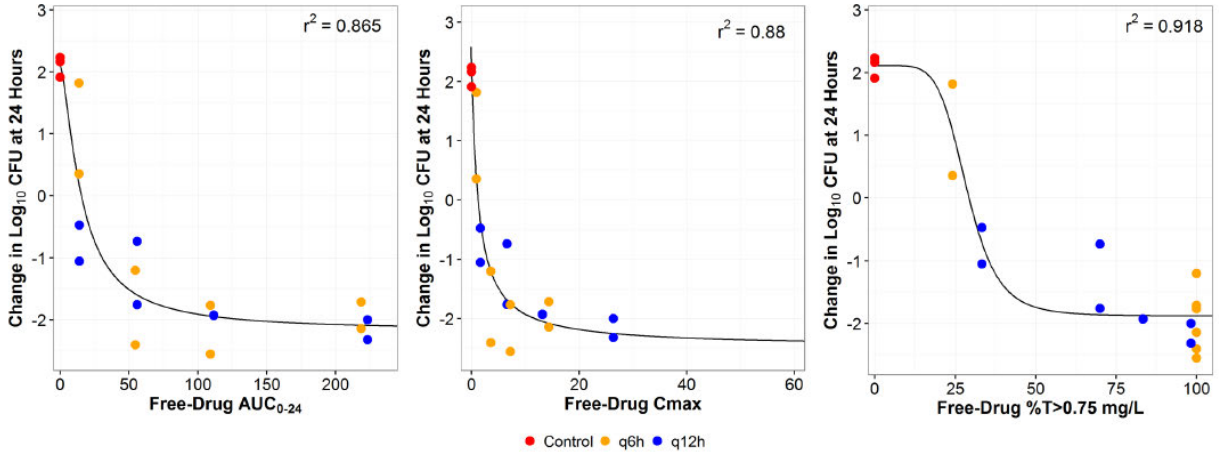
Sulbactam

The percentage of time during a dosing interval when the unbound drug concentration exceeds the minimum inhibitory concentration (*f*T > MIC) has been identified as the PK/ pharmacodynamics (PD) index that best correlates with the bactericidal activity of most β-lactam drugs. In vitro experiments that were carried out in hollow-fiber model against the pan-susceptible *A. baumannii* isolate ARC2058 confirmed the PK/PD driver for sulbactam to be *f*T > MIC.

Durlobactam

Dose fractionation studies were carried out in a one-compartment chemostat model using the MDR *A. baumannii* strain ARC5081 to identify the PK/PD index of durlobactam. Clinical unbound plasma exposures of sulbactam associated with 2.0 g sulbactam administered every 6 hours (q6h) were utilized (8.0 g sulbactam /day). Durlobactam doses were administered with q6h dosing spanning an $AUC_{0-24}$ range of 18.5 to 591 h*µg/mL. Figure 9 shows the relationship between the change in $log_{10}$ colony-forming units (CFU)/mL from baseline and durlobactam PK/PD indices including free drug $AUC_{0-24}$, free drug $C_{max}$, and time as a percentage of the dosing interval that the free drug concentration remains above 0.75 µg/mL %*f*T > threshold value of 0.75 µg/mL, for *A. baumannii* ARC 5081 (OXA-23; OXA-94).

**Figure 9. Relationship Between the Change in $log_{10}$ CFU/mL From Baseline and Durlobactam PK/PD Indices for *A. baumannii* ARC 5081 (OXA-23; OXA-94)**




Abbreviations: $AUC_{0-24}$ = area under the plasma concentration-time curve from time 0 to 24 hours; CFU = colony-forming units $C_{max}$ = maximum plasma concentration; $r^2$ = correlation coefficient.
Note: %*f*T>0.75 µg/mL, time as a percentage of the dosing interval that the drug concentration remains above 0.75 µg/mL.
Source: Summary-clin-pharm, Figure 40
Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics; q6h, every 6 hours; q12h, every 12 hours

These results suggest the PK/PD index most closely associated with the activity of durlobactam is the percentage of time durlobactam concentrations remain above a critical threshold ($C_T$). In a divided dosing study, with more frequent administration, the area under the unbound concentration-time (*f*AUC)/MIC appears to improve its correlation to activity. In addition, given the short half-life of both sulbactam and durlobactam in the clinical setting and that more frequent dosing would likely be necessary, it is more feasible to calculate $fAUC_{0-24}$/MIC than %*f*T > $C_T$. Therefore, the Applicant proposed *f*AUC/MIC to be the PK/PD index of durlobactam for dose selection.

*Reviewer's Comments: Based on the results from the in vitro study, the percentage of time durlobactam concentrations remain above a critical threshold appears to best correlate with the activity of durlobactam. However, considering that AUC is highly correlated to the time-dependent PK index such as %fT > $C_T$ and a good correlation of fAUC with the change in log10 CFU/mL was observed for durlobactam from the in vitro model ($R^2$=0.865), it is acceptable to use fAUC/MIC as the PK/PD index of durlobactam.*

**Identification of PK/PD Targets**

Sulbactam

An efficacy study was performed in neutropenic mice utilizing a thigh abscess infection model. The *A. baumannii* strains used for this study included 6 clinical isolates demonstrating a broad range of sulbactam-durlobactam MIC values. The dose range of sulbactam was 2.5 to 320 mg/kg, spanning an unbound exposure range of 0 to 71% *f*T > MIC. The addition of durlobactam to sulbactam at a 4:1 ratio restored the activity of sulbactam against nonsusceptible MDR *A. baumannii* strains in a neutropenic thigh infection model. Drug concentration data were collected in infected satellite PK groups administered increasing doses of sulbactam, sulbactam-durlobactam combinations. Exposure-response data generated in this study were utilized in

PK/PD exposure magnitude and target setting analysis. The results of %*f*T > MIC to achieve 1-$\log_{10}$ kill, 2-$\log_{10}$ kill, and $EC_{80}$ are presented in Table 96.

Efficacy of sulbactam and a 4:1 fixed dose ratio of sulbactam-durlobactam were evaluated in a murine neutropenic lung model to determine activity of the combination against a MDR *A. baumannii* pneumonia infection. The dose range of sulbactam was 1.0 to 120 mg/kg, addition of durlobactam to sulbactam at a 4:1 ratio restored the activity of sulbactam against nonsusceptible MDR *A. baumannii* strains in a neutropenic lung infection model. The results of %*f*T > MIC to achieve 1-$\log_{10}$ kill, 2-log10 kill, and $EC_{80}$ are presented in Table 97.

In both neutropenic thigh and lung models, *f*T > MIC was the most highly correlated index ($R^2 \geq 0.95$) to sulbactam activity. The %*f*T > MIC values associated PK/PD endpoints of stasis, 1-$\log_{10}$ kill, 2-$\log_{10}$ kill, and 3-$\log_{10}$ kill were 21.0, 32.9, 43.6, and 57.3%, respectively, in the thigh model and 20.4, 24.5, 29.3, and 37.3%, respectively, in the lung model.

The mean values of %*f*T > MIC magnitude determined from respective murine thigh and lung models were summarized in Table 98. For a %*f*T > MIC magnitude target, a value of 50% was selected based upon an observed mean value of 45.5% established from a 1-$\log_{10}$ kill PK/PD endpoint across the four MDR strains used in the neutropenic lung infection model.

**Table 96. Sulbactam Percent Unbound Plasma Time Above MIC Estimates to Achieve PK/PD Endpoints in Neutropenic Thigh Model (4:1 Sulbactam: Durlobactam Fixed Dose Ratio)**

| Isolate ID | β-lactamase | Minimum Inhibitory Concentration (µg/mL) | PK/PD Endpoint | | |
|---|---|---|---|---|---|
| | | | 1-$\log_{10}$ kill | 2-$\log_{10}$ kill | $EC_{80}$ |
| ARC2058 | OXA-95 | 2[a] | 20.5 | 31.5 | 47.0 |
| ARC3484 | OXA-23; OXA-64; TEM-1 | 0.5[b] | 36.2 | 40.2 | 42.8 |
| ARC3486 | OXA-66; OXA-72; TEM-1 | 0.5[b] | 45.7 | 52.9 | 55.3 |
| ARC5079 | OXA-65; OXA-72 | 1[b] | 36.4 | 42.0 | 53.2 |
| ARC5081 | OXA-23; OXA-94 | 2[b] | 26.3 | 28.8 | 32.0 |
| ARC5091 | OXA-23; OXA-78 | 1[b] | 26.2 | 29.3 | 30.4 |

Abbreviations: $EC_{80}$ = effective concentration producing 80% of response; ID = identifier; MIC = minimum inhibitory concentration; PD = pharmacodynamics; PK = pharmacokinetics.
[a] Sulbactam MIC.
[b] Sulbactam MIC in the presence of 4 µg/mL durlobactam.
Source: Summary-clin-pharm, Table 121

**Table 97. Sulbactam Percent Unbound Plasma Time Above MIC Estimates to Achieve PK/PD Endpoints in Neutropenic Lung Model (4:1 Sulbactam: Durlobactam Fixed Dose Ratio)**

| Strain ID | β-lactamase | Minimum Inhibitory Concentration (µg/mL) | PK/PD Endpoint | | |
|---|---|---|---|---|---|
| | | | 1-$log_{10}$ kill | 2-$log_{10}$ kill | $EC_{80}$ |
| ARC2058 | OXA-95 | 2[a] | 37.8 | 50.1 | 68.5 |
| ARC3484 | OXA-23; OXA-64; TEM-1 | 0.5[b] | 58.1 | 70.9 | 96.6 |
| ARC3486 | OXA-66; OXA-72; TEM-1 | 0.5[b] | 45.0 | 54.5 | 81.5 |
| ARC5079 | OXA-65; OXA-72 | 1[b] | 41.7 | 52.8 | 90.6 |
| ARC5081 | OXA-23; OXA-66 | 2[b] | 37.1 | 43.9 | 70.0 |

Abbreviations: $EC_{80}$ = effective concentration producing 80% of response; ID = identifier; MIC = minimum inhibitory concentration; PD = pharmacodynamics; PK = pharmacokinetics.
[a] Sulbactam MIC
[b] Sulbactam MIC in the presence of 4 µg/mL durlobactam
Source: Summary-clin-pharm, Table 122

**Table 98. Mean Sulbactam %fT > MIC Values Associated With 1-log10 kill, 2-log10 kill, and $EC_{80}$ PK/PD Endpoints Vs. MDR Strains Evaluated in Thigh and Lung Studies**

| Model | Number of Strains | PK/PD Endpoint | | |
|---|---|---|---|---|
| | | 1-$log_{10}$ kill | 2-$log_{10}$ kill | $EC_{80}$ |
| In vivo thigh (4:1 dose) | 5 | 34.3 | 38.6 | 42.7 |
| In vivo lung (4:1 dose) | 4 | 45.5 | 55.5 | 84.8 |

Abbreviations: $EC_{80}$ = effective concentration producing 80% of response; MDR = multi-drug resistant; MIC = minimum inhibitory concentration; PD = pharmacodynamics; PK = pharmacokinetics.
Source: Summary-clin-pharm, Table 123
Abbreviations: %fT > MIC, percent of time free drug remains above the minimum inhibitory concentration

Durlobactam

The efficacy of sulbactam alone and regimens of sulbactam in combination with durlobactam were evaluated in a murine neutropenic thigh infection model against MDR *A. baumannii* strains ARC3486, ARC5079, and ARC5081. A constant sulbactam dose of 15 mg/kg q3h was selected with varied doses of durlobactam (1.0 to 120 mg/kg q3h) to determine the dose/exposure of durlobactam required for restoration of sulbactam activity. Additional neutropenic thigh studies using a fixed sulbactam dose of 15 mg/kg q3h, 75 mg/kg q3h, and 150 g/kg q3h were performed to determine the PK/PD target of durlobactam.

PK studies were conducted in infected neutropenic CD-1 mice. Population PK models were derived for sulbactam alone, for sulbactam when co-administered with durlobactam and for durlobactam co-administered with sulbactam at a dose ratio of 4:1 sulbactam: durlobactam. Predicted exposures from the population PK model were utilized in the PK/PD analyses.

Table 99 summarizes the durlobactam *f*AUC/MIC values associated with 1-$log_{10}$ kill, 2-$log_{10}$ kill, and $EC_{80}$ PK/PD endpoints from in vitro and in vivo studies. Results demonstrated that a 1-$log_{10}$ kill can be achieved at *f*AUC/MIC of 10 and a 2-$log_{10}$ kill can be achieved at *f*AUC/MIC of 30.

**Table 99. Durlobactam *f*AUC/MIC Values Associated With 1-log10 kill, 2-log10 kill, and $EC_{80}$ PK/PD Endpoints From In Vitro and In Vivo Studies**

| Model | Number of Strains | $R^2$ | PK/PD Endpoint | | |
|---|---|---|---|---|---|
| | | | 1-$log_{10}$ kill | 2-$log_{10}$ kill | $EC_{80}$ |
| In vitro chemostat[a] | 1 | 0.87 | 10.0 | 30.0 | NC |
| In vivo thigh (4:1 dose)[b] | 5 | 0.86 | 8.0 | 16.0 | 15.1 |
| In vivo lung (4:1 dose)[c] | 4 | 0.91 | 10.6 | 22.4 | 78.6 |
| In vivo thigh (set SUL dose)[d] | 6 | 0.82 | 7.5 | 31.8 | 38.2 |
| **Mean±SD:** | | | 9.03±1.51 | 25.1±7.3 | 44.0±32.1 |

Abbreviations: $EC_{80}$ = drug concentration that gives 80% of maximal effective concentration; $E_{max}$ = maximum drug effect; %*f*T>MIC = time as percentage of dosing interval the unbound drug concentration exceeds the minimum inhibition concentration;; NC = not calculated; PD = pharmacodynamics; PK = pharmacokinetics; $R^2$ = correlation coefficient; SD = standard deviation.
Note: $E_{max}$ analysis detailed in PC2514-2021-0011, Appendix B.
[a] Sulbactam exposure at >50%T>MIC.
[b] Sulbactam mean exposure of 32.9 to 43.5% T>MIC.
[c] Sulbactam mean exposure of 43.9 to 81.5% T>MIC.
[d] Sulbactam exposure range of 18.2 to 52.7% T>MIC.
Source: Summary-clin-pharm, Table 131
Abbreviations: *f*AUC/MIC, relationship between area under the free concentration–time curve and minimum inhibitory concentration ratio; SUL, sulbactam

## Mouse ELF Penetration of Durlobactam and Sulbactam

To determine epithelial lining fluid (ELF) penetration of sulbactam and durlobactam, neutropenic CD-1 mice infected with *A. baumannii* ARC2058 received a single subcutaneous injection of either 100 mg/kg sulbactam or a mixture of sulbactam-durlobactam at a ratio of 100:25 mg/kg. Plasma and ELF samples were collected from groups of four mice each at 1, 3, 6 and 12 hours after administration. As shown in Table 100, the total drug AUC ratio in ELF to plasma is 0.32 for sulbactam and 0.63 for durlobactam in mice.

**Table 100. Plasma and ELF Exposures of Sulbactam: Durlobactam in Neutropenic Mice Infected With *A. baumannii* ARC2058**

| Time (h) | Sulbactam Concentration (µg/mL) | | Durlobactam Concentration (µg/mL) | |
|---|---|---|---|---|
| | Plasma (Mean ± SEM) | ELF (Mean ± SEM) | Plasma (Mean ± SEM) | ELF (Mean ± SEM) |
| 1 | 18.55±5.87 | 5.70±1.15 | 4.07±1.79 | 2.48±0.91 |
| 3 | 1.69±0.56 | 0.54±0.12 | 0.33±0.13 | 0.26±0.15 |
| 6 | 0.10±0.05 | 0.29±0.14 | 0.03±0.01 | 0.002±0.001 |
| 12 | 0.02±0.01 | 0.06±0.01 | 0.01±0.00 | BLQ[a] |
| AUC (h•µg/mL) | 32.3 | 10.3 | 7.0 | 4.4 |
| $AUC_{ELF}/AUC_{plasma}$ | - | 0.32 | - | 0.63 |

Abbreviations: AUC = area under the concentration-time curve; $AUC_{ELF}$ = area under the concentration-time curve in epithelial lining fluid; $AUC_{plasma}$ = area under the plasma concentration-time curve; BLQ = below the limit of quantitation; ELF = epithelial lining fluid; SEM = standard error of the mean.
[a] BLQ = 0.001 µg/mL.
Source: Summary-clin-pharm, Table 129

*Reviewer's Comments: Given the difference in the lung penetration of SUL and DUR observed between mice (total drug AUC ELF/plasma ratios: 0.32 for SUL, 0.63 for DUR) and humans (total drug AUC ELF/plasma ratios: 0.50 for SUL, 0.37 for DUR), we agree with the Applicant's*

*probability of target attainment (PTA) analyses for ELF exposures by using the same PK/PD targets for plasma PTA.*

## 14.1.2. In Vitro ADME and Drug-Drug Interaction Studies

**Protein Binding Studies**

Sulbactam has been found to be approximately 38% reversibly bound to human serum protein (UNASYN USPI (Pfizer 1986)).

Durlobactam plasma protein binding (PPB) has been studied in vitro in mouse, rat, guinea pig, dog (beagle), and human plasma (study PC2514-2016-0024).

The reported durlobactam PPB values were determined by ultracentrifugation and equilibrium dialysis methods. The durlobactam fraction unbound determined by ultrafiltration, expressed as a percentage, ranged from 78.3% ± 15.8% to 128.3% ± 12.5% across all species and concentrations, and durlobactam PPB estimates were found to be independent of concentration from 1 to 100 µM. The durlobactam fraction unbound determined by equilibrium dialysis method, expressed as a percentage, ranged from 81% to 90% across all species at a concentration of 5 µM. Unbound fraction values of >100% were attributed to assay variability associated with the bioanalytical method, and a value of 100% used for means reported >100%. No significant differences in PPB between species in either method were reported.

*Reviewer's Comments: The review of the Applicant submitted information suggests that durlobactam is not highly bound to plasma proteins with mean estimates of the bound durlobactam fraction (expressed as a percentage) ranging from 0% to 19%.*

*Therefore, we agree with the Applicant's proposed labelling that the binding of sulbactam and durlobactam to human plasma proteins is approximately 38% and 10%, respectively and independent of drug concentration.*

**Table 101. Report: Assessment of the Cytochrome P450 Inhibition Potential of AZD2514 (AZ13572514) in Human Liver Microsomes for CYP2A6, CYP2B6, CYP2C8, CYP2E1 and CYP3A4/5**

| Category | Study Details |
|---|---|
| Test drug(s) and concentrations | AZD2514 (concentrations 1.67, 5, 16.7, 50, 167 and 500 µM)<br><br>AZD2514 is also referenced as AZ13572514, ETX2514 and durlobactam. |
| Positive control(s) and concentrations | Reference inhibitors included a cocktail of three standard inhibitors: tranylcypromine (0.00333, 0.01, 0.0333, 0.1, 0.333 and 1 µM) for CYP2A6, quercetin (0.6667, 2, 6.667, 20, 66.67 and 200 µM) for CYP2B6/CYP2C8/CYP2E1, and ketoconazole (0.001, 0.003, 0.01, 0.03, 0.1 and 0.3 µM) for CYP3A4/3A5.<br><br>Marker substrates studied included a cocktail of coumarin (0.2 µM) for CYP2A6, bupropion (40 µM) for CYP2B6, amodiaquine (1 µM) for CYP2C8, chlorzoxazone (40 µM) for CYP2E1 and nifedipine (2 µM) for CYP3A4/5. Marker substrates concentration is equivalent to their Km value. |
| Report number | PC2514-2016-0014 (ADME-AZS-Wave3-150120) |

| Category | Study Details |
|---|---|
| Study system | Pooled human liver microsomes |
| Method | To examine its ability to act as an inhibitor of CYP enzymes, AZD2514 was pre-incubated at 37±1°C with a cocktail of marker substrates, and human pooled liver microsomes for approximately 10 minutes, then NADPH is added with an additional incubation for approximately 10 minutes. Metabolism reactions were determined by analysis of analytes 7-hydroxycoumarin for CYP2A6, 4-hydroxybupropion for CYP2B6, N-desethylamodiaquine for CYP2C8, 6-hydroxychlozoxazone for CYP2E1, and oxidized nifedipine for CYP3A4/3A5 by LC-MS/MS. All experiments are performed in triplicate. |
| Results | Under the experimental conditions examined, there was evidence that AZD2514 produced minor reversible inhibition of CYP2A6 and CYP3A4/5 activity (2.99% and 7.22%, respectively) at the highest concentrations of AZD2514 evaluated (500 µM, or at >5-fold clinical $C_{max}$); however, this level of inhibition was not sufficient to determine an $IC_{50}$. There was no evidence that AZD2514 inhibited CYP2B6, CYP2C8 and CYP2E1 over the concentration range tested (1.67-500 µM). The positive control inhibitors for metabolism-dependent inhibition inhibited enzyme activity as expected. |
| Discussion/conclusion | AZD2514 did not inhibit CYP2B6, CYP2C8 and CYP2E1.<br>AZD2514 was a metabolism-dependent inhibitor of CYP2A6 and CYP3A4/5 at concentration >500 µM, suggesting no concern for CYP inhibition at clinically relevant concentrations. |

Source: Reviewer's analysis
Abbreviations: ADME, absorption, distribution, metabolism, and excretion; $C_{max}$, maximum plasma concentration; CYP, cytochrome P450; ETX2514, durlobactam; $IC_{50}$, the concentration at which 50% inhibition of transport of a sensitive substrate occurs; Km; Michaelis constant; LC- /MS/MS, liquid chromatography with tandem mass spectrometry; NADPH, nicotinamide adenine dinucleotide phosphate

**Table 102. Report: Assessment of the Cytochrome P450 Inhibition Potential of AZD2514 (AZ13572514) in Human Liver Microsomes for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5**

| Category | Study Details |
|---|---|
| Test drug(s) and concentrations | AZD2514 (concentrations 1, 3, 10, 30, 100 and 300 µM)<br>AZD2514 is also referenced as AZ13572514, ETX2514 and durlobactam. |
| Positive control(s) and concentrations | Reference inhibitors included a cocktail of five standard inhibitors: α-naphthoflavone (0.0017, 0.005, 0.017, 0.05, 0.17 and 0.5 µM) for CYP1A2, sulphaphenazole (0.033, 0.10, 0.33, 1.0, 3.3 and 10.0 µM) for CYP2C9, N-3-benzylnirvanol (0.055, 0.167, 0.55, 1.67, 5.55 and 16.7 µM) for CYP2C19, quinidine (0.0017, 0.005, 0.017, 0.05, 0.17 and 0.5 µM) for CYP2D6, and ketoconazole (0.0017, 0.005, 0.017, 0.05, 0.17 and 0.5 µM) for CYP3A4/3A5.<br><br>Marker substrates studied included a cocktail of phenacetin (30 µM) for CYP1A2, diclofenac (10 µM) for CYP2C9, S-mephenytoin (35 µM) for CYP2C19, bufuralol (5 µM) for CYP2D6 and midazolam (3 µM) for CYP3A4/5. Marker substrates concentration is equivalent to their Km value. |
| Report number | PC2514-2016-0015 (ADME-AZS-Wave3-150116) |
| Study system | Pooled human liver microsomes |
| Method | To examine its ability to act as an inhibitor of CYP enzymes, AZD2514 was pre-incubated at 37±1°C with a cocktail of marker substrates, human pooled liver microsomes for approximately 10 minutes, then NADPH is added with an additional incubation for approximately 5 minutes. Metabolism reactions were determined by analysis of analytes paracetamol for CYP1A2, 4-OH-diclofenac for CYP2C9, 4-OH-mephenytoin for CYP2C19, 1-OH-bufuralol for CYP2D6, 1-OH-midazolam for CYP3A4/3A5 by LC-MS/MS. |

| Category | Study Details |
|---|---|
| Results | Under the experimental conditions examined, there was no evidence that AZD2514 inhibited CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 over the concentration range tested (1-300 µM). The positive control inhibitors for direct inhibition and metabolism-dependent inhibition inhibited enzyme activity as expected. |
| Discussion/conclusion | AZD2514 did not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5. |

Source: Reviewer's analysis
Abbreviations: ADME, absorption, distribution, metabolism, and excretion; CYP, cytochrome P450; ETX2514, durlobactam; LC-/MS/MS, liquid chromatography with tandem mass spectrometry; NADPH, nicotinamide adenine dinucleotide-phosphate; -OH-, hydroxy metabolite

**Table 103. Report: Assessment of the Cytochrome P450 Time Dependent Inhibition Potential of AZD2514 (AZ13572514) in Human Liver Microsomes**

| Category | Study Details |
|---|---|
| Test drug(s) and concentrations | AZD2514 (concentrations, 10 and 50 µM)<br>AZD2514 is also referenced as AZ13572514, ETX2514 and durlobactam. |
| Positive control(s) and concentrations | Reference inhibitors included a cocktail of five standard inhibitors: furafylline (10 µM) for CYP1A2, tienilic acid (2.5 µM) for CYP2C9, ticlopidine HCl (5 µM) for CYP2C19, paroxetine HCl (5 µM) for CYP2D6 and troleandomycin (1.5 µM) for CYP3A4/5.<br>Marker substrates studied included a cocktail of phenacetin (90 µM) for CYP1A2, diclofenac (30 µM) for CYP2C9, S-mephenytoin (105 µM) for CYP2C19, bufuralol (15 µM) for CYP2D6 and midazolam (9 µM) for CYP3A4/5. Marker substrates concentration is equivalent to their 3 times Km value. |
| Report number | PC2514-2016-0036 (ADME-AZS-Wave3-150119) |
| Study system | Pooled human liver microsomes |
| Method | To examine its ability to act as a time-dependent inhibitor of CYP enzymes, AZD2514 was pre-incubated at 37±1°C with human pooled liver microsomes, and in presence and absence of NADPH for approximately 30 minutes, then diluted 10-fold and co-incubated with a cocktail of marker substrates at three times their Km concentration and NADPH for approximately 15 minutes. Metabolism reactions were determined by analysis of analytes paracetamol for CYP1A2, 4-OH-diclofenac for CYP2C9, 4-OH-mephenytoin for CYP2C19, 1-OH-bufuralol for CYP2D6, and 1-OH-midazolam for CYP3A4/3A5 by LC/MS/MS. The projected %TDI is calculated from the decrease in the formation of these metabolites compared to the without NADPH control and vehicle control. All experiments are performed in duplicate. |
| Results | Under the experimental conditions examined, there was no evidence that AZD2514 inhibited CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 over the concentration range tested (10-50 µM). The positive control inhibitors for time-dependent inhibition inhibited enzyme activity as expected. |
| Discussion/conclusion | AZD2514 at 10 µM and 50 µM did not exhibit time dependent inhibition for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. |

Source: Reviewer's analysis
Abbreviations: ADME, absorption, distribution, metabolism, and excretion; CYP, cytochrome P450; Km; Michaelis constant; ETX2514, durlobactam; LC-/MS/MS, liquid chromatography with tandem mass spectrometry; NADPH, nicotinamide adenine dinucleotide-phosphate; -OH-, hydroxy metabolite; %TDI, percent time dependent inhibition

**Table 104. Report: Assessment of the Human P-gp (ABCB1) Inhibition Potential of AZ13572514 (AZD2514) in MDCKII-MDR1 Cells**

| Category | Study Details |
|---|---|
| Test drug(s) and concentrations | AZD2514 (concentrations 1, 3, 10, 30, 100 and 300 µM)<br>AZD2514 is also referenced as AZ13572514, ETX2514 and durlobactam. |
| Positive control(s) and concentrations | Reference inhibitor: verapamil (1, 3, 10, 30, 100 and 300 µM)<br>Marker substrates studied [3H]-digoxin (5 µM), purity =97% |
| Report number | PC2514-2016-0016 (Pgp inhib_10Oct13_AZ13572514) |
| Study system | Madin-Darby Canine Kidney type II cells stably expressing the human efflux transporter P-gp (MDCKII-MDR1) |
| Method | To examine its ability to act as an inhibitor of the human efflux transporter P-gp (MDR1, ABCB1) when expressed in MDCKII-MDR1 cells, AZD2514 was examined using the following methodology:<br>Cell culture: MDCKII-MDR1 cells were cultured to confluency, trypsinized and seeded onto Millicell multiwell membrane inserts at a density of approximately 363,600 cells/$cm^2$. The cell monolayers were fed with culture medium (Dulbecco's Modified Eagle Medium with GlutamaxTM, 10% (v/v) Fetal Bovine Serum) and transport studies conducted 3-4 days postseeding.<br>Transport inhibition studies: The effect of AZD2514 on the P-gp-mediated transport of [3H]-digoxin was assessed by determining the basolateral (donor well) to apical (receiver well) ([B→A]) transport of [3H]-digoxin for 90 minutes at 37°C, in the absence or presence of AZD2514 (applied in both apical and basolateral wells). The dose range was determined due to the limited solubility of AZD2514. Verapamil, a potent inhibitor of P-gp, was included as a positive control for P-gp inhibition.<br>Measurement of inhibition of transport: Following preincubation, plates were incubated at 37ºC for 90 minutes. All samples were analyzed for total radioactivity using a liquid scintillation counter. The cell monolayer integrity was evaluated by measuring the Lucifer yellow concentrations in the receiver wells. Fluorescence was determined using a fluorescence plate reader, using wavelengths of $\lambda_{exitation}$ =485 nm and $\lambda_{emission}$ =520 nm. Assays conducted in triplicate. |
| Results | Experiments were regarded as valid where quality control parameters were within acceptable limits. Acceptable values for the assay were: The measured radiochemical purity of the [3H]-digoxin used in this study was >90% (measured value 97%), Lucifer yellow <1.5%; the positive control inhibitor verapamil $IC_{50}$ value within the range 1.6 to 11.8 µM (actual $IC_{50}$ value of 2.4 µM); [3H]-digoxin mass balance ≥80%.<br>The [B→A] apparent permeability for [3H]-digoxin in the absence of inhibitor was 15.0±0.5 cm/s × $10^{-6}$ and in the presence of the P-gp inhibitor verapamil (300 µM, positive control) was 2.6±0.3 cm/s × $10^{-6}$ (17% of digoxin alone transport). These results demonstrated the functional expression of human P-gp in the MDCKII-MDR1 cell line. The positive control rate is considered to represent the passive transport component of [3H]-digoxin. At all tested concentrations, no marked inhibition of digoxin transport was observed with AZD2514 (apparent permeability range 13.2±1.5 to 16.3±2.0 cm/s × $10^{-6}$, with no trend regarding concentration). The data demonstrate that AZD2514 up to 300 µM does not inhibit digoxin transport via P-gp under these assay conditions. |
| Discussion/conclusion | AZD2514 did not inhibit human transport of digoxin via human P-glycoprotein in vitro at the concentration range of 1-300 µM. |

Source: Reviewer's analysis
Abbreviations: ETX2514, durlobactam; $IC_{50}$, the concentration at which 50% inhibition of transport of a sensitive substrate occurs; MDCKII-MDR1, Madin-Darby Canine Kidney type II cells stably expressing the human efflux transporter P-gp; P-gp, permeability glycoprotein; λemission, emission spectra; λexitation, exitation spectra

# 14.2. In Vivo Studies

**Table 105. Study CS2514-2016-0001: A Phase I, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Intravenous ETX2514 Administered in Healthy Subjects**

| Category | Study Details |
|---|---|
| Title | A Phase I, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Intravenous ETX2514 Administered in Healthy Subjects |
| Brief description of study design | This was a phase 1, single-center, randomized, double-blind, and placebo-controlled study to investigate the safety, tolerability, and PK profile of SAD and MAD of durlobactam when administered IV alone and in combination with sulbactam and/or imipenem/cilastatin in healthy adult subjects. The study was conducted in 4 parts; Part A, SAD of durlobactam; Part B, MAD of durlobactam; Part C, single-dose DDI; and Part D, multiple-dose DDI cohort.<br>Part A: Durlobactam 0.25, 0.5, 1.0, 2.0, 4.0, or 8.0 g 2- or 3-hour IV infusion (N=64)<br>Part B: Durlobactam 0.25, 0.5, 1.0, or 2.0 g 3-hour IV infusion (N=32)<br>Part C (single-dose DDI): Durlobactam 1.0 g 3-hour IV infusion with sulbactam 1.0 g IV or imipenem/cilastatin 0.5 g IV<br>Cohort 13:<br>• Day 1 - single dose of 1.0 g IV ETX2514/placebo infused over 3 hours<br>• Day 3 - single dose of 1.0 g IV sulbactam infused over 3 hours<br>• Day 5 - single dose of 1.0 g IV ETX2514/placebo plus 1.0 g sulbactam infused over 3 hours at the same time<br>Cohort 14:<br>• Day 1 - single dose of 1.0 g IV ETX2514/placebo infused over 3 hours<br>• Day 3 - single dose of 0.5 g IV imipenem/cilastatin infused over 30 minutes<br>• Day 5 - single dose of 1.0 g IV ETX2514/placebo infused over 3 hours plus 0.5 g imipenem/cilastatin infused over 30 minutes initiated at the same time as ETX2514/placebo<br>• Day 8 - single dose of 1.0 g IV ETX2514/placebo plus 1.0 g sulbactam infused over 3 hours at the same time plus 0.5 g imipenem/cilastatin infused over 30 minutes initiated at the same time as ETX2514/placebo (N=16)<br>Part D (multiple-dose DDI cohort): 10 subjects received 1.0 g durlobactam in combination with 1.0 g sulbactam, both infused over 3 hours, and 0.5 g imipenem/cilastatin, infused over 30 minutes every 6 hours, for 10 days and 1 dose on Day 11, and 2 subjects received placebo in combination with 1.0 g sulbactam and 0.5 g imipenem/cilastatin. |
| PK sample collection times | Blood and urine were collected at specified time points from subjects to determine plasma and urine concentrations of ETX2514 after the administration of investigational product.<br>In addition, plasma and urine concentrations of sulbactam, imipenem, and cilastatin were evaluated in subjects receiving 1 or more of these agents. |
| Bioanalysis | Validated LC/MS/MS methods were used to determine concentrations of ETX2514, sulbactam, imipenem and cilastatin in human plasma and urine. |

| Category | Study Details |
|---|---|
| Results | Twelve subjects, 6 male and 6 female, all of Han nationality, were included in the analysis dataset. |

**Table 106. Mean ± SD PK Parameters of Durlobactam Following Administration of Single Ascending Doses Ranging From 0.25–8.0 g (Part A), Including an Elderly Cohort (Cohort 8)**

| Treatment Group | $t_{1/2}$ (h) | $C_{max}$ (µg/mL) | $AUC_{0-\infty}$ (h•µg/mL) | CL (L/h) | $V_{ss}$ (L) |
|---|---|---|---|---|---|
| Cohort 1<br>Durlobactam 0.25 g<br>IV (3-hour infusion) | 1.45±0.11 | 6.95±0.95 | 25.5±3.70 | 9.99±1.57 | 16.6±3.55 |
| Cohort 2<br>Durlobactam 0.5 g<br>IV (3-hour infusion) | 2.04±0.40 | 9.93±2.03 | 47.7±7.56 | 10.7±1.86 | 25.8±2.85 |
| Cohort 3<br>Durlobactam 1.0 g<br>IV (3-hour infusion) | 1.99±0.26 | 20.7±2.77 | 76.1±10.5 | 13.4±1.85 | 25.7±4.95 |
| Cohort 4<br>Durlobactam 1.0 g<br>IV (2-hour infusion) | 2.23±0.23 | 31.3±6.90 | 101±28.9 | 10.6±2.73 | 22.7±6.35 |
| Cohort 5<br>Durlobactam 2.0 g<br>IV (3-hour infusion) | 2.16±0.18 | 41.5±6.37 | 173±25.6 | 11.8±1.89 | 24.3±3.19 |
| Cohort 6<br>Durlobactam 4.0 g<br>IV (3-hour infusion) | 2.710±0.58 | 96.2±13.6 | 368±55.9 | 11.1±1.76 | 22.4±3.55 |
| Cohort 7<br>Durlobactam 8.0 g<br>IV (3-hour infusion) | 2.77±0.38 | 176±29.0 | 732±163 | 11.4±2.34 | 28.1±9.53 |
| Cohort 8 (Elderly Subjects)<br>Durlobactam 1.0 g IV<br>(3-hour infusion) | 2.40±0.26 | 37.8±2.52 | 151±14.1 | 6.66±0.61 | 14.7±2.00 |

Abbreviations: $AUC_{0-\infty}$ = area under the curve from time of dosing extrapolated to infinity; CL = clearance; $C_{max}$ = maximum plasma concentration; IV = intravenous; PK = pharmacokinetic; SD = standard deviation; $t_{½}$ = terminal half-life; $V_{ss}$ = steady-state volume of distribution.

Source: Summary-clin-pharm, Table 3

| Category | Study Details |
|---|---|

**Table 107. Mean ± SD PK Parameters of Durlobactam Following Administration of Multiple Ascending Doses Ranging From 0.25–2.0 g (Part B)**

| Treatment Group | Day of Dosing | $t_{1/2}$ (h) | $C_{max}$ (µg/mL) | $AUC_{0\text{-}tau}$ (h•µg/mL) | CL (L/h) | $V_{ss}$ (L) |
|---|---|---|---|---|---|---|
| Cohort 9: Durlobactam 0.25 g IV q6h | 1 | ND | 6.89±1.38 | 23.1±4.92 | ND | ND |
| | 8 | 1.87±0.43 | 7.47±1.34 | 26.2±5.16 | 9.81±1.65 | 18.5±2.91 |
| Cohort 10: Durlobactam 0.5 g IV q6h | 1 | ND | 14.9±2.21 | 50.3±8.97 | ND | ND |
| | 8 | 2.61±0.05 | 14.8±1.11 | 53.4±4.79 | 9.42±0.91 | 18.1±1.80 |
| Cohort 11: Durlobactam 1.0 g IV q6h | 1 | ND | 26.9±13.1 | 79.8±35.9 | ND | ND |
| | 8 | 3.51±0.85 | 33.4±6.02 | 109±13.9 | 9.31±1.14 | 17.2±1.97 |
| Cohort 12: Durlobactam 2.0 g IV q6h | 1 | ND | 51.9±8.01 | 179±29.9 | ND | ND |
| | 8 | 10.1±2.92 | 53.3±7.75 | 193±31.2 | 10.6±1.52 | 21.8±2.01 |

Abbreviations: $AUC_{0\text{-}tau}$ = area under the curve over the dosing interval; CL = clearance; $C_{max}$ = maximum plasma concentration; IV = intravenous; ND = not determined; PK = pharmacokinetic; q6h = every 6 hours; SD = standard deviation; t½ = terminal half-life; $V_{ss}$ = steady-state volume of distribution.
Source: Summary-clin-pharm, Table 4

**Table 108. Mean ± SD PK Parameters of Durlobactam and Sulbactam Following Single Dose Administration of Durlobactam and Sulbactam, Alone and in Combination (Part C, Cohort 13)**

| Treatment Group | $t_{1/2}$ (h) | $C_{max}$ (µg/mL) | $AUC_{0\text{-}\infty}$ (h•µg/mL) | CL (L/h) | $V_{dss}$ (L) |
|---|---|---|---|---|---|
| **Durlobactam PK (n=6)** | | | | | |
| Durlobactam only | 2.04 ± 0.38 | 26.9 ± 3.55 | 104± 6.65 | 9.60 ± 0.61 | 17.6 ± 2.08 |
| Durlobactam + Sulbactam | 2.02 ± 0.44 | 28.1 ± 2.49 | 105 ± 6.43 | 9.52 ± 0.56 | 17.4 ± 1.69 |
| **Sulbactam PK (n=6)** | | | | | |
| Sulbactam only | 1.30 ± 0.09 | 20.7 ± 0.69 | 68.5 ± 4.74 | 14.7 ± 1.02 | 18.0 ± 1.56 |
| Durlobactam + Sulbactam | 1.29 ± 0.08 | 22.0 ± 2.72 | 73.0 ± 6.18 | 13.8 ± 1.16 | 18.1 ± 1.68 |

Abbreviations: $AUC_{0\text{-}\infty}$ = area under the curve from time of dosing extrapolated to infinity; CL = clearance; $C_{max}$ = maximum plasma concentration; PK = pharmacokinetic; SD = standard deviation; t½ = terminal half-life; $V_{dss}$ = steady-state volume of distribution.
Source: Summary-clin-pharm, Table 5

| Category | Study Details |
|---|---|

**Table 109. Mean ± SD PK Parameters of Durlobactam, Sulbactam, Imipenem, and Cilastatin Following Single-Dose Administration of Durlobactam, Sulbactam, and Imipenem/Cilastatin Alone and in Combination (Part C, Cohort 14)**

| Treatment Group | $t_{1/2}$ (h) | $C_{max}$ (µg/mL) | $AUC_{0-\infty}$ (h*µg/mL) | CL (L/h) | $V_{ss}$ (L) |
|---|---|---|---|---|---|
| **Sulbactam PK (n=6)** | | | | | |
| Durlobactam + sulbactam + imipenem/cilastatin | 1.26 ± 0.07 | 23.7 ± 6.12 | 80.6 ± 21.2 | 13.0 ± 2.57 | 15.2 ± 2.72 |
| Sulbactam + imipenem/cilastatin | 1.31 ± 0.06 | 24.0 ± 1.98 | 81.7 ± 5.17 | 12.3 ± 0.77 | 15.4 ± 1.49 |
| **Durlobactam PK (n=6)** | | | | | |
| Durlobactam | 1.76 ± 0.43 | 30.0 ± 9.24 | 107 ± 31.3 | 9.89 ± 2.09 | 15.9 ± 2.64 |
| Durlobactam + imipenem/cilastatin | 1.65 ± 0.29 | 26.6 ± 5.14 | 104 ± 22.5 | 9.93 ± 1.83 | 15.4 ± 1.87 |
| Durlobactam + imipenem/cilastatin + sulbactam | 1.90 ± 0.42 | 30.4 ± 7.76 | 116 ± 28.3 | 9.00 ± 1.76 | 14.9 ± 2.31 |
| **Imipenem PK (n=6)** | | | | | |
| Imipenem/cilastatin | 1.20 ± 0.14 | 34.4 ± 5.26 | 43.7 ± 9.24 | 11.8 ± 2.05 | 14.3 ± 2.16 |
| Imipenem/cilastatin + durlobactam | 1.21 ± 0.16 | 31.3 ± 2.31 | 42.2 ± 5.62 | 12.0 ± 1.43 | 15.2 ± 1.21 |
| Imipenem/cilastatin + durlobactam + sulbactam | 1.21 ± 0.07 | 32.7 ± 3.97 | 45.7 ± 5.12 | 11.0 ± 1.16 | 13.9 ± 0.93 |
| Imipenem/cilastatin + sulbactam[a] | 1.32 ± 0.004 | 30.9 ± 2.40 | 44.3 ± 3.90 | 11.3 ± 1.00 | 15.0 ± 0.96 |
| **Cilastatin PK (n=6)** | | | | | |
| Imipenem/cilastatin | 1.19 ± 0.19 | 46.0 ± 8.27 | 49.6 ± 9.79 | 10.4 ± 1.80 | 9.61 ± 1.40 |
| Imipenem/cilastatin + durlobactam | 1.22 ± 0.20 | 44.0 ± 6.11 | 47.1 ± 7.20 | 10.8 ± 1.81 | 9.87 ± 1.17 |
| Imipenem/cilastatin + durlobactam + sulbactam | 1.23 ± 0.23 | 40.7 ± 4.91 | 46.9 ± 6.61 | 10.8 ± 1.60 | 10.4 ± 0.90 |
| Imipenem/cilastatin + sulbactam[a] | 1.37 ± 0.13 | 42.0 ± 8.20 | 49.8 ± 3.89 | 10.1 ± 0.79 | 11.1 ± 2.10 |

Abbreviations: $AUC_{0-\infty}$ = area under the curve from time of dosing extrapolated to infinity; CL = clearance; $C_{max}$ = maximum plasma concentration; PK = pharmacokinetic; SD = standard deviation; t½ = terminal half-life; Vss = steady-state volume of distribution.
[a] n=2
Source: Summary-clin-pharm, Table 5

In Part D of the study, mean $C_{trough}$ values collected predose on days 2, 4, and 11 were all within one standard deviation for both durlobactam and sulbactam, indicating that both durlobactam and sulbactam reach steady state within 2 days.
Complete urine results were only available for Cohorts 6 (4.0 g), 7 (8.0 g), and 8 (1.0 g, elderly subjects). Across these cohorts, %Fe ranged from 55-76%. Following multiple doses, the %Fe was greater than 50%.

| | |
|---|---|
| Discussion/conclusion | Durlobactam, administered as single doses, demonstrated dose-proportional exposure across the entire dose range studied (0.25 to 8.0 g). When administered as multiple doses (29 doses), durlobactam demonstrated linear dose-proportional exposure across the entire dose range studied (0.25 to 2.0 g infused over 3 hours q6h) with minimal accumulation.<br>Renal excretion was the predominant mode of elimination with Fe unchanged in urine >50% when evaluated after the first dose in the MAD cohorts.<br>There was no significant DDI between durlobactam and sulbactam and no significant DDI between sulbactam-durlobactam and imipenem/cilastatin. Both durlobactam and sulbactam reach steady state by two days (administration of four doses). |

Source: Clinical study report of Study CS2514-2016-0001 and reviewer's analysis
Abbreviations: DDI, drug-drug interaction; ETX2514, durlobactam; %Fe, fraction excreted; IV, intravenous; LC/MS/MS, liquid chromatography with tandem mass spectrometry MAD, multiple-ascending dose; N, number of subjects; PK, pharmacokinetics; SAD, single ascending dose

**Table 110. Study ZL-2402-001: A Phase I, Open-Label Clinical Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Single Intravenous Administration of Sulbactam-ETX2514 in Chinese Healthy Subjects**

| Category | Study Details |
|---|---|
| Title | A Phase I, Open-label Clinical Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Single Intravenous Administration of Sulbactam-ETX2514 in Chinese Healthy Subjects |
| Brief description of study design | This was a single-center, single-dose phase 1 clinical study in Chinese healthy adult subjects (n=12). A single dose of intravenous sulbactam-ETX2514 (1.0 g sulbactam and 1.0 g ETX2514 infused over 3-hour) was administered. ETX2514 is also known as durlobactam. |
| PK sample collection times | Plasma samples (3 mL each) for sulbactam and ETX2514 PK were collected predose on Day 1 at 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 h postdose. Urine samples for sulbactam and ETX2514 PK were collected predose on Day 1 and at the following intervals 0-6, 6-12, 12-24, and 24-48 h postdose. |
| Bioanalysis | A validated UHPLC method was used to determine in sulbactam and ETX2514 in human plasma and urine. |
| Results | Twelve subjects, 6 male and 6 female, all of Han nationality, were included in the analysis dataset. |

**Table 111. Summary of Plasma PK Parameters[1] of Sulbactam and ETX2514 Following Single Dose of Intravenous Sulbactam-ETX2514 (1.0 g Sulbactam and 1.0 g ETX2514 Infused Over 3-Hours)**

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| Analyte | N | $C_{max}$ (µg/mL) | $AUC_{0\text{-}tlast}$ (h*µg/mL) | $AUC_{0\text{-}inf}$ (h*µg/mL) | $T_{max}$[2] (h) | $t_{1/2}$ (h) | $V_z$ (L) | $V_{ss}$ (L) | CL (L/h) | $k_e$ (1/h |
|---|---|---|---|---|---|---|---|---|---|---|
| Sulbactam | 12 | 28.9 ± 4.88 (16.9) | 89.5 ± 15.4 (17.2) | 89.8 ± 15.4 (17.2) | 2.98 (2.98, 3.00) | 1.39 ± 0.132 (9.5) | 22.8 ± 3.51 (15.4) | 16.7 ± 2.49 (15.0) | 11.4 ± 1.79 (15.7) | 0.501 ± 0.0464 (9.3 |
| ETX2514 | 12 | 39.3 ± 5.77 (14.7) | 136 ± 20.8 (15.2) | 136 ± 20.7 (15.2) | 2.98 (2.98, 3.00) | 2.18 ± 0.261 (12.0) | 23.4 ± 3.70 (15.8) | 14.7 ± 2.11 (14.3) | 7.48 ± 1.06 (14.1) | 0.324 ± 0.0501 (15.5 |

Source: ZL-2402-001 Table 10
[1] Mean ± standard deviation (%CV)
[2] Median (range)
Abbreviations: $AUC_{0\text{-}inf}$, area under the curve from time of dosing extrapolated to infinity; $AUC_{0\text{-}tlast}$, area under the curve from time to the last quantifiable concentration; $C_{max,}$ maximum plasma concentration; CV, coefficient of variation; n, number of subjects in category; ETX2514, durlobactam; $k_{el}$, elimination rate constant; PK, pharmacokinetic; $t_{max}$, time to maximum plasma concentration; $t_{1/2}$, terminal half-life; $V_{ss}$, steady-state volume of distribution; $V_z$, volume of elimination

**Table 112. Summary of Urine PK Parameters[1] of Sulbactam and ETX2514 Following Single Dose of Intravenous Sulbactam-ETX2514 (1.0 g Sulbactam and 1.0 g ETX2514 Infused Over 3-Hour)**

| Analyte | n | $A_e$ (µg) | $f_e$ (%) | $CL_R$ (L/h) |
|---|---|---|---|---|
| Sulbactam | 12 | 924000 (3.6) | 92.4 (3.6) | 10.6 (17.6) |
| ETX2514 | 12 | 843000 (4.5) | 84.3 (4.5) | 6.32 (16.9) |

Source: ZL-2402-001 Table 11
[1] Mean (%CV) 2Median (range)
Abbreviations: Ae, total amount excreted; $CL_R$, renal clearance; CV, coefficient of variation; ETX2514, durlobactam; Fe, fraction excreted; n, number of subjects in category; PK, pharmacokinetics

| | |
|---|---|
| Discussion/ conclusion | The results of study ZL-2402-001 are acceptable. The results of this study are generally comparable to those seen in non-Chinese healthy volunteers, suggesting that the pharmacokinetics are not impacted by race. The final population pharmacokinetic model did identify the covariate East Asian region (which grouped patients from mainland China, Taiwan, and South Korea) as statistically significantly related to the inter-individual variability in durlobactam CL and Vc, however it is not considered a clinically relevant difference. Therefore, the proposed label does not adjust dosing based on race. |

Source: Clinical study report of Study ZL-2402-001 and reviewer's analysis
Abbreviations: CL, clearance; ETX2514, durlobactam; n, number of subjects in category; PK, pharmacokinetics; Vc, central compartment volume, UHPLC, ultra-high-performance liquid chromatography

**Table 113. Study CS2514-2017-0001 (Lung Pharmacokinetic Study): A Phase 1, Multiple-Dose, Open-Label, PK Study to Determine and Compare Plasma, ELF, and Alveolar Macrophage Concentrations of Durlobactam and Sulbactam in Healthy Adult Subjects**

| Category | Study Details |
|---|---|
| Title | A Phase I Study to Determine and Compare Plasma, Epithelial Lining Fluid, and Alveolar Macrophage Concentrations of Intravenous ETX2514 and Sulbactam Administered to Healthy Adult Subjects |
| Brief description of study design | This was a phase 1, multiple dose, open-label pharmacokinetic study in healthy adult male and female subjects. Thirty healthy subjects received a total of 3 doses of ETX2514 1.0 g and sulbactam 1.0 g via IV infusion administered every 6 hours with each drug infused over 3 hours.<br>All infusions were administered as separate infusions. ETX2514 and sulbactam infusions were initiated at the same time and both drugs were infused over 3 hours. |
| PK sample collection times | Each subject underwent 1 standardized bronchoscopy with bronchoalveolar lavage at 1 of several time points (1.0, 2.5, 3.25, 4.0, or 6.0 hours, 6 subjects per sampling period) after the start of the infusion of the third dose. Plasma samples were collected within 5 minutes before administration and at various time points after each dose. |
| Bioanalysis | Durlobactam and sulbactam concentrations were measured by using a validated LC/MS/MS method |
| Results | **Table 114. Intrapulmonary Penetration of Sulbactam and Durlobactam**<br>Sampling Site / $AUC_{0-6}$ (h* µg/mL) / Plasma (Total) / Epithelial Lining Fluid / Ratio<br>Sulbactam / 68.87 / 34.71 / 0.50<br>Durlobactam / 107.80 / 40.07 / 0.37<br>Abbreviations: $AUC_{0-6}$ = area under the plasma concentration-time curve from 0 to 6 hours after dosing<br>Note: $AUC_{0-6}$ is based on mean concentrations<br>Source: Summary-clin-pharm, Table 7 |
| Discussion/ conclusion | Sulbactam-durlobactam demonstrated penetration into the ELF at clinically relevant doses, with total drug AUC ELF/plasma ratios of 0.5 for sulbactam and 0.37 for durlobactam. |

Source: Clinical study report of Study CS2514-2017-0001 and reviewer's analysis
Abbreviations: AUC, area under the curve; ELF, epithelium lining fluid; ETX2514, durlobactam; IV, intravenous; LC/MS/MS, liquid chromatography with tandem mass spectrometry; PK, pharmacokinetics.

**Table 115. Study CS2514-2018-0002 (ADME Study): A Phase 1, Single-Dose, Open-Label, Nonrandomized Study to Evaluate the PK, Distribution, Metabolism, and Excretion of $^{14}C$-Durlobactam Administered IV in Healthy Male Subjects**

| Category | Study Details |
|---|---|
| Title | Single Period, Open-Label, Phase 1 Study to Determine the Excretion and Metabolism of $^{14}C$-ETX2514 Administered Intravenously in Healthy Male Subjects |
| Brief description of study design | A total of 8 subjects were enrolled in the study and each received a single IV dose of 1.0 g of nonlabeled durlobactam and 1 µCi of $^{14}C$-labeled durlobactam as a 3-hour IV infusion. |
| PK sample collection times | Blood, urine, and feces were collected over 168 hours. Whole blood, plasma, urine, and feces were measured for total radioactivity, and plasma, urine, and feces metabolite profiling of durlobactam was determined. |
| Bioanalysis | $^{14}C$ was measured by accelerator mass spectrometry (AMS) in screening sample(s) of urine and/or blood (either whole blood or plasma). Metabolite profiling of plasma, urine, and feces was performed using HPLC and AMS. |

| Category | Study Details |
|---|---|
| Results | The mean cumulative recovery of radioactivity over the 168-hour collection period was 93.0%. The majority (73.7%) of the excreted $^{14}$C-labeled dose was recovered from urine in the first 6 hours after the start of infusion. Over the 168-hour collection period, 92.3% of the radioactivity was recovered in the urine and 0.692% of the dose was recovered from feces.<br>In plasma, the parent compound accounted for approximately 27.6% of the total radioactivity contained in the $AUC_{0\text{-}72h}$ plasma pool. Components P3, P7, and P8 accounted for 20.7%, 11.7%, and 12.7% respectively of the plasma radioactivity. Unchanged parent durlobactam was identified as the major radioactive component in urine (78.1%). The hydrolysis product ETX-014799 accounted for 10.6% of the recovered dose in urine.<br>Exposure ($AUC_{0\text{-}168}$) of total radioactivity in plasma was higher than that of the unlabeled drug in plasma, confirming circulating metabolites. The $t_{1/2}$ of $^{14}$C-labeled durlobactam drug-related materials in human plasma was approximately 78-fold longer than the $t_{1/2}$ of durlobactam in plasma. Mean concentrations of total radioactivity in whole blood and plasma indicated no extensive partitioning into the red blood cells. |
| Discussion/ conclusion | The mean cumulative recovery of radiolabeled durlobactam over the 168-hour collection period was 93.0% with nearly all the radioactivity recovered in urine and 78.1% of unchanged parent durlobactam, indicating that urinary excretion of durlobactam was the predominant clearance mechanism in human subjects. |

Source: Clinical study report of Study CS2514-2018-0002 and reviewer's analysis
Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AMS, accelerator mass spectrometry; $AUC_{0\text{-}168}$, area under the curve from 0 to 168 hours; ETX2514, durlobactam; HPLC, high performance liquid chromatography; IV, intravenous; PK, pharmacokinetic; $t_{1/2}$, terminal half-life

**Table 116. Study CS2514-2017-0002 (Renal Impairment Study): A Phase 1, Single-Dose, Open-Label, Nonrandomized Study to Evaluate the PK, Safety, and Tolerability of Sulbactam-Durlobactam in Healthy Adult Subjects and Adult Subjects With Renal Insufficiency**

| Category | Study Details |
|---|---|
| Title | Evaluation of the Pharmacokinetics, Safety, and Tolerability of Intravenous ETX2514 and Sulbactam Administered Concurrently to Subjects with Various Degrees of Renal Impairment and Healthy Matched Control Subjects |
| Brief description of study design | The study was composed of 5 cohorts of subjects with mild (6 subjects), moderate (6 subjects), or severe (8 subjects) renal impairment, ESRD on hemodialysis (6 subjects), and healthy matched control subjects with normal renal function (8 subjects). The severity of renal impairment was assessed based on estimated CLcr or eGFR and subjects were assigned into the following cohorts:<br><br>**Table 117. Study Cohorts Based on Renal Function Classification**<br><br>Cohort 1: Normal; $CL_{CR}$ ≥90 mL/min; 8<br>Cohort 2: Mild Impairment; eGFR ≥60 to <90 mL/min/1.73 $m^2$; 6<br>Cohort 3: Moderate Impairment; eGFR ≥30 to <60 mL/min/1.73 $m^2$; 6<br>Cohort 4: Severe Impairment; eGFR <30 mL/min/1.73 $m^2$; 8<br>Cohort 5: ESRD on HD; Not applicable; 6<br><br>Abbreviations: $CL_{CR}$ = creatinine clearance; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HD = hemodialysis.<br>Source: CSR CS2514-2017-0002<br><br>All subjects in Cohorts 1 through 3 received a single IV infusion of 1.0 g sulbactam and 1.0 g durlobactam (on Day 1). After completion of Cohorts 2 and 3, safety and PK data were evaluated, and the dose of sulbactam 0.5 g / durlobactam 0.5 g was determined for Cohorts 4 and 5; therefore, Cohort 4 subjects received a single IV infusion of sulbactam 0.5 g / durlobactam 0.5 g (on Day 1) and Cohort 5 subjects received a single dose of sulbactam-durlobactam twice: after hemodialysis (on Day 1 for Period 1) and before hemodialysis (on Day 1 for Period 2), with at least 1-week washout between doses. In Period 2, dialysis was started approximately 1 hour after the end of infusion. |
| PK sample collection times | For Cohorts 1–4, plasma and urine samples were collected at various time points after administration of sulbactam-durlobactam.<br>For Cohort 5, plasma samples were collected both after hemodialysis (Period 1) and before hemodialysis (Period 2), and dialysate samples were collected at various time points after administration of sulbactam-durlobactam in Period 2. |
| Bioanalysis | Durlobactam and sulbactam concentrations were measured by using a validated LC-MS/MS method. |
| Results | Key sulbactam and durlobactam PK parameters are summarized in the tables below. |

**Category** **Study Details**

**Table 118. Geometric Mean (%CV) PK Parameters of Sulbactam by Cohort and Period**

| Cohort | | Dose (g) | N | $C_{max}$ (µg/mL) | $AUC_{0\text{-last}}$ (h•µg/mL) | $AUC_{0\text{-}\infty}$ (h•µg/mL) | $t_{1/2}$ (h) | CL (L/h) |
|---|---|---|---|---|---|---|---|---|
| Healthy | | 1.0 | 8 | 17.0 (17.1) | 62.8 (14.7) | 63.0 (14.7) | 1.75 (37.9) | 15.9 (14.7) |
| Mild | | 1.0 | 6 | 22.1 (25.3) | 85.3 (28.7) | 85.8 (28.1) | 1.95 (15.1) | 11.7 (28.1) |
| Moderate | | 1.0 | 6 | 27.1 (28.9) | 126 (42.3) | 126 (42.0) | 2.95 (43.6) | 7.93 (42.0) |
| Severe | | 0.5 | 7 | 20.2 (26.0) | 136 (40.2) | 136 (40.2) | 4.74 (34.0) | 3.66 (40.4) |
| ESRD on HD | Period 1 | 0.5 | 5 | 23.7 (32.8) | 280 (71.5) | 288 (73.9) | 9.23 (52.8) | 1.74 (73.9) |
| | Period 2 | 0.5 | 6 | 20.1 (23.2) | 127 (37.1) | 131 (43.1)[a] | 9.96 (51.6)[a] | 3.82 (43.1)[a] |

Abbreviations: $AUC_{0\text{-last}}$ = area under the plasma concentration versus time curve from time zero to time of last quantifiable concentration after dosing; $AUC_{0\text{-}\infty}$ = area under the concentration-time curve extrapolated to infinity; $C_{max}$ = maximum observed plasma drug concentration; CV = coefficient of variation; ESRD = end-stage renal disease; HD = hemodialysis; PK = pharmacokinetic; $t_{1/2}$ = half-life.
Source: Summary-clin-pharm, Table 11

**Table 119. Geometric Mean (%CV) PK Parameters of Durlobactam by Cohort and Period**

| Cohort | | Dose (g) | N | $C_{max}$ (µg/mL) | $AUC_{0\text{-last}}$ (h•µg/mL) | $AUC_{0\text{-}\infty}$ (h•µg/mL) | $t_{1/2}$ (h) | CL (L/h) |
|---|---|---|---|---|---|---|---|---|
| Healthy | | 1.0 | 8 | 27.0 (19.3) | 109 (16.7) | 110 (17.6)[a] | 2.34 (4.26)[a] | 9.09 (17.6)[a] |
| Mild | | 1.0 | 6 | 33.3 (18.9) | 151 (19.1) | 151 (19.1) | 2.97 (14.8) | 6.64 (19.1) |
| Moderate | | 1.0 | 6 | 38.7 (20.9) | 209 (33.2) | 209 (33.2) | 3.77 (21.9) | 4.79 (33.2) |
| Severe | | 0.5 | 7 | 25.5 (21.4) | 202 (24.0) | 202 (24.0) | 5.38 (20.5) | 2.47 (24.2) |
| ESRD on HD | Period 1 | 0.5 | 5 | 28.6 (27.5) | 278 (45.2) | 280 (45.6) | 7.12 (36.6) | 1.78 (45.6) |
| | Period 2 | 0.5 | 6 | 21.9 (22.7) | 123 (28.5) | 123 (32.1)[b] | 7.13 (32.7)[b] | 4.07 (32.1)[b] |

Abbreviations: $AUC_{0\text{-last}}$ = area under the plasma concentration versus time curve from time zero to time of last quantifiable concentration after dosing; $AUC_{0\text{-}\infty}$ = area under the concentration-time curve extrapolated to infinity; CL = total body clearance from plasma; $C_{max}$ = maximum observed plasma drug concentration; CV = coefficient of variation; ESRD = end-stage renal disease; HD = hemodialysis; PK = pharmacokinetic; $t_{1/2}$ = half-life.
[a] N=7.
[b] N=5.
Source: Summary-clin-pharm, Table 12

**Table 120. Dose Normalized Fold AUC Increase in Subjects With Renal Impairment Compared to Subjects With CLcr ≥90 mL/min**

| Estimated eGFR (mL/min/1.73 $m^2$) | Sulbactam | Durlobactam |
|---|---|---|
| ≥60 to <90 | 1.4 | 1.4 |
| ≥30 to <60 | 2.0 | 1.9 |
| <30 | 4.3 | 3.7 |

Source: Draft label, Table 4
Abbreviations: AUC, area under the curve; CLcr, creatinine clearance; eGFR, estimated glomerular filtration rate

Dialysis effectively removed sulbactam and durlobactam from plasma; the geometric least squares mean ratio for sulbactam and durlobactam $AUC_{0\text{-}\infty}$ was approximately 45% when comparing initiation of dialysis 1 hour after the end of sulbactam-durlobactam administration with completion of dialysis before the start of sulbactam-durlobactam administration. The estimated CLD for ESRD subjects in Cohort 5 was on par with renal clearance for healthy subjects in Cohort 1. Approximately 65% to 93% of the sulbactam-durlobactam dose was eliminated in urine for subjects in Cohorts 1 through 3, with most excretion occurring within 24 hours of dosing. For subjects in Cohort 4, approximately 40% of the dose was excreted in urine, while approximately 33% (durlobactam) to 40% (sulbactam) of the dose was excreted in dialysate for Cohort 5.

| Category | Study Details |
|---|---|
| Discussion/ conclusion | Sulbactam and durlobactam exposures increased at all levels of renal impairment compared to healthy subjects. The $AUC_{0-\infty}$ was approximately 2- and 4-fold higher in subjects with moderate RI and severe RI, respectively, than those with normal renal function, for both sulbactam and durlobactam. In Cohort 5 (ESRD), $AUC_{0-\infty}$ was approximately 9-fold higher and 5-fold higher for sulbactam and durlobactam, respectively, compared to subjects with normal renal function.<br>Differences in AUC were <2-fold between Cohort 2 (mild RI) and Cohort 1(healthy).<br>Approximately 65% to 93% of the sulbactam-durlobactam dose was eliminated in urine for subjects in Cohorts 1 through 3, which further supports that sulbactam and durlobactam are primarily renally eliminated.<br>Further, the HD data suggest that dialysis may be effective in removing sulbactam and durlobactam from plasma. |

Source: Clinical study report of Study CS2514-2017-0002 and reviewer's analysis
Abbreviations: AUC, area under the curve; $AUC_{0-\infty}$, area under the curve from time of dosing extrapolated to infinity; CLcr; creatinine clearance; CLD, hemodialysis recovery clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ETX2514, durlobactam; HD, hemodialysis; IV, intravenous; LC/MS/MS, liquid chromatography with tandem mass spectrometry; PK, pharmacokinetic; RI, resistive index

## 14.3. Bioanalytical Method Validation and Performance

The bioanalytical methods validation was performed for determination of durlobactam and sulbactam in plasma, urine, bronchoalveolar lavage fluid, and dialysate. Methods validation for determination of urea in plasma and bronchoalveolar lavage fluid was also performed. Clinical studies utilized validated high-performance liquid chromatography with tandem mass spectrometry bioanalytical methods for quantification of sulbactam and durlobactam in PK samples.

The bioanalytical methods used to measure concentrations of sulbactam and durlobactam in human biological samples were sensitive, selective, accurate, and reproducible. Stability of analytes was demonstrated during sample processing and long-term storage.

Briefly, the bioanalytical methods' validation and performance, as summarized in Table 121, Table 122, and Table 123, met the criteria recommended in the Bioanalytical Method Validation Guidance for Industry (November 2022). Incurred sample re-analysis (ISR) was completed for all studies and acceptance criteria per FDA guidance were met, with at least two-thirds (66.7%) of ISR results meeting acceptance criteria.

**Table 121. Summary of Bioanalytical Method Validation and Performance for Sulbactam-Durlobactam**

| Method Parameters | Method Details | | | | | | |
|---|---|---|---|---|---|---|---|
| Study no. | CS2514-2016-0001 (Durlobactam only), CS2514-2017-0001, CS2514-2017-0002, CS2514-2017-0003 | | CS2514-2018-0003, CS2514-2017-0004 | | ZL-2402-001, CS2514-2017-0004 | | CS2514-2018-0002 |
| Biological matrix | Human plasma | | | | | | |
| Anticoagulant | $K_2$EDTA | | | | | | |
| Extraction methods | Protein precipitation extraction | | | | | | |
| Drug | Sulbactam | Durlobactam | Sulbactam | Durlobactam | Sulbactam | Durlobactam | Durlobactam |
| Internal standard | sulbactam-d2 | ETX2514-$^{13}C_2$-$^{15}N_2$ | sulbactam -d2 | ETX2514-$^{13}C_2$-$^{15}N_2$ | sulbactam-d2 | ETX2514-$^{13}C_2$-$^{15}N_2$ | ETX-011178-03-01 |
| Validation range (ng/mL) | 5 to 5000 | | 5 to 5000 | | 15 to 2500 | 5 to 5000 | 5 to 5000 |
| QC levels (ng/mL) | 5, 15, 175, 2000, 4000, and 25000 | | 5, 15, 150, and 4000 | | 15, 45, 200, 1000, 1800 | 5, 15, 150, 2000, 3750 | 5, 15, 300, and 4000 |
| Inter-day accuracy (RE%)[a] | -5.3 to 4.5 | -11.2 to 6.3 | -4.8 to 6.0 | -3.4 to 4.7 | -10.7 to -2.0 | -11.6 to -2.0 | -5.33 to 3.00 |
| Inter-day precision (CV%)[a] | 4.5 to 10.5 | 2.8 to 9.6 | 2.7 to 10.0 | 2.6 to 7.0 | 1.6 to 7.6 | 1.4 to 7.7 | 5.23 to 7.34 |
| Incurred sample reanalysis[b] | 85 to 97.9 | 80 to 100 | 100 | 96.5 to 97.1 | 100 | 100 | 95.0 |
| Bio-analytical laboratory | [redacted] (b) (4) | | | | | | |
| Bioanalytical report(s) | 8355766, 8371374, 8377369, and 8377370 | | RPT19229-SA1-0.1 and RPT19264-SA1-1.0 | | 404486-202558-PSA and 404486-202560-PSA | | 179514-M-SHPL |
| Validation report(s) | 8351072, and Addendum 1, 8351072B, and Addendum 1 | | (b) (4) 18314-M1.0, addendums RPT18314-AD-1.0 and AD2-1.0 | | 404486-192166-PMV and Amendment 01 | | 179514-M-VHPL |

Source: Reviewer's analysis
[a] The inter-day accuracy and precision values from validation and performance reports are combined and presented as an overall range.
[b] At least 10% of samples reanalyzed
Abbreviations: CV%, co-efficient of variation expressed as percent; ETX2514, durlobactam; $K_2$EDTA, dipotassium ethylenediaminetetraacetic acid; QC, quality control; RE%, relative error expressed as percent

**Table 122. Summary of Bioanalytical Method Validation and Performance for Sulbactam-Durlobactam (Cont.)**

| Method Parameters | Method Details | | | | |
|---|---|---|---|---|---|
| Study no. | CS2514-2016-0001 (Durlobactam only), CS2514-2017-0002 | | ZL-2402-001 | | CS2514-2018-0002 |
| Biological matrix | Human urine | | | | |
| Extraction methods | Protein precipitation extraction | | | | |
| Drug | Sulbactam | Durlobactam | Sulbactam | Durlobactam | Durlobactam |
| Internal standard | sulbactam-d2 | ETX2514-$^{13}C_2$-$^{15}N_2$ | sulbactam-d2 | ETX2514-$^{13}C_2$-$^{15}N_2$ | ETX-011178-03-01 |
| Validation range (ng/mL) | 50 to 50000 | | 150 to 25000 | 50 to 50000 | 50 to 50000 |
| QC levels (ng/mL) | 50, 150, 1200, 20000, and 40000 | | 150, 450, 2000, 10000, and 19000 | 50, 150, 1500, 20000, and 37500 | 50, 150, 3000, and 40000 |
| Inter-day accuracy (RE%)[a] | -6.8 to -0.7 | -8.6 to 7.5 | -4.7 to 2.0 | -2.2 to 0.7 | -3.67 to 3.4 |
| Inter-day precision (CV%)[a] | 2.2 to 7.3 | 1.5 to 13.7 | 1.8 to 5.4 | 2.1 to 6.7 | 2.06 to 10.31 |
| Incurred sample reanalysis[b] | 95.5 | 54.0[c] to 100 | 100 | 100 | 96.7 |
| Bio-analytical laboratory | (b) (4) | | | | |
| Bioanalytical report | 8355766, and 8377369 | | 404486-202559-PSA | | 179514-M-SHUR |
| Validation report | 8351071, and 8351071C | | 404486-192167-PMV | | 179514-M-VHUR |

Source: Reviewer's analysis
[a] The inter-day accuracy and precision values from validation and performance reports are combined and presented as an overall range.
[b] At least 10% of samples reanalyzed
[c] Bioanalytical report 8355766 references CAPA investigation which determined no root cause for finding, and the decision to report data 'as is' with a comment in the final sample analysis report that the concentration data should be used and interpreted with extreme caution due to the performance issues of the urine assays.
Abbreviations: CAPA, Corrective and Preventative Action; CV%, co-efficient of variation expressed as percent; ETX2514, durlobactam; QC, quality control; RE%, relative error expressed as percent

**Table 123. Summary of Bioanalytical Method Validation and Performance for Sulbactam-Durlobactam (Cont.)**

| Method Parameters | Method Details | |
|---|---|---|
| Study no. | CS2514-2017-0001 | |
| Biological matrix | Human Bronchoalveolar Lavage Fluid | |
| Extraction methods | liquid-liquid extraction | |
| Drug | Sulbactam | Durlobactam |
| Internal standard | sulbactam-d2 | ETX2514-$^{13}C_2$-$^{15}N_2$ |
| Validation range (ng/mL) | 2 to 1000 | |
| QC levels (ng/mL) | 2, 6, 250, and 750 | |
| Inter-day accuracy (RE%)[a] | -10.84 to -2.21 | -9.72 to -2.53 |
| Inter-day precision (CV%)[a] | 1.82 to 11.58 | 2.08 to 7.95 |
| Incurred sample reanalysis[b] | 100 | 100 |
| Bio-analytical laboratory | (b) (4) | |
| Bioanalytical report | 171001.00 | |
| Validation report | 170505.00 | |
| Study no. | CS2514-2017-0002 | |
| Biological matrix | Human dialysate | |
| Extraction methods | Dilution | |
| Drug | Sulbactam | Durlobactam |
| Internal standard | sulbactam-d2 | ETX2514-$^{13}C_2$-$^{15}N_2$ |
| Validation range (ng/mL) | 1 to 1000 | |
| QC levels (ng/mL) | 1, 3, 45, 400, 800 | |
| Inter-day accuracy (RE%)[a] | 1.0 to 5.1 | -2.8 to 10.0 |
| Inter-day precision (CV%)[a] | 3.3 to 12.6 | 4.8 to 11.5 |
| Incurred sample reanalysis[b] | 76.1 | 65.0[c] |
| Bio-analytical laboratory | (b) (4) | |
| Bioanalytical report | 8377369 | |
| Validation report | 8372079 | |

Source: Reviewer's analysis
[a] The inter-day accuracy and precision values from validation and performance reports are combined and presented as an overall range.
[b] At least 10% of samples reanalyzed
[c] Bioanalytical report 8377369 attributes the failure of the ISR evaluation to the small sample size analyzed. Only 21 individual dialysate samples had concentrations greater than 3x the LLOQ of the assay which were eligible for ISR analysis. This analysis had two samples with RPD values between +20 and +25%, and two samples with 2 RPD values between +25 and +30%.
Abbreviations: CV%, co-efficient of variation expressed as percent; ETX2514, durlobactam; ISR, incurred sample reanalysis; LLOQ, lower limit of quantitation; QC, quality control; RE%, relative error expressed as percent; RPD, relative percent difference

## 14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

N/A

## 14.5. Pharmacometrics Assessment

### 14.5.1. N/APopulation PK Analysis

#### 14.5.1.1. Review Summary

In general, the Applicant's population PK analysis is considered acceptable for the purpose of describing SUL and DUR exposures in plasma, ELF and hemodialysis (HD), and describing the effects of intrinsic and/or extrinsic factors on SUL and DUR exposure. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 124**.**

**Table 124. Specific Comments on Applicant's Final Population PK Model**

| Utility of the Final Model | | | Reviewer's Comments |
|---|---|---|---|
| Support Applicant's proposed labeling statements about intrinsic and extrinsic factors | Intrinsic factor | No clinically significant differences in the pharmacokinetics of SUL or DUR were observed based on age, gender, weight, and race. | The statement regarding age, gender, weight, race is acceptable.<br><br>Covariate analysis using the Applicant's final population model demonstrates that no evident difference exists based on age, gender and race.<br><br>Body weight was identified as a statistically significant covariate for the variability in CL and Vc for SUL and DUR, with lower drug exposures in subjects with high body weights. Additional %PTA analysis confirmed that the proposed dose is adequate that providing sufficient %PTA ≥90% at various body weight bands. Therefore, no dose adjustment is recommended. |
| Derive exposure metrics for exposure-response analyses | $C_{min}$, $C_{max}$, $C_{avg}$, AUC | | The Applicant's final model is acceptable for generating exposure metrics for exposure-response analysis. |
| Predict exposures at alternative dosing regimen | Patients with renal impairment<br>• To maintain systemic exposures similar to patients with normal renal function, dose adjustment is recommended for patients with renal impairment.<br>Patients with CLcr 130 mL/min or greater<br>• Increased SUL and DUR clearance have been observed in patients with CLcr of 130 mL/min or greater. A XACDURO (1.0 (b) (4) g sulbactam and 1.0 (b) -g durlobactam) dose every (b) (4) 4 hours infused over 3 hours provided SUL and DUR exposures comparable to those in patients with CLcr 90 to 129 mL/min.<br>XACDURO is indicated in adults for the treatment of HABP and VABP, caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex. | | Population PK analysis showed a statistically significant relationship between CL and renal function for both SUL and DUR. Therefore, dose adjustment is recommended for patients with renal impairment. Population PK analysis showed that the $AUC_{0-24}$ distribution was generally comparable across renal function categories at the proposed adjusted dose regimen based on renal function (Figure 15, Figure 16, Table 128). Additional %PTA analysis confirmed that the proposed renal function adjusted dose is adequate that providing sufficient %PTA ≥90% at various renal function groups.<br><br>Infection type was identified as a statistically significant covariate for the variability in CL and Vc for SUL and Vc for DUR in the population PK model. However, population PK analysis showed that drug exposures of SUL and DUR are generally similar across the evaluated infection types, and thus no dose adjustment is recommended for different infection types (Figure 17). |

Source: Reviewer's analysis
Abbreviations: AUC, area under the curve; $AUC_{0-24}$, area under the curve from 0 to 24 hours; CL, clearance; CLcr; creatinine clearance; $C_{avg}$, average plasma concentration; $C_{max}$, maximum plasma concentration; $C_{min}$, minimum plasma concentration; DUR, durlobactam; HABP, hospital-acquired bacterial pneumonia; PK, pharmacokinetic; %PTA, probability of target attainment; SUL, sulbactam; VABP, ventilator-associated bacterial pneumonia; Vc, central compartment volume; XACDURO, sulbactam and durlobactam

#### 14.5.1.2. Introduction

The primary objectives of Applicant's analysis were to:

- To evaluate the population PK of SUL and DUR in adult healthy volunteers, and in patients with complicated urinary tract infections (cUTI) and with infections caused by *Acinetobacter baumannii-calcoaceticus* complex (ABC)
- To develop ELF and HD sub population PK models to 1) estimate ELF penetration in subjects enrolled in study 2017-0001 and 2) estimate the effect of hemodialysis in subjects with renal impairment enrolled in study 2017-0002
- Describe the effects of intrinsic and/or extrinsic factors on SUL and DUR exposure
- Generate individual plasma, and ELF PK exposure estimates for patients in phase 2 and phase 3 trials

#### 14.5.1.3. Model Development

**Data**

The analyses were based on PK data from nine studies. The study design, study population, and timing of blood samples varied among the 9 clinical studies are briefly described in Table 125.

The NONMEM data file from the Applicant's proposed final model for analysis contained 8100 plasma and 60 ELF PK observations from 393 subjects. Table 127 provides summary statistics of the baseline demographic covariates in the analysis dataset.

**Table 125. Summary of Studies With PK Sampling Included in Population PK Analysis**

| Protocol Number and Study Design | Dosage Regimen and Study Description | Number of Subjects in PopPK Analysis, Subject Type and Food Status | Dose(s) [mg] |
|---|---|---|---|
| Study 2016-0001 (SAD/MAD Phase 1) | A Phase I, double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of intravenous SUL-DUR administered in healthy subjects<br><br>PK sampling:<br>Part A (Cohorts 1 to 8): predose and 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 h after the start of infusion.<br><br>Part B (Cohorts 9 to 12): predose and 1, 2, 3, 3.5, 4, 5, 6 (immediately prior to second dose), 8, and 12 immediately prior to third dose) h after the start of infusion on Days 1 and 8.<br><br>Part C (Cohort 13): predose and 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 h postdose.<br><br>Part C (Cohort 14): predose and 0.5, 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 h postdose<br><br>Part D (Cohort 15): predose and 1, 2, 3, 3.5, 4, 5, 6, 8, and 12 h after the start of infusion on Days 1 and 11. Additional samples were collected prior to the second dose administered on Days 2 and 4 and at 24, 36, and 48 h after the start of infusion on Day 11. | N=124<br>Subject: healthy subjects | Part A (Cohorts 1 to 8): single dose of 0.25g, 0.5 g, 1.0 g, 2.0 g, 4.0 g, 8.0 g IV DUR/placebo infused over 3 hours, and 1.0 g IV infusion over 2 hours<br><br>Part B (Cohorts 9 to 12): SUL-DUR/placebo dose of 0.25 g, 0.5 g, 1.0 g and 2.0 g.<br><br>Part C (Cohorts 13 - 14): DUR 1.0 administered as a single dose in combination with 1 g SUL) and/or imipenem/cilastatin (0.5 g)<br><br>Part D (Cohort 15): multiple doses of combined IV DUR/sulbactam (1.0 g)/imipenem/cilastatin (0.5g) |
| Study 2017-0001 (ELF study) | Multiple-dose, open-label Phase 1 study to determine and compare plasma, ELF, and alveolar macrophage concentrations of SUL-DUR in healthy adults.<br><br>PK sampling:<br>Prior infusion, and 1, 2, 2.5, 2.95, 3.05, 3.25, 3.5, 4, 5, and 6 h after start of the third dose. | N=30 | SUL-DUR 1 g / 1 g administered IV over 3 h q6h for three doses. |

| Protocol Number and Study Design | Dosage Regimen and Study Description | Number of Subjects in PopPK Analysis, Subject Type and Food Status | Dose(s) [mg] |
|---|---|---|---|
| Study 2017-0002 (Renal Impairment study) | Open-label, nonrandomized Phase 1 study to assess the effects of renal impairment on SUL-DUR pharmacokinetics.<br><br>PK sampling:<br>Cohort 1 and 2: predose and at 0.5, 1, 2, 3, 3.5, 4, 5, 6, 7, 8, 12, 24, 36, and 48 h.<br><br>Cohorts 3 and 4: predose and at 0.5, 1, 2, 3, 3.5, 4, 5, 6, 7, 8, 12, 24, 36, 48, and 60 h.<br><br>Cohort 5: predose and at 0.5, 1, 2, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, and 60 h. In period 2, samples were also collected from the venous and arterial lines at 4, 5, 6, and 7 hours after the start of infusion. | N=34<br>Healthy subjects and subjects with renal impairment | Cohorts 1, 2 and 3 received single dose of DUR (1 g) and SUL (1 g)<br><br>Cohort 4 received single dose of DUR (0.5 g) and SUL (0.5 g).<br><br>Cohort 5 received doses of DUR (0.5 g) and SUL (0.5 g), both post-HD (Period 1) and preHD (Period 2). |
| Study 2018-0002 (Metabolism and Excretion study) | Single dose, open-label Phase 1 study to determine the excretion and metabolism of DUR in healthy male subjects<br><br>PK sampling:<br>Predose and at 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, and 168 h after the start of the infusion. | N=8 | Dose: 1 g DUR and 1 µg of 14C-DUR administered IV over 3 h. SUL was not administered in this study. |
| Study 2018-0003 (Thorough QT study) | A randomized, three-period crossover thorough QT study in healthy volunteers.<br><br>PK sampling:<br>45, 30, and 15 min prior to the start of infusion and at 1.5, 3, 3.25, 3.5, 4, 5, 6, 7, 8, 12, and 24 h after the start of the infusion. | N=32 | Dose:<br>Treatment A: A single 3-h IV infusion of 4 g DUR (supratherapeutic dose).<br><br>Treatment B: A single 3-h IV infusion of placebo for DUR.<br><br>Treatment C: A single 3-h IV infusion of placebo for DUR and a single oral dose of 400 mg open-label moxifloxacin given at the end of the infusion |

| Protocol Number and Study Design | Dosage Regimen and Study Description | Number of Subjects in PopPK Analysis, Subject Type and Food Status | Dose(s) [mg] |
|---|---|---|---|
| ZL-2402-001<br>(Chinese Phase 1 study) | Open-label Phase 1 study to assess the safety, tolerability, and PK of SUL-DUR in healthy Chinese subjects<br><br>PK sampling:<br>Prior to the start of infusion and<br>at 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 h after the start of the infusion | N=12<br>Healthy subjects | Dose: SUL-DUR 1 g / 1 g |
| 2017-0003<br>(Phase 2 study) | A Phase 2, double-blind, randomized study conducted to evaluate the safety and efficacy of SUL-DUR versus placebo in patients with cUTI including AP.<br><br>PK sampling:<br>Predose on Day 1 and the following time points postdose on either Days 3, 4, or 5: end of infusion, and 0.5, 2, and 3 hours after the end of infusion. | N=80 | Dose: SUL-DUR 1 g / 1 g. all patients were administered background therapy with 500 mg – 500 mg of imipenem-cilastatin IV q6h infused over 30 minutes. Treatment duration was a minimum of seven and a maximum of 14 days. |

| Protocol Number and Study Design | Dosage Regimen and Study Description | Number of Subjects in PopPK Analysis, Subject Type and Food Status | Dose(s) [mg] |
|---|---|---|---|
| 2017-0004<br>(Phase 3 study) | A randomized, active-controlled, Phase 3 study designed to evaluate the efficacy and safety of intravenous SUL-DUR in the treatment of patients with infections caused by ABC.<br><br>PK sampling:<br>Intense PK sampling was performed on the first approximately 30 patients in Part A.<br><br>Day 1: End of infusion, 1.5 h after the end of infusion and immediately prior to the start of the next infusion.<br><br>Day 4: End of infusion, and immediately prior to the start of the next infusion.<br><br>All other patients enrolled in the study (Parts A and B) had spare PK samples collected on:<br>On Day 1, prior the next infusion and<br>On Day 4, immediately prior the start of the next infusion. | N=152 | **Table 126. SUL-DUR 1 g / 1 g. and Dose Adjustment Based on Renal Functions**<br>**Estimated CLcr (ml/min)** / **SUL-DUR**<br>130 – 200 / 1.5 g/ 1.5 g q6h<br>90 – 129 / 1.0 g/ 1.0 g q6h<br>60 – 89 / 1.0 g/ 1.0 g q6h<br>(b) (4)<br>15 - 29 / 1.0 g/ 1.0 g q8h<br>0 - 14 / 1.0 g/1.0 g q 12h<br>Abbreviations: CLcr, creatinine clearance; DUR, durlobactam; SUL, sulbactam |

Source: Applicant's Clinical Study reports
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; AP, acute pyelonephritis; cUTI, complicated urinary tract infection; DUR, durlobactam; ELF, epithelium lining fluid; h, hour; HD, hemodialysis; IV, intravenous; MAD, multiple-ascending dose; N, number of subjects; PK, pharmacokinetic; PopPK, population pharmacokinetic; QT, time between the start of the QRS complex and the end of the T wave; q6h, every 6 hours; SAD, single ascending dose; SUL, su bactam

**Table 127. Summary of Baseline Demographic Covariates for Analysis**

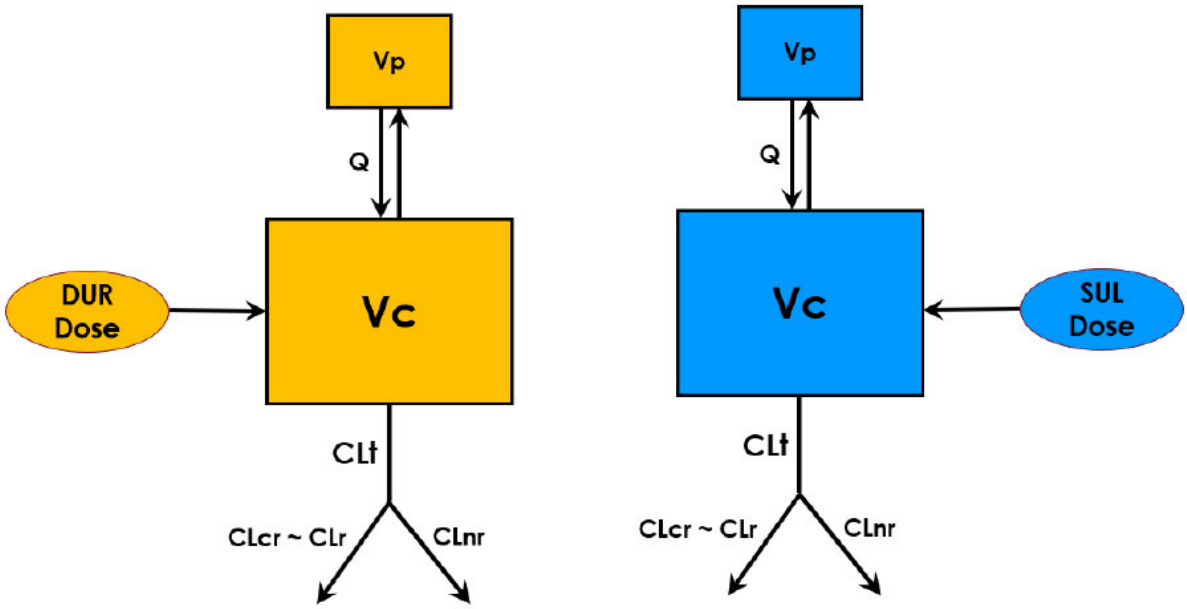
| Covariate | Statistic | Total (N=377) |
|---|---|---|
| Weight (kg) | Mean (CV%) | 76.4 (22.3%) |
| | Median (min, max) | 75 (35.8-150) |
| Age (yr) | Mean (CV%) | 46.5 (41.2%) |
| | Median (min, max) | 46 (18-91) |
| CLcr (mL/min/1.73 $m^2$) | Mean (CV%) | 91.4 (46.9%) |
| | Median (min, max) | 91.4 (5.61-364) |
| Sex | | |
| Male | N (%) | 236 (62.6) |
| Female | N (%) | 141 (37.4) |
| Race | | |
| White | N (%) | 245 (65) |
| Black | N (%) | 49 (13) |
| Asian | N (%) | 63 (16.7) |
| American Indian/ Alaska Native | N (%) | 7 (1.86) |
| Other | N (%) | 13 (3.45) |
| Country of origin | | |
| China | N (%) | 35 (9.28) |
| Other | N (%) | 342 (90.7) |
| Region | | |
| East Asia | N (%) | 45 (11.9) |
| Other | N (%) | 332 (88.1) |

Source: Applicant's Population PK Report 2022-0007 Table 5 (Page 53 - 54).
Abbreviations: CLcr; creatinine clearance; CV, coefficient of variation; max, maximum; min, minimum; N, number of subjects

## Applicant's Base Model

The base model for both SUL and DUR proposed by the Applicant was a four-compartment (two compartments per drug) model with linear kinetics. Total clearance was estimated as the sum of renal and nonrenal clearance, and individual renal clearances are scaled to baseline creatinine clearance (CLcr). For DUR, a significant correlation was found between CL and Vc and therefore an off-diagonal omega relationship was added to the base model. Residual variability was well characterized by a combined additive and proportional error model. The structural base model for SUL-DUR is presented in Figure 10**.**

**Figure 10. Scheme of Applicant's Base PopPK Model Structure**




Source: Applicant's Population PK report 2022-0007, Figure 7.
Abbreviations: CLcr; creatinine clearance; CLnr, non-renal clearance; CLr, renal clearance; CLt, total clearance; DUR, durlobactam; PopPK, population pharmacokinetics; Q, distributional clearance; SUL, su bactam; Vc, central compartment volume; Vp, ventilator pneumonia

## Covariate Analysis

The following covariates were formally evaluated in NONMEM: age, weight, height, BSA, BMI, CLcr, sex, race, country of origin, region, and indication. The Fe (fraction of renal elimination) for final population PK model using the values of 0.660 for DUR and 0.648 for SUL, derived from the subjects with normal renal function enrolled in study 2017-0002. Covariate model development identified several subject characteristics that are associated with the variability in SUL-DUR PK as following:

SUL

- Weight, infection type, and CLcr were significantly related to the interindividual variability (IIV) in SUL CL;
- Weight and infection type were significantly related to the IIV in SUL Vc.

DUR

- Weight, East Asian region, and CLcr were significantly related to the IIV in DUR CL;
- Weight, infection type, and east Asian region were significantly related to the IIV in DUR Vc.

Age, country of origin (China Mainland versus other), race, and sex were not identified as statistically significant covariates in the SUL-DUR population PK model.

### 14.5.1.4. Applicant's Final Model

The parameter estimates for the final covariate model are listed in Table 128. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 11. The Visual Predictive Check plot for the final covariate model with all data is shown in Figure 12.

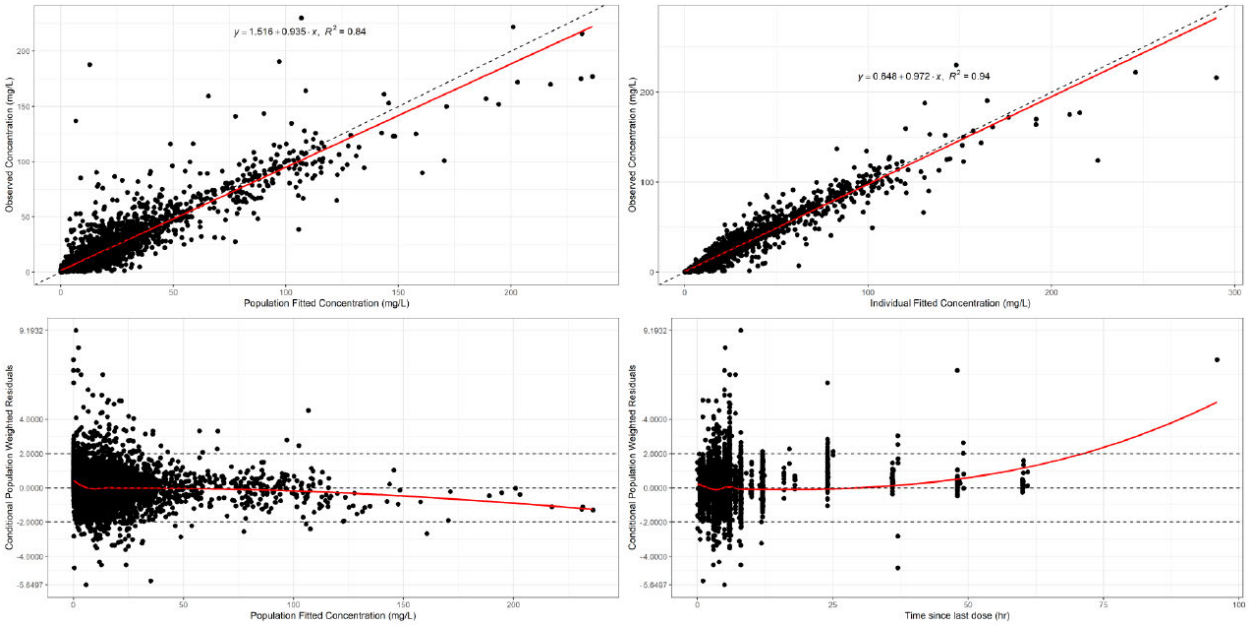
**Table 128. Parameter Estimates (RSE) and Median (95% CI) for the Applicant's Final Model**

| Parameter | Final Model | | |
|---|---|---|---|
| | Estimate | %SEM | Shrink. |
| **Durlobactam** | | | |
| CL (L/h) | 9.36 | 3.06 | |
| $CL_{R, CLcr\ power}$ | 0.694 | 10.8 | |
| Vc (L) | 12.5 | 2.97 | |
| Q (L/h) | 4.42 | 3.76 | |
| $V_P$ (L) | 5.83 | 3.45 | |
| FE (%) | 0.660 | | |
| CLEASIAFL1 | -0.191 | 33.5 | |
| CLWTKG1 | 0.664 | 17.9 | |
| V1INFTYPN1&2 (HABP and VABP) | 1.52 | 25.7 | |
| V1INFTYPN3 (cUTI) | 0.312 | 68 | |
| V1INFTYPN4 (Bacteremia) | 3.42 | 52.4 | |
| V1WTKG1 | 0.518 | 27.1 | |
| V1EASIAFL1 | -0.261 | 49.5 | |
| BCLCRNLT30 | -0.508 | 11.2 | |
| $\omega^2_{CL}$ | 0.0726 (26.9 %CV) | 9.16 | 9.64 |
| $\omega^2_{Vc}$ | 0.0760 (27.6 %CV) | 13.5 | 25.7 |
| $\omega^2_{Vp}$ | 0.0773 (27.8 %CV) | 9.78 | 37.6 |
| Covariance ($\omega^2_{CL}$, $\omega^2_{Vc}$) | 0.0482 ($r^2$ = 0.421) | 17.4 | |
| $\sigma^2_{plasma,\ Proportional\ Phase\ 1}$ | 0.019 (13.8 %CV) | 1.91 | 8.67 |
| $\sigma^2_{plasma,\ Additive\ Phase\ 1}$ | 0.00136 (0.0369 mg/L) | 3.69 | 8.67 |
| $\sigma^2_{plasma,\ Proportional\ Phase\ 2}$ | 0.0794 (28.2 %CV) | 13.3 | 12.0 |
| $\sigma^2_{plasma,\ Proportional\ Phase\ 3}$ | 0.206 (45.4 %CV) | 9.85 | 8.30 |
| **Sulbactam** | | | |
| CL (L/h) | 13.6 | 13.2 | |
| $CL_{R, CLcr\ power}$ | 0.932 | 18.3 | |
| Vc (L) | 12.1 | 8.70 | |
| Q (L/h) | 7.82 | 18.9 | |
| $V_P$ (L) | 6.98 | 9.21 | |
| FE (%) | 0.648 | | |
| CLINFTYPN1 (HABP) | -0.423 | 18.7 | |
| CLINFTYPN2 (VABP) | -0.294 | 35.6 | |
| CLINFTYPN3 (cUTI) | -0.147 | 103 | |
| CLINFTYPN4 (Bacteremia) | -0.445 | 20 | |
| CLINFTYPN5 (AP) | -0.385 | 27.8 | |
| CLWTKG1 | 1.03 | 25.5 | |
| V3INFTYPN1 (HABP) | 0.818 | 24.8 | |
| V3INFTYPN2 (VABP) | 1.38 | 19.5 | |
| V3INFTYPN3 (cUTI) | 0.167 | 88.8 | |
| V3INFTYPN4 (Bacteremia) | 1.84 | 44.6 | |

| Parameter | Final Model | | |
|---|---|---|---|
| | Estimate | %SEM | Shrink. |
| V3INFTYPN5 (AP) | -0.707 | 12.9 | |
| V3WTKG1 | 0.828 | 26.5 | |
| BCLCRNLT30 | -0.56 | 15.2 | |
| $\omega^2_{CL}$ | 0.212 (46.0 %CV) | 10.3 | 19.2 |
| $\omega^2_{Vc}$ | 0.0926 (30.4 %CV) | 25.3 | 44.2 |
| $\omega^2_{Vp}$ | 0.197 (44.4 %CV) | 25.8 | 49.9 |
| Covariance ($\omega^2_{CL}$, $\omega^2_{Vc}$) | 0.0747 ($r^2$ = 0.284) | 32.6 | |
| $\sigma^2_{plasma, Proportional}$ | 0.0435 (20.9 %CV) | 2.51 | 12.1 |
| $\sigma^2_{plasma, Additive}$ | 0.00539 (0.0734 mg/L) | 6.37 | 12.1 |

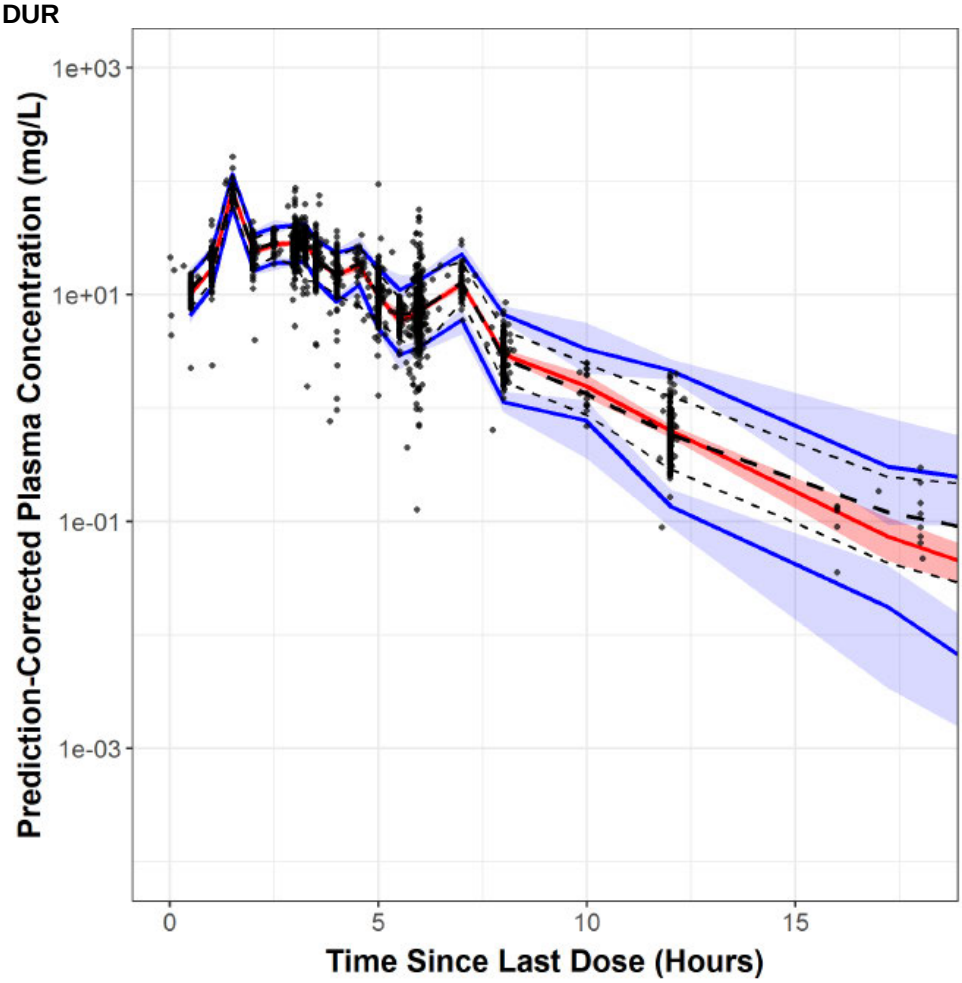
Source: Applicant's population PK report 2022-0007, Table 12.
Abbreviations: AP, acute pyelonephritis; cUTI, complicated urinary tract infections; CI, confidence interval; CL, clearance; CLcr; creatinine; CLr, renal clearance; %CV, percentage coefficient of variation; FE, fraction excreted renally; HABP, hospital-acquired bacterial pneumonia; INFTYPN, Infection type flag; IIV, interindividual variability; IV, intravenous; Q, distributional clearance; %RSE, percentage relative standard error; SEM, standard error of the mean; VABP, ventilator-associated bacterial pneumonia; Vc, central compartment volume; Vp, ventilator pneumonia; WT, body weight

**Figure 11. Standard Goodness-of-Fit Plots for the Applicant's Final Covariate Model**



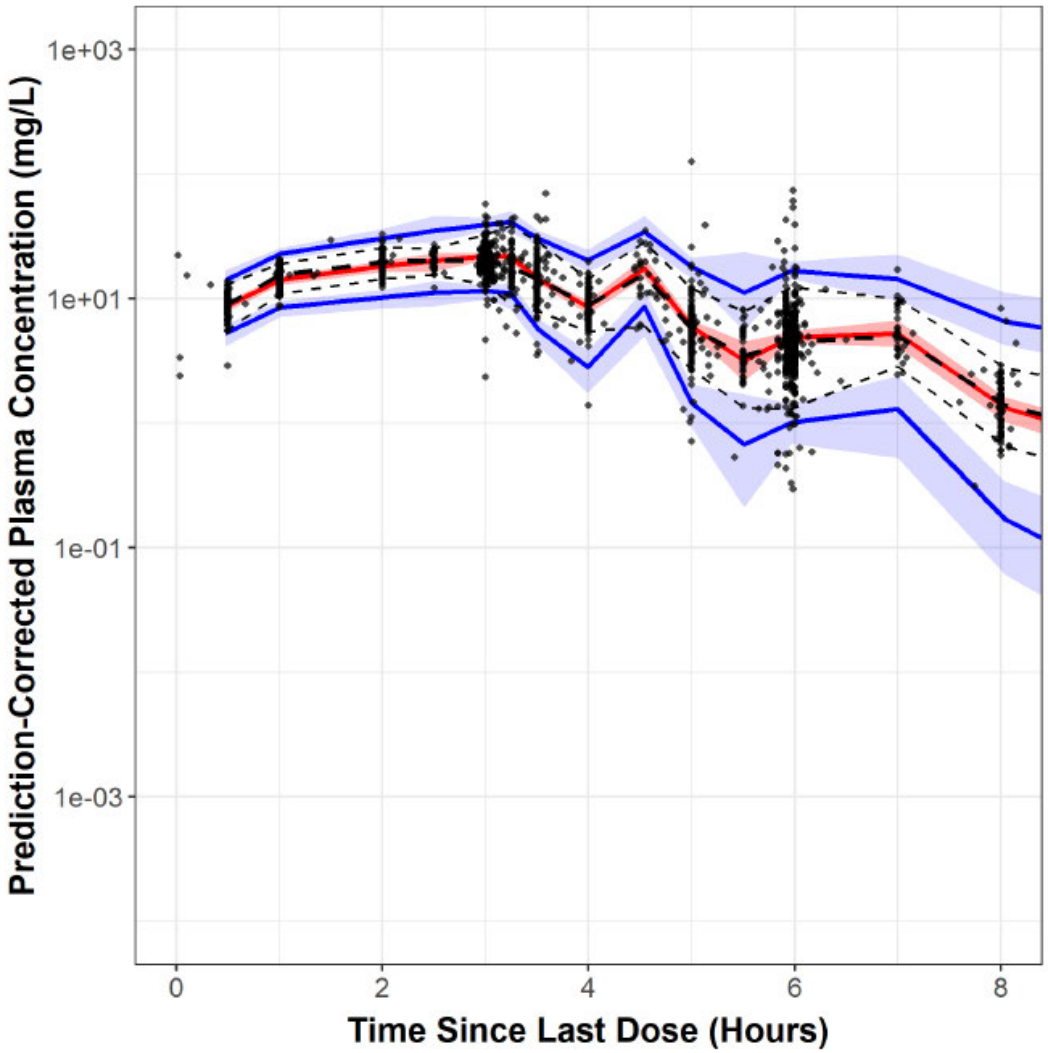

Source: Applicant's population PK report, Figure A8.1 (Appendix 8).
Note: The circles represent individual data points; the red lines represent loess smooth curves; and the dashed lines represent either the line of unity (y = x), or the unity line at 0 (y =0).
Abbreviations: PK, pharmacokinetic

**Figure 12. Prediction-Corrected Visual Predictive Check Plot for the Final Population PK Model for DUR**




Source: Applicant's population PK report 2002-0007, Figure A8.3, Page 299.
Note: Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations.
Abbreviations: DUR, durlobactam; PK, pharmacokinetic

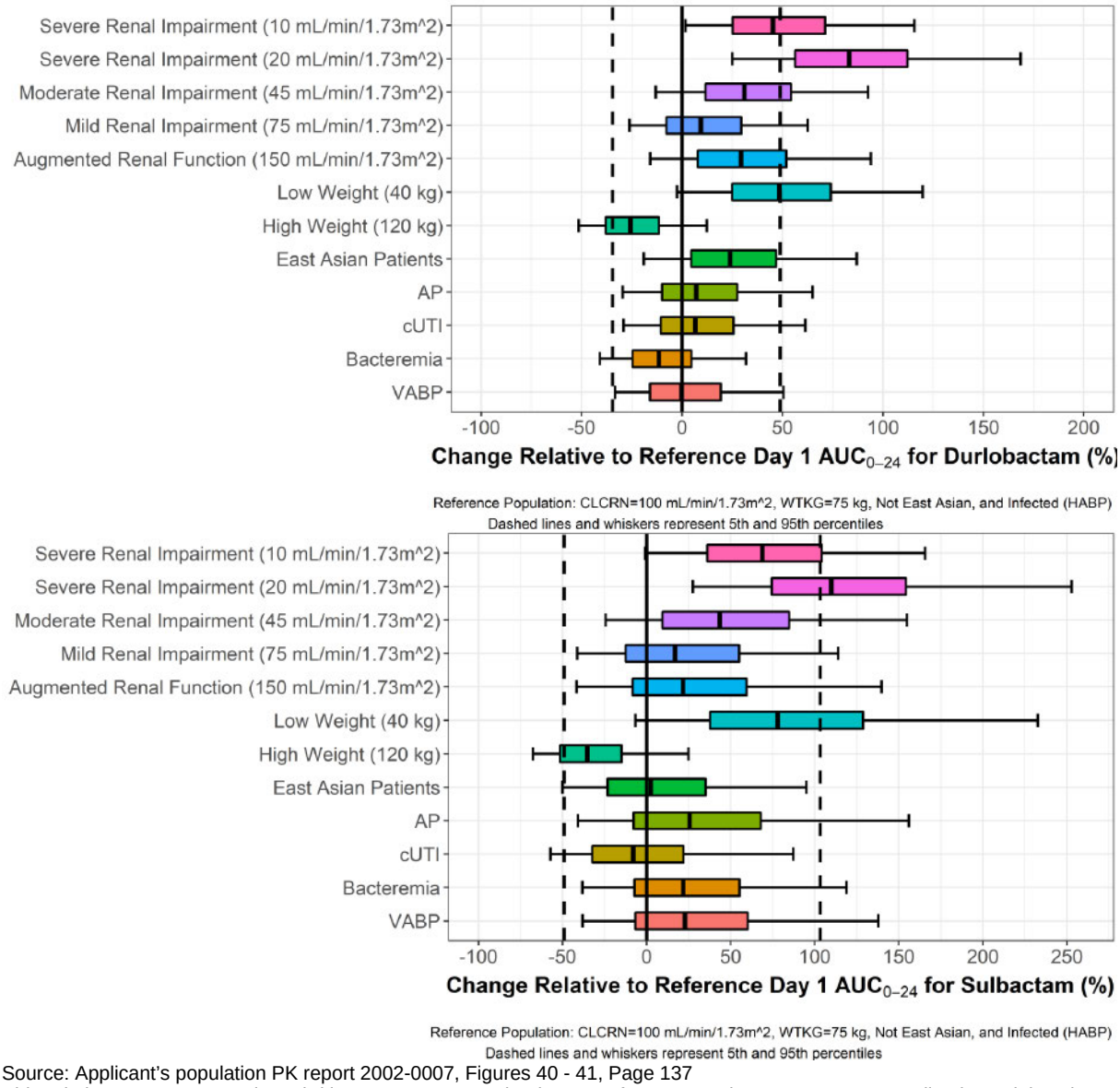
**Figure 13. Prediction-Corrected Visual Predictive Check Plot for the Final Population PK Model for SUL**




Source: Applicant's population PK report 2002-0007, Figure A8.4, Page 300
Note: Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations.
Abbreviations: PK, pharmacokinetic; SUL, sulbactam

The effects of renal function, body weight, region of patients, infection types on the exposure of SUL and DUR are shown on Figure 14.

**Figure 14. Applicant's Forest Plots Showing Impact of Statistically Significant Covariate-Parameter Relationships on SUL and DUR $AUC_{0-24}$ on Day 1**




Source: Applicant's population PK report 2002-0007, Figures 40 - 41, Page 137
Abbreviations: AP, acute pyelonephritis; $AUC_{0-24}$, area under the curve from 0 to 24 hours; CLCRN, normalized creatinine clearance; cUTI, complicated urinary tract infections; DUR, durlobactam; HABP, hospital-acquired bacterial pneumonia; PK, pharmacokinetic; SUL, sulbactam; VABP, ventilator-associated bacterial pneumonia; WT, weight

## Effect of the Renal Function on the PK of SUL and DUR

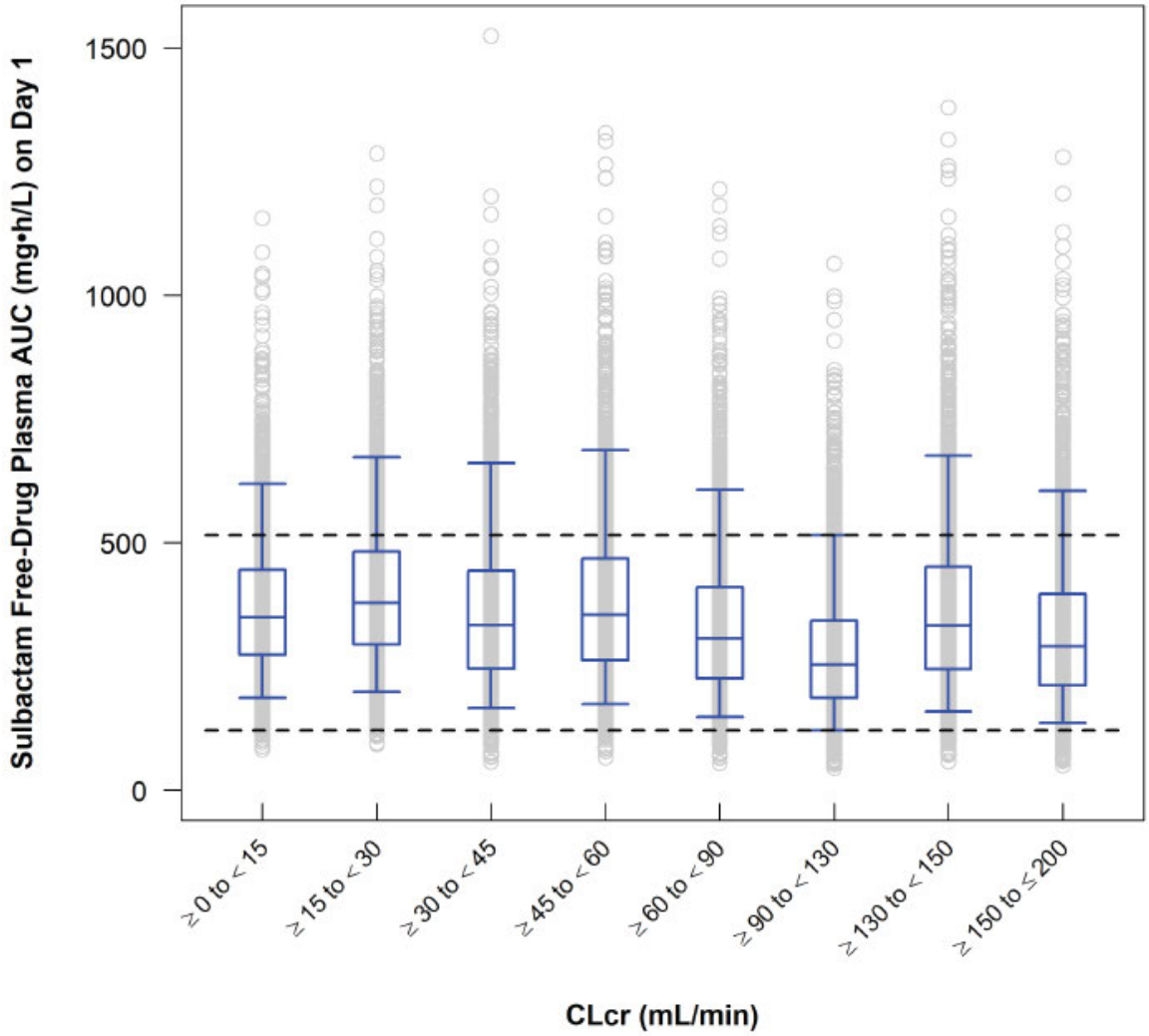
SUL and DUR free-drug plasma AUCs at steady state (Day 3) among simulated patients across renal function categories after administration of the adjusted doses listed in Table 129 were estimated and are presented in Figure 15 and Figure 16. The results show that the AUC distribution among simulated patients was generally comparable across renal function categories at the initially proposed dose regimen.

**Table 129. Initially Proposed Dosage of XACDURO in Adults**

| Estimated CLcr (mL/Min) | Proposed Dosage of Sulbactam-Durlobactam | Frequency | Infusion Time |
|---|---|---|---|
| ≥130 | 1.5 g/1.5 g | Every 6 hours | 3 hours |
| 45-129 | 1 g/1 g | Every 6 hours | 3 hours |
| 30-44 | 1 g/1 g | Every 8 hours | 3 hours |
| 15-29 | Loading dose of 1 g/1 g followed by 0.5 g/0.5 g | Every 8 hours | 3 hours |
| <15† | Loading dose of 1 g/1 g followed by 0.5 g/0.5 g | Every 12 hours | 3 hours |

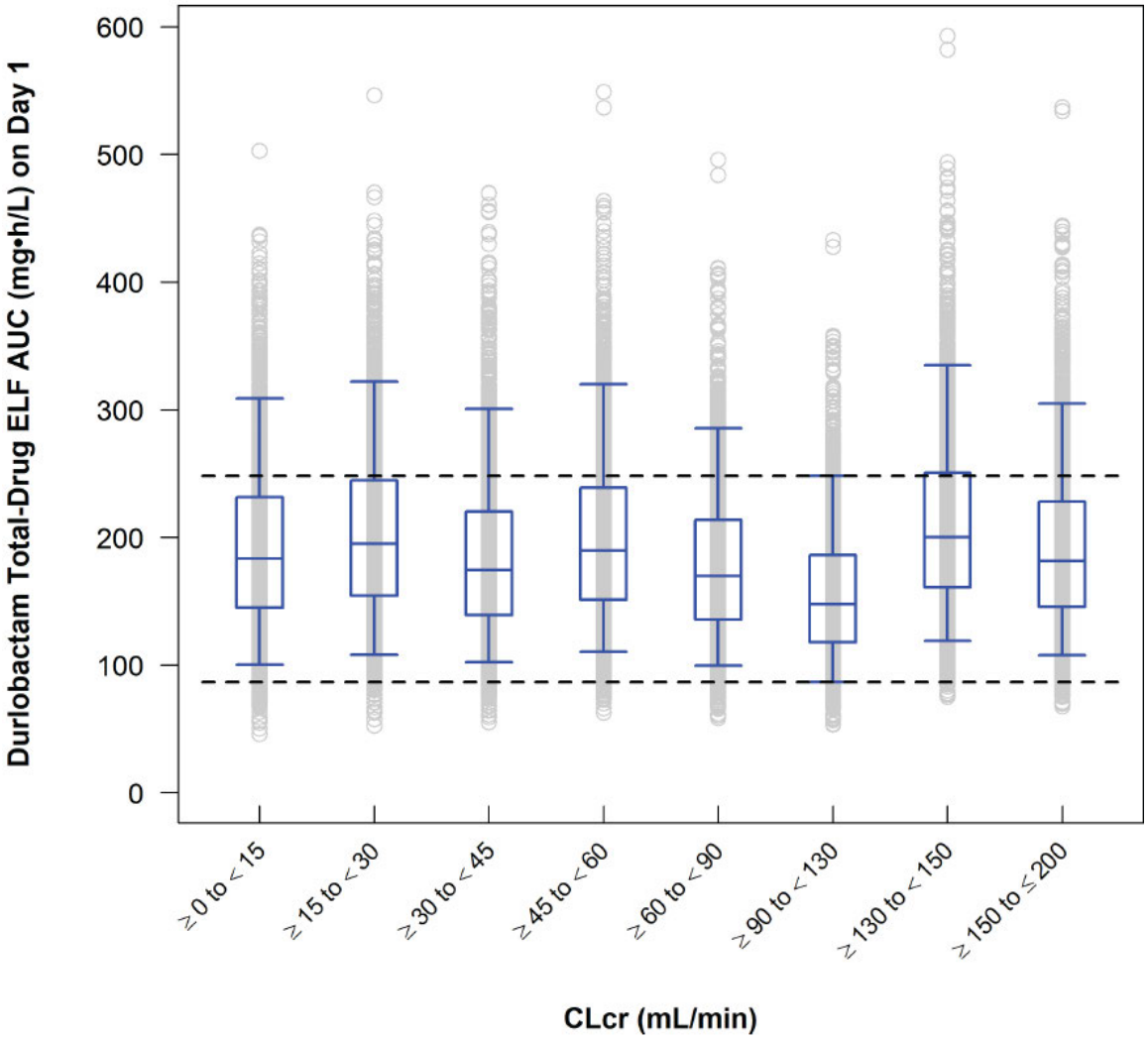
Source: Table 39 of Applicant's module 2.7.2 Summary of Clinical Pharmacology
Abbreviations: CLcr; creatinine clearance

**Figure 15. Box-and-Whisker Plots of DUR Free-Drug Plasma AUC on Day 1 Among Simulated Patients by CLcr Group After Administration of SUL 1 g/ DUR 1 g IV q6h and Dosing Regimens Adjusted for Renal Impairment and Augmented Renal Function**




Source: PK/PD study report 2022-0008. Figure 13. Page 112
Note: Simulated patients were administered the SUL-DUR dosing regimens adjusted by renal function (Table 129). The horizontal dashed lines represent the 90% prediction interval of the ≥90 to <130 mL/min group, which is defined as the 5th and 95th percentiles for sulbactam free-drug plasma AUC on Day 1.
Abbreviations: AUC, area under the curve; CLcr; creatinine clearance; DUR, durlobactam; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; SUL, sulbactam; q6h, every 6 hours

**Figure 16. Box-and-Whisker Plots by CLcr Group of DUR Total-Drug ELF AUC on Day 1 Among Simulated Patients After Administration of SUL 1 g/ DUR 1 g IV q6h and Dosing Regimens Adjusted for Renal Impairment and Augmented Renal Function**



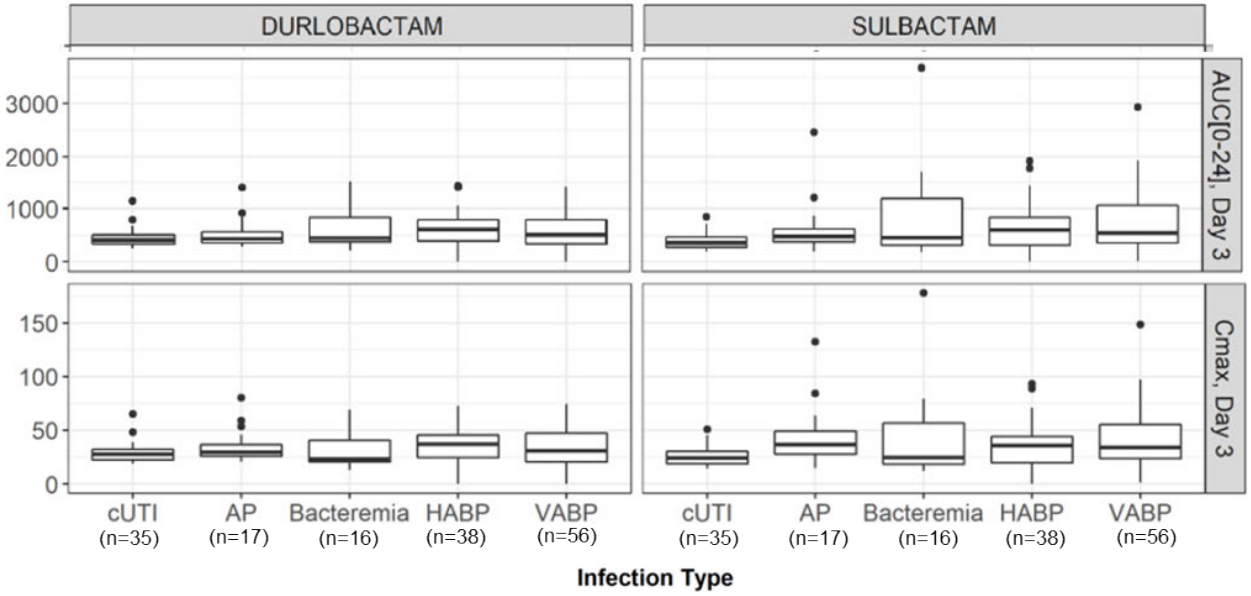

Source: PK/PD study report 2022-0008. Figure 14. Page 114.
Note: Simulated patients were administered the SUL-DUR dosing regimens adjusted by renal function (Table 129). The horizontal dashed lines represent the 90% prediction interval of the ≥90 to <130 mL/min group, which is defined as the 5th and 95th percentiles for sulbactam free-drug plasma AUC on Day 1.
Abbreviations: AUC, area under the curve; CLcr; creatinine clearance; DUR, durlobactam; ELF, epithelium lining fluid; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; SUL, sulbactam; q6h, every 6 hours

## Effect of the Evaluated Infection Type on the PK of SUL and DUR

In the population PK covariate analysis conducted by the Applicant, by pooling the plasma PK data from Phase 1, 2, and 3 studies, infected patients were evaluated as a pooled group (i.e., yes/no infected) and as distinct infection categories (e.g., cUTI, acute pyelonephritis, bacteremia, HABP, VABP) to understand the impact of disease on the PK of SUL-DUR. Infection type was identified as a statistically significant predictor of the variability in CL and Vc for SUL and Vc for DUR. However, analyses of the distributions of $AUC_{0-24}$ and $C_{max}$ on Days 1 through 3 revealed considerable overlap across infection type for subjects enrolled in the Phase 2 and 3

studies (Figure 17 shows data from Day 3). Therefore, drug exposures of SUL-DUR are generally similar across the evaluated infection types.

**Figure 17. Durlobactam and Sulbactam Plasma AUC0-24 and Cmax at Steady State (on Day 3) Across Infection Type**




Source: Adapted from Figure 13 of Applicant's module 2.7.2 Summary of Clinical Pharmacology for NDA216974
Abbreviations: AP, aspiration pneumonia; $AUC_{0-24}$, area under the concentration-time curve from time 0 to 24 hours; $C_{max}$, maximum concentration, cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; n, number of subjects in category; VABP, ventilator-associated bacterial pneumonia

Applicant's HD Sub-Model

HD sub-models were to be developed for SUL and DUR, separately. The final HD sub-models are nearly exactly the same as the final plasma population PK model. The plasma terms are all fixed the population mean parameter values with IIV applied for each subject and an HDEFFECT term with IIV was applied to CL for each of the two analyte sub-models.

The PK parameter estimates and associated standard errors for the HD sub-models for both SUL and DUR are provided in Table 130. The CL-HDEFFECT parameters are simply multiplicative terms with IIV applied to them so they vary by subject. This means that the effects of HD for DUR and SUL are an increase CL by 6.24-fold and 8.19-fold respectively.

**Table 130. Parameter Estimates and Their Associated Precision (%SEM) for the HD Sub-Models Fit to Study CS2514-2017-0002 Data**

| Parameter | Final estimate | %SEM | Shrinkage |
|---|---|---|---|
| CL-HDEFFECT (DUR) | 6.24 | 14.5 | N/A |
| CL-HDEFFECT (SUL) | 8.19 | 23.2 | |
| $\omega^2_{CL\text{-}HDEFFECT}$ (DUR) | 0.124 (35.2 %CV) | 40.9 | 57.8 |
| $\omega^2_{CL\text{-}HDEFFECT}$ (SUL) | 0.316 (56.2 %CV) | 52.3 | 58.1 |

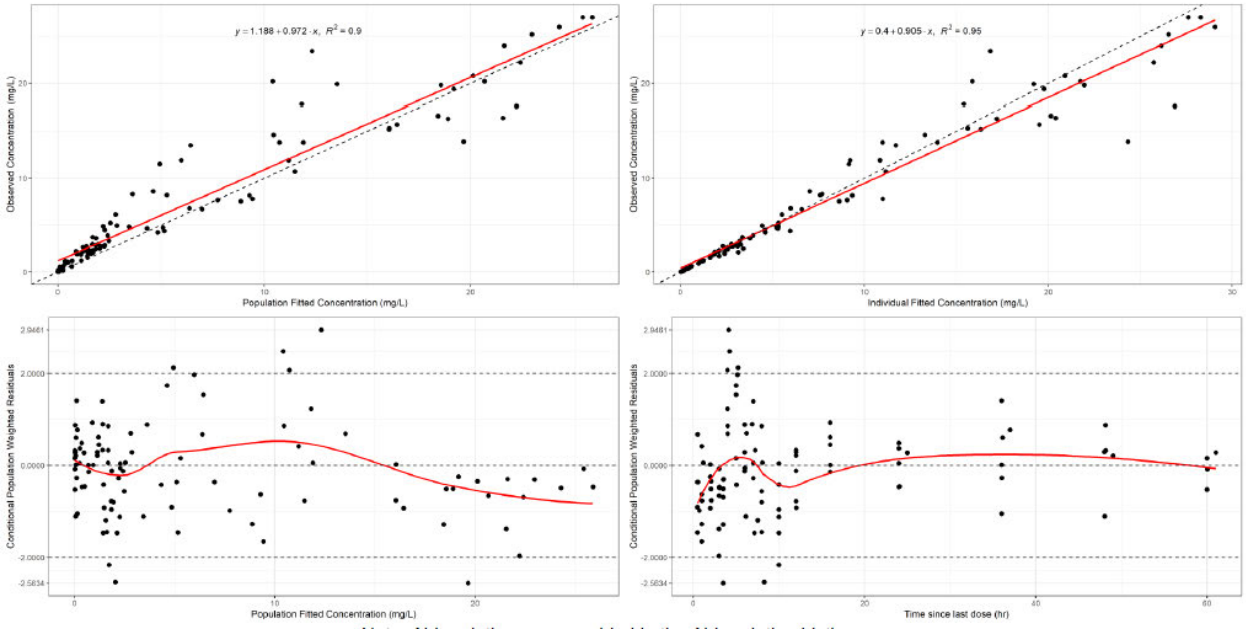
Source: Adapted from Table 14 of Applicant's population PK report pc2514-2022-0007 for NDA216974
Abbreviations: CL-HDEFFECT, hemodialysis effect clearance; CV, coefficient of variation; DUR, durlobactam; HD, hemodialysis; N/A, not applicable; SEM, standard error of the mean; SUL, sulbactam

**Table 131. Summary Statistics [Geometric Mean (CV%)] for Key SUL-DUR Exposures for Subjects With Severe Renal Impairment Receiving HD**

| | Durlobactam (n = 6) | | Sulbactam (n = 6) | |
|---|---|---|---|---|
| **Parameter** | **Period 1 (after HD)** | **Period 2 (with HD)** | **Period 1 (after HD)** | **Period 2 (with HD)** |
| $AUC_{0-8}$ (mg*h/L) | 135 (20.8%) | 93.3 (20.5%) | 117 (29.4%) | 93.0 (33.9%) |
| $AUC_{0-12}$ (mg*h/L) | 181 (25.8%) | 104 (21.5%) | 163 (36.8%) | 104 (33.9%) |
| $AUC_{0-24}$ (mg*h/L) with HD[a] | 299 (24.5%) | | 271 (34.2%) | |
| $AUC_{0-24}$ (mg*h/L) without HD[b] | 435 (30.9%) | | 410 (44.9%) | |
| $C_{max}$ (mg/L) | 25.4 (15.6%) | 25.4 (15.0%) | 21.5 (20.1%) | 21.5 (20.1%) |

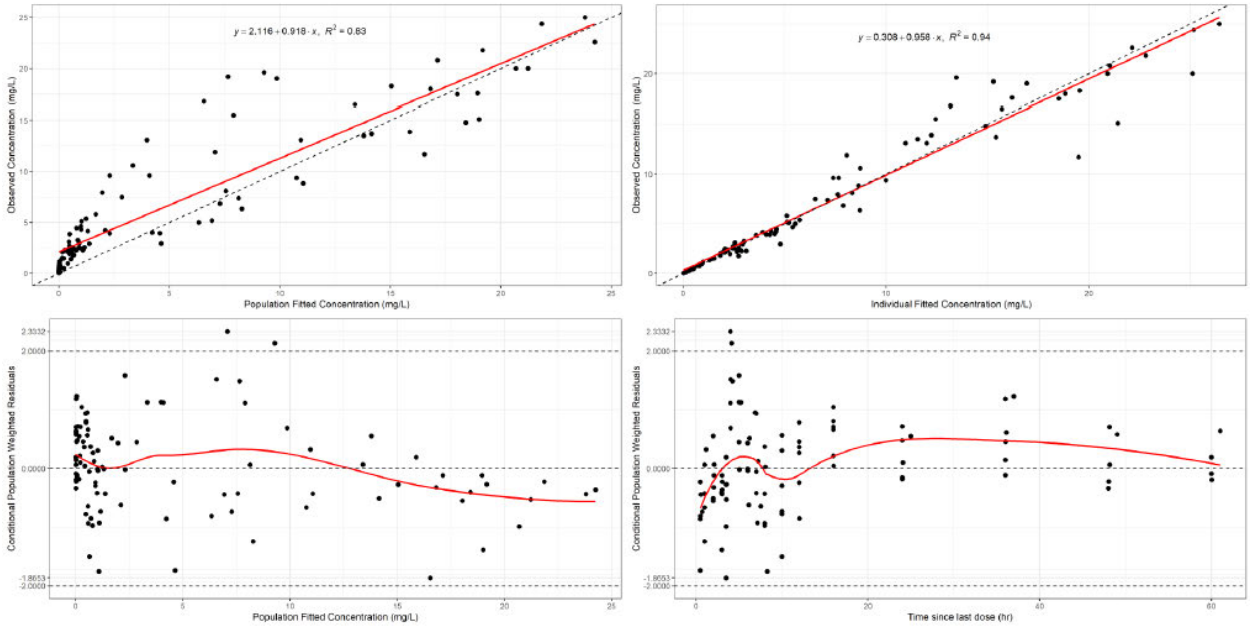
Source: Adapted from Table 15 of Applicant's population PK report pc2514-2022-0007 for NDA216974
[a] Calculated by simulating the concentration profile for 24 hours with two 500 mg/500 mg SUL-DUR doses given 12 hours apart with intermittent HD started one hour after the end of the morning infusion
[b] Calculated by simulating the concentration profile for 24 hours with two 500 mg/500 mg SUL-DUR doses given 12 hours apart and no HD
Abbreviations: $AUC_{0-8}$, area under the curve from 0 to 8 hours; $AUC_{0-12}$, area under the curve from 0 to 12 hours; $AUC_{0-24}$, area under the curve from 0 to 24 hours; $C_{max}$, maximum plasma concentration; CV, coefficient of variation; DUR, durlobactam; HD, hemodialysis; n, number of subjects in category; SUL, sulbactam

**Figure 18. Standard Goodness-of-Fit Plots for the DUR Hemodialysis Sub-Model**




Source: Adapted from Figure 20 of Applicant's population PK report pc2514-2022-0007 for NDA216974
Abbreviations: DUR, durlobactam

**Figure 19. Standard Goodness-of-Fit Plots for the SUL Hemodialysis Sub-Model**




Source: Adapted from Figure 21 of Applicant's population PK report pc2514-2022-0007 for NDA216974
Abbreviations: SUL, sulbactam

## Applicant's ELF Penetration Sub-Model

ELF penetration sub-models were to be developed for SUL-DUR separately. The final ELF penetration sub-models are nearly exactly the same as the final plasma population PK model. The plasma terms are all fixed to the population mean parameter values with IIV applied for each subject and a plasma to ELF ratio term was estimated for each of the two analyte sub-models.

The PK parameter estimates and associated standard errors for the ELF sub-models for both DUR and SUL are provided in Table 132.

**Table 132. Parameter Estimates and Their Associated Precision (%SEM) for the ELF Sub-Models Fit to Study CS2514-2017-0001 Data**

| Parameter | Final estimate | %SEM | Shrinkage |
|---|---|---|---|
| PLASMA-ELF ratio (DUR) | 0.372 | 3.6 | N/A |
| PLASMA-ELF ratio (SUL) | 0.533 | 5.41 | |
| $\sigma^2_{ELF,\ Proportional}$ (DUR) | 0.0322 (17.9 %CV) | 31.8 | 3.91 |
| $\sigma^2_{ELF,\ Proportional}$ (SUL) | 0.0628 (25.1 %CV) | 32.6 | 2.56 |

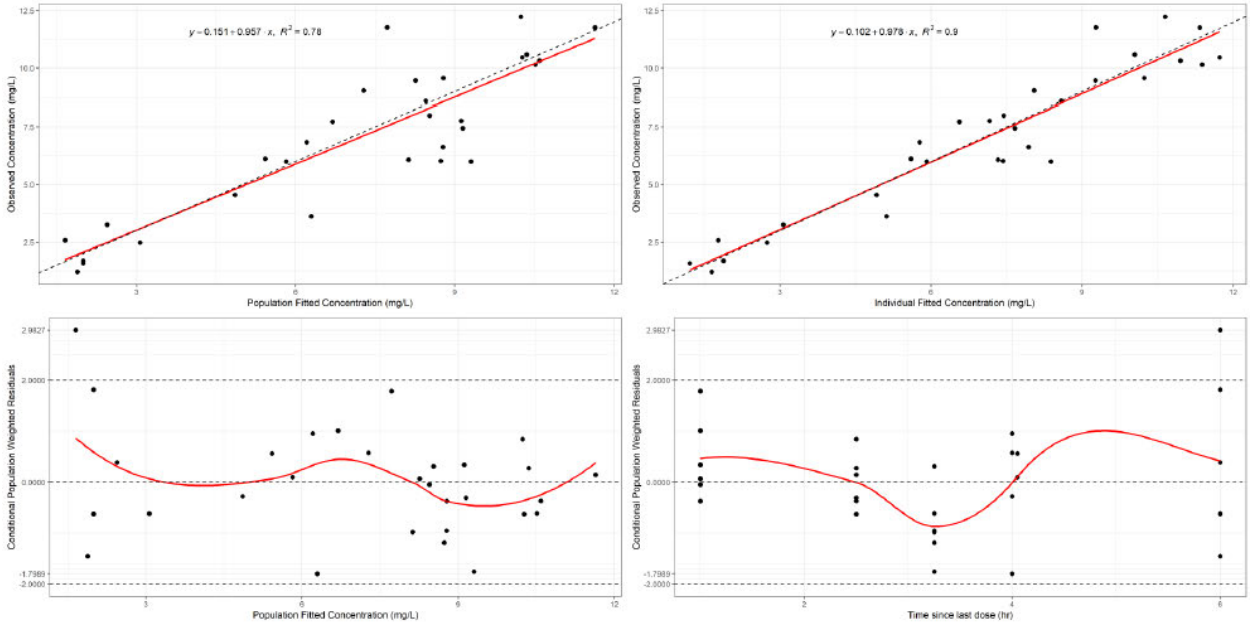
Source: Adapted from Table 16 of Applicant's population PK report pc2514-2022-0007 for NDA216974
Abbreviations: CV, coefficient of variation; DUR, durlobactam; ELF, epithelium lining fluid; SEM, standard error of the mean; SUL, sulbactam

**Table 133. Summary Statistics [Geometric Mean (CV%)] for Key SUL-DUR Exposures in ELF and Plasma for Subjects Enrolled in the ELF Penetration Study 2017-0001**

| | Durlobactam (n = 30) | | Sulbactam (n = 30) | |
|---|---|---|---|---|
| **Parameter** | **ELF** | **Plasma** | **ELF** | **Plasma** |
| $AUC_{0-24}$ (mg*h/L) | 118 (19.2%) | 316 (19.2%) | 103 (21.7%) | 193 (21.7%) |
| $C_{max}$ (mg/L) | 11.0 (17.6%) | 29.5 (17.6%) | 10.2 (19.9%) | 19.1 (19.9%) |

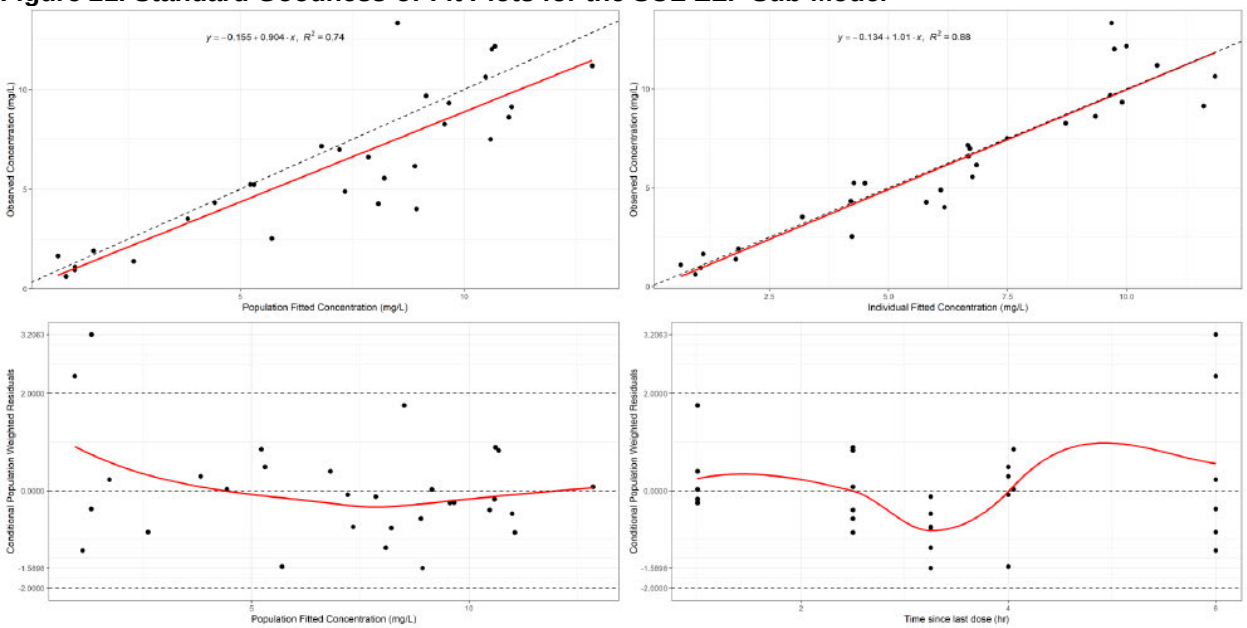
Source: Adapted from Table 17 of Applicant's population PK report pc2514-2022-0007 for NDA216974
Abbreviations: $AUC_{0-24}$, area under the curve from 0 to 24 hours; $C_{max}$, maximum plasma concentration; CV, coefficient of variation; DUR, durlobactam; ELF, epithelium lining fluid; n, number of subjects in category; SUL, sulbactam

**Figure 20. Standard Goodness-of-Fit Plots for the DUR ELF Sub-Model**




Source: Adapted from Figure 24 of Applicant's population PK report pc2514-2022-0007 for NDA216974
Abbreviations: DUR, durlobactam; ELF, epithelium lining fluid

**Figure 21. Standard Goodness-of-Fit Plots for the SUL ELF Sub-Model**




Source: Adapted from Figure 25 of Applicant's population PK report pc2514-2022-0007 for NDA216974
Abbreviations: ELF, epithelium lining fluid; SUL, sulbactam

*Reviewer's Comments: In the final PopPK model, 2481 below the lower limit of quantitation (BLQ) samples and 8 predose samples out of a total 8160 evaluable plasma samples were ignored during the PopPK analysis. This comprises approximately 30% of the evaluable PK samples in the final PopPK dataset. Therefore, an IR was sent to Applicant on 01/27/2023. We requested the Applicant to conduct sensitivity analysis using M3 approach to handle the BLQ and predose data from the SUL-DUR arm in the PopPK analysis for the final model, HD sub-models and ELF sub-models.*

**Table 134. Description of Data Excluded From Population PK Analysis**

| Study | Matrix | Subjects[a]/ records at start | LLOQ samples excluded[b] | Missing samples excluded | Samples without time excluded | Out of protocol samples excluded | Pre-dose samples excluded | Not done samples excluded | Subjects/Records at end |
|---|---|---|---|---|---|---|---|---|---|
| ZL-2402-001 | Plasma | 12/312 | 85 | 0 | 0 | 0 | 0 | 0 | 12/227 |
| CS2514-2016-0001 | Plasma | 114/3268 | 1322 | 0 | 10 | 0 | 2 | 0 | 96/1934 |
| CS2514-2017-0001 | ELF | 30/60 | 0 | 0 | 0 | 0 | 0 | 0 | 30/60 |
| CS2514-2017-0001 | Plasma | 30/780 | 59 | 0 | 0 | 0 | 1 | 0 | 30/720 |
| CS2514-2017-0002 | Plasma | 34/1302 | 180 | 0 | 0 | 0 | 2 | 3 | 34/1117 |
| CS2514-2017-0003 | Plasma | 68/670 | 253 | 0 | 0 | 0 | 1 | 0 | 52/416 |
| CS2514-2017-0004 | Plasma | 135/770 | 8 | 140 | 0 | 14 | 2 | 0 | 112/606 |
| CS2514-2018-0002 | Plasma | 8/144 | 66 | 0 | 0 | 0 | 0 | 0 | 8/78 |
| CS2514-2018-0003 | Plasma | 31/854 | 508 | 6 | 0 | 0 | 0 | 0 | 31/340 |
| **Total Plasma[c]** | | 432/8100 | 2481 | 146 | 10 | 14 | 8 | 3 | 375/5438 |

Source: Adapted from Table 3 of Applicant's population PK report pc2514-2022-0007 for NDA216974
[a] Number of subjects or patients included in the PK population of each study.
[b] Plasma BLQ samples and outlier observations were retained in the dataset but flagged so that they were ignored by NONMEM. It should be noted that 1576 of the 2481 BLQ samples in the dataset were either drawn prior to a SUL-DUR dose or were drawn after placebo/control.
[c] Does not include ELF samples.
Note: For this table, "records" are individual concentration observations, not plasma samples.
Abbreviations: BLQ, below the limit of quantification; DUR, durlobactam; ELF, epithelium lining fluid; LLOQ, lower limit of quantitation; NONMEM, Nonlinear mixed effects modeling; PK, pharmacokinetic; SUL, su bactam

According to the Applicant's response, the high number of BLQ samples was a result of the short half-life of SUL-DUR and the extended sampling scheme in the phase 1 studies; 1% of BLQ samples occurred in the first 12 hours after a dose, while 30% were between 24 and 36 hours after a dose and 69% occurred ≥48 hours after a dose.

**Table 135. Comparison of SUL Population PK Estimates From the Original Plasma Model and the M3 Approach**

| Analyte | Parameter | Original Parameter Estimate | M3 Parameter Estimate | Percent difference |
|---|---|---|---|---|
| Sulbactam | CL (L/h) | 13.6 | 13.5 | 0.735 |
| Sulbactam | $CL_{R, CLcr\ power}$ | 0.932 | 0.941 | 0.966 |
| Sulbactam | Vc (L) | 12.1 | 12.1 | 0.00 |
| Sulbactam | Q (L/h) | 7.82 | 7.43 | 4.99 |
| Sulbactam | Vp (L) | 6.98 | 6.88 | 1.43 |
| Sulbactam | CLINFTYPN (HABP) | -0.423 | -0.44 | 4.02 |
| Sulbactam | CLINFTYPN2 (VABP) | -0.294 | -0.32 | 8.84 |
| Sulbactam | CLINFTYPN3 (cUTI) | -0.147 | -0.158 | 7.48 |
| Sulbactam | CLINFTYPN4 (Bacteremia) | -0.445 | -0.464 | 4.27 |
| Sulbactam | CLINFTYPN5 (AP) | -0.385 | -0.399 | 3.64 |
| Sulbactam | CLWTKG1 | 1.03 | 1.04 | 0.971 |
| Sulbactam | VcINFTYPN1 (HABP) | 0.818 | 0.75 | 8.31 |
| Sulbactam | VcINFTYPN2 (VABP) | 1.38 | 1.22 | 11.6 |
| Sulbactam | VcINFTYPN3 (cUTI) | 0.167 | 0.159 | 4.79 |
| Sulbactam | VcINFTYPN4 (bacteremia) | 1.84 | 1.75 | 4.89 |
| Sulbactam | VcINFTYPN5 (AP) | -0.707 | -0.729 | 3.11 |
| Sulbactam | VcWTKG1 | 0.828 | 0.853 | 3.02 |
| Sulbactam | BCLCRNLT30 | -0.56 | -0.563 | 0.536 |
| Sulbactam | IIV_CL | 0.212 | 0.209 | 1.42 |
| Sulbactam | IIV_Vc | 0.0926 | 0.0774 | 16.4 |
| Sulbactam | IIV_Vp | 0.197 | 0.168 | 14.7 |
| Sulbactam | Covariance (IIV_CL, IIV_Vc) | 0.0746497 | 0.0761002 | 1.94 |
| Sulbactam | $\sigma^2_{plasma,\ Proportional}$ | 0.0435 | 0.046 | 5.75 |
| Sulbactam | $\sigma^2_{plasma,\ Additive}$ | 0.00539 | 0.00274 | 0.49 |

Source: Adapted from Table 1 of Applicant's responses to information request for NDA216974 SDN 0027
Abbreviations: $\sigma^2$, residual variability; AP, acute pyelonephritis; CL, clearance; $CL_R$, renal clearance; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; IIV, interindividual variability; PK, pharmacokinetic; Q, distributional clearance; SUL, su bactam; VABP, ventilator-associated bacterial pneumonia; Vc, volume of distribution in the central compartment; Vp, volume of distribution in the peripheral compartment

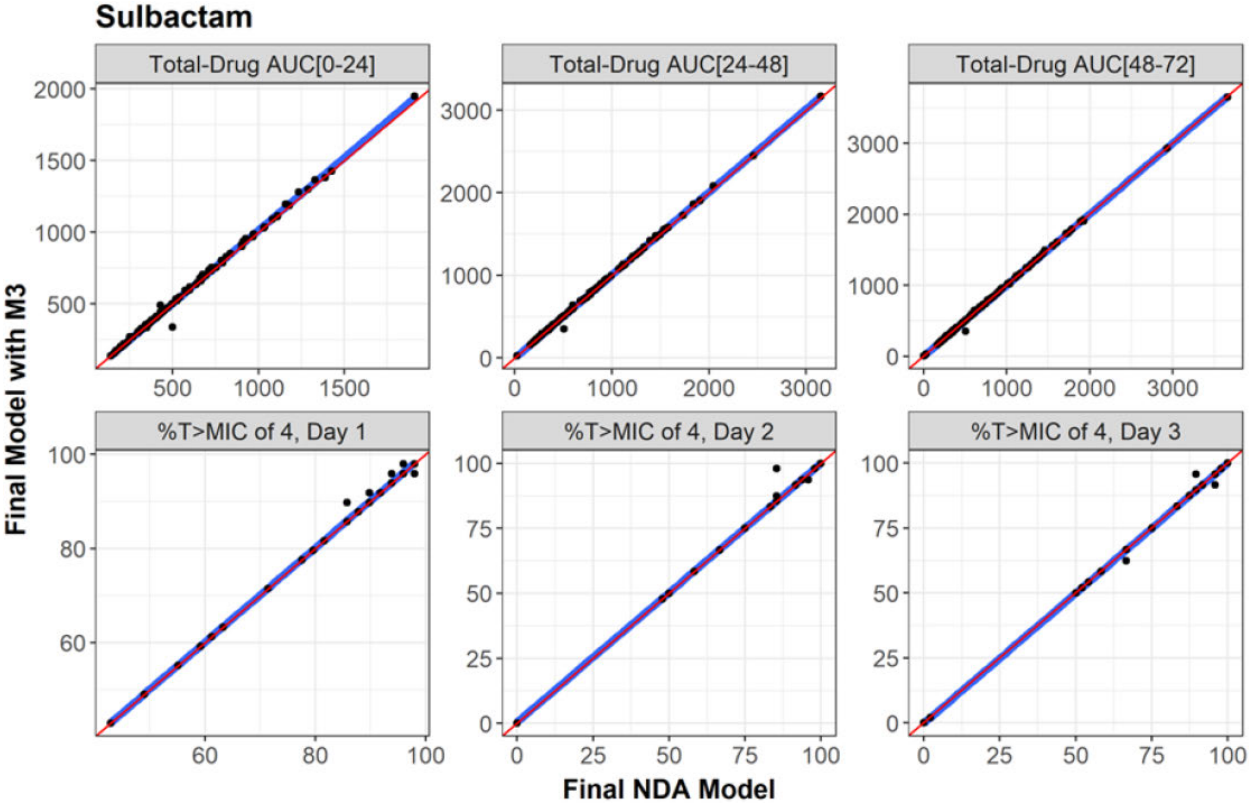
**Table 136. Comparison of DUR Population PK Estimates From the Original Plasma Model and the M3 Approach**

| Analyte | Parameter | Original Parameter Estimate | M3 Parameter Estimate | Percent difference |
|---|---|---|---|---|
| Durlobactam | CL (L/h) | 9.36 | 9.23 | 1.39 |
| Durlobactam | $CL_{R, CLcr\ power}$ | 0.694 | 0.698 | 0.576 |
| Durlobactam | Vc (L) | 12.5 | 12.7 | 1.60 |
| Durlobactam | Q (L/h) | 4.42 | 3.92 | 11.3 |
| Durlobactam | Vp (L) | 5.83 | 5.61 | 3.77 |
| Durlobactam | CLEASIAFL1 | -0.191 | -0.204 | 6.81 |
| Durlobactam | CLWTKG1 | 0.664 | 0.649 | 2.26 |
| Durlobactam | V1INFTYPN1&2 (HABP and VAPB) | 1.52 | 1.67 | 9.87 |
| Durlobactam | VcINFTYPN3 (cUTI) | 0.312 | 0.329 | 5.45 |
| Durlobactam | VcINFTYPN4 (bacteremia) | 3.42 | 3.3 | 3.51 |
| Durlobactam | VcWTKG1 | 0.518 | 0.525 | 1.35 |
| Durlobactam | VcEASIAFL1 | -0.261 | -0.272 | 4.21 |
| Durlobactam | BCLCRNLT30 | -0.508 | -0.503 | 0.984 |
| Durlobactam | IIV_CL | 0.0726 | 0.0713 | 1.79 |
| Durlobactam | IIV_Vc | 0.076 | 0.0728 | 4.21 |
| Durlobactam | IIV_Vp | 0.0773 | 0.0669 | 13.5 |
| Durlobactam | Covariance (IIV_CL, IIV_Vc) | 0.048223 | 0.0470626 | 2.41 |
| Durlobactam | $\sigma^2_{plasma, Proportional\ Phase\ 1}$ | 0.019 | 0.0213 | 12.1 |

Source: Adapted from Table 2 of Applicant's responses to information request for NDA216974 SDN 0027
Abbreviations: σ2, residual variability; DUR, durlobactam; CL, clearance; $CL_R$, renal clearance; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; IIV, interindividual variability; PK, pharmacokinetic; Q, distributional clearance; VABP, ventilator-associated bacterial pneumonia; Vc, volume of distribution in the central compartment; Vp, volume of distribution in the peripheral compartment

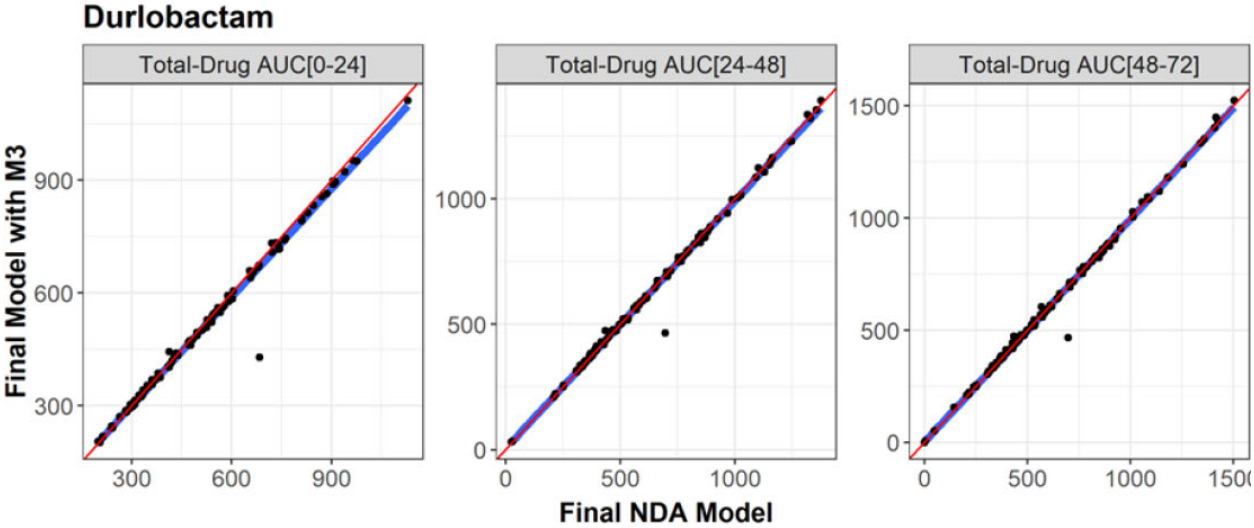
*Reviewer's Comments: The results show that the percent difference in PK parameter estimates ranged from 0-16.4% for SUL and 0.565-13.5% for DUR. Only 3 parameter estimates changed by more than 10% for each of SUL (VcINFTYPN2 (VABP), IIV_Vc, IIV_Vp) and DUR (Q, IIV_Vp, σ2 plasma, Proportional Phase 1). The goodness-of-fits show that both models fit the data adequately. In addition, there was good agreement in exposure measures between the final model with M3 and the final model originally submitted in the NDA. As %T > MIC and AUC/MIC are the PK/PD efficacy index for SUL and DUR respectively. The correlation indicates that the percent PTA using the originally submitted model is unlikely to change.*

**Figure 22. Relationship in SUL Exposure Measures on Day 1, Day 2, and Day 3 Between the Final Model With M3 and the Final Model Submitted in the NDA**




Source: Adapted from Figure 7 of Applicant's responses to information request for NDA216974 SDN 0027
Abbreviations: $AUC_{0-24}$, area under the curve from 0 to 24 hours; $AUC_{24-48}$, area under the curve from 24 to 48 hours; $AUC_{48-72}$, area under the curve from 48 to 72 hours; SUL, sulbactam; %T > MIC; percent of time free drug remains above the minimum inh bitory concentration

**Figure 23. Relationship in DUR AUC on Day 1, Day 2, and Day 3 Between the Final Model With M3 and the Final Model Submitted in the NDA**




Source: Adapted from Figure 8 of Applicant's responses to information request for NDA216974 SDN 0027
Abbreviations: DUR, durlobactam; $AUC_{0-24}$, area under the curve from 0 to 24 hours; $AUC_{24-48}$, area under the curve from 24 to 48 hours; $AUC_{48-72}$, area under the curve from 48 to 72 hours

*Reviewer's Comments: For the ELF sub-model and HD sub-model, the estimates, including SUL and DUR ELF penetration ratios, changed by <1%, indicating the BLQs by the M3 approach had a minimal effect on the sub-models.*

*Overall, the M3 approach had minimal to no effect on the PK parameter estimates.*

*The reviewer's assessment is that the final population PK characterization of SUL-DUR in patients with cUTI and with infections caused by ABC is acceptable. It is adequate to using PopPK derived individual PK exposure for additional assessment.*

## 14.5.2. Exposure-Response Analysis

### 14.5.2.1. Objectives

- To conduct PK/PD analyses for efficacy using data from SUL-DUR-treated patients with infections caused by ABC from study 2017-0004;
- To conduct PK/PD target attainment analyses to provide support for SUL-DUR dose selection for the treatment of patients with infections caused by ABC with varying degrees of renal function and interpretive criteria recommendations for the in vitro susceptibility testing of SUL-DUR against *Acinetobacter* spp.

### 14.5.2.2. Methods

**Data**

PK/PD target attainment analyses were carried out using 2 sets of simulated data using demographic data from patients with infections caused by ABC in the phase 3 study 2017-0004. 1) The first set included groups of simulated patients that were assessed for each CLcr (mL/min) interval in a set of mutually exclusive CLcr intervals, collectively covering a range from ≥0 to ≤200 mL/min. This set was used to determine dose adjustments based on varying degrees of renal function that would yield SUL-DUR exposures from 1.0 g SUL/1.0 g DUR q6h in patients with normal renal function. 2) The second set of simulated patients was generated to resemble the clinical study population of patients with ABC infections (HABP, VABP, ventilated pneumonia [VP], or bacteremia) from the phase 3 study 2017-0004.

The subjects in the study (n = 203) were replicated 15 times to generate a simulated subject population that contained 3,045 simulated patients, with distributions of demographic variables that resembled the observed target population. The results of analyses based on the second set of simulations were used to evaluate SUL-DUR dosing regimens that were determined based on the first set of simulations and interpretive criteria for the in vitro susceptibility testing of ABC.

Thus, the following doses were simulated across a total of 24,360 subjects, with 3,045 in each of 8 renal function categories below:

- Augmented renal function (≥130 to <150 mL/min and ≥150 to ≤200 mL/min): 1.5 g SUL/1.5 g DUR q6h via 3-hour infusion

- Normal renal function (≥90 to <130 mL/min): 1.0 g SUL/1.0 g DUR q6h via 3-hour infusion
- Mild renal impairment (≥60 to <90 mL/min): 1.0 g SUL/1.0 g DUR q6h via 3-hour infusion
- Moderate renal impairment:
  - ≥45 to <60 mL/min: 1.0 g SUL/1.0 g DUR q6h via 3-hour infusion
  - ≥30 to <45 mL/min: 1.0 g SUL /1.0 g DUR q8h via 3-hour infusion
- Severe renal impairment:
  - ≥15 to <30 mL/min: loading dose of 1.0 g SUL /1.0 g DUR followed by 0.5 g SUL /0.5 g DUR q8h via 3-hour infusion and,
  - 0 to <15 mL/min: loading dose of 1.0 g SUL/1.0 g DUR followed by 0.5 g SUL /0.5 g DUR q12h via 3-hour infusion

Of note, the doses used in the Monte Carlo simulations for the PTA analyses for patients with severe renal impairment and some patients with moderate renal impairment are different than those used in the phase 3 clinical study.

*PK Exposure:* the final population PK model for SUL-DUR was used to generate SUL and DUR exposures.

*In vitro surveillance data:* in vitro surveillance data for 7,026 *Acinetobacter* isolates collected from relevant geographic areas worldwide over a period between 2013 and 2020 was used to interpret the findings of the PK/PD target attainment analyses. The MIC distributions for SUL and SUL-DUR against ABC that were used to interpret the PK/PD target attainment results and calculate overall percent probabilities of PK/PD target attainment.

**Table 137. Sulbactam and Sulbactam-Durlobactam MIC Distributions for 7,026 *Acinetobacter* Isolates Collected Worldwide[a]**

| Drug | Number of occurrences (cumulative %) by MIC (µg/mL)[b] | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤0.03 | ≤0.06 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | ≥16 | 32 | 64 | ≥64 | 128 | ≥128 | ≥256 | $MIC_{50}$ | $MIC_{90}$ |
| Sulbactam | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 8 (0.1) | 73 (1.2) | 833 (13.0) | 1242 (30.7) | 498 (37.8) | 538 (45.4) | 1098 (61.1) | 0 (61.1) | 1548 (83.1) | 796 (94.4) | 133 (96.3) | 51 (97.0) | 199 (99.9) | 9 (100) | 16 | 64 |
| Sulbactam-durlobactam | 29 (0.4) | 11 (0.6) | 8 (0.7) | 88 (1.9) | 661 (11.3) | 1990 (39.7) | 2325 (72.8) | 1333 (91.7) | 467 (98.4) | 48 (99.1) | 22 (99.4) | 0 (99.4) | 22 (99.7) | 13 (99.9) | 1 (99.9) | 0 (99.9) | 8 (100) | 0 (100) | 1 | 2 |

Source: PK/PD Study Report 2022-0008.
[a] *Acinetobacter* isolates were collected from medical centers worldwide
[b] Shaded cells represent the MIC values up to and/or including the $MIC_{90}$ value
Abbreviations: MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic

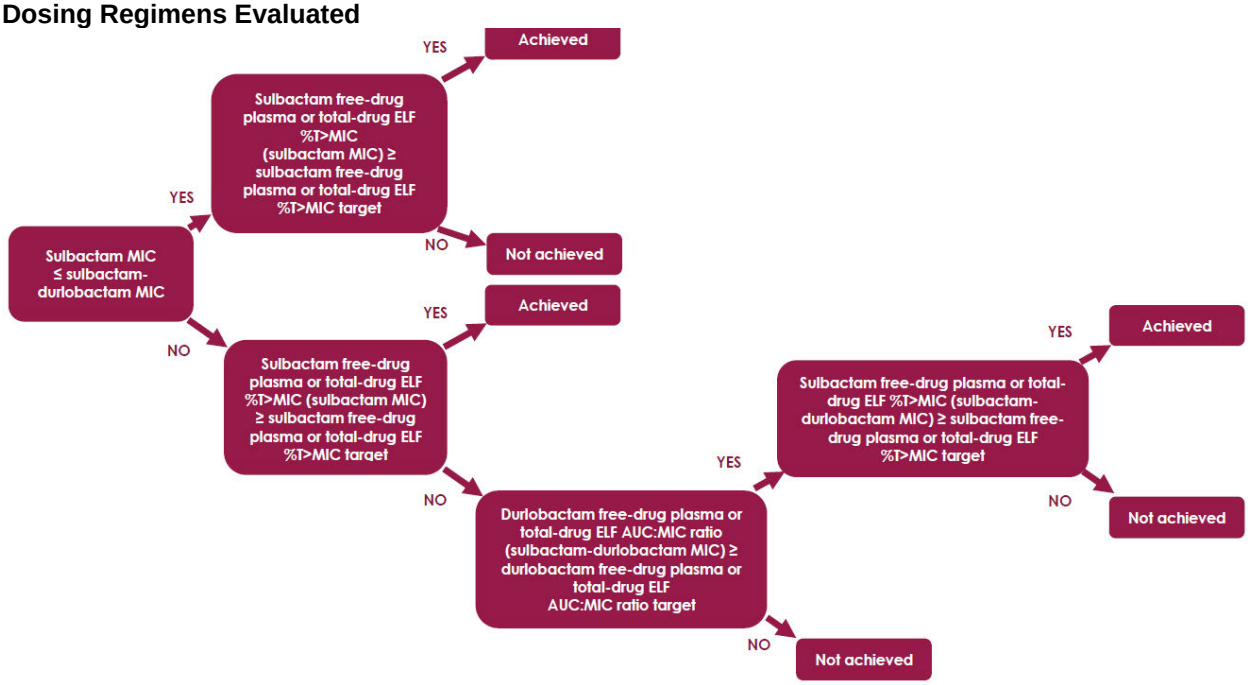
Nonclinical PK/PD Targets

- Sulbactam %T > MIC ≥50% and DUR AUC:MIC ratio ≥10 targets, were associated with a 1-$\log_{10}$ CFU reduction from baseline.
- Sulbactam %T > MIC ≥50% and DUR AUC:MIC ratio ≥30 targets, were associated with a 2-$\log_{10}$ CFU reduction from baseline.

Percent Probabilities of PK/PD Target (%PTA) Attainment

Percent probabilities of PK/PD target attainment by MIC were determined using free-drug plasma and total-drug ELF exposures. Using the above-described PK/PD targets and in vitro surveillance data, an algorithm was used to assess percent probabilities of PK/PD target attainment by MIC for the SUL-DUR dosing regimens evaluated.

**Figure 24. Algorithm to Calculate Percent Probabilities of PK/PD Target Attainment for SUL-DUR Dosing Regimens Evaluated**




Source: PK/PD Study Report 2022-0008.
Abbreviations: AUC, area under the curve; DUR, durlobactam; ELF, epithelium lining fluid; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; %T > MIC; percent of time free drug remains above the minimum inhibitory concentration; SUL, sulbactam

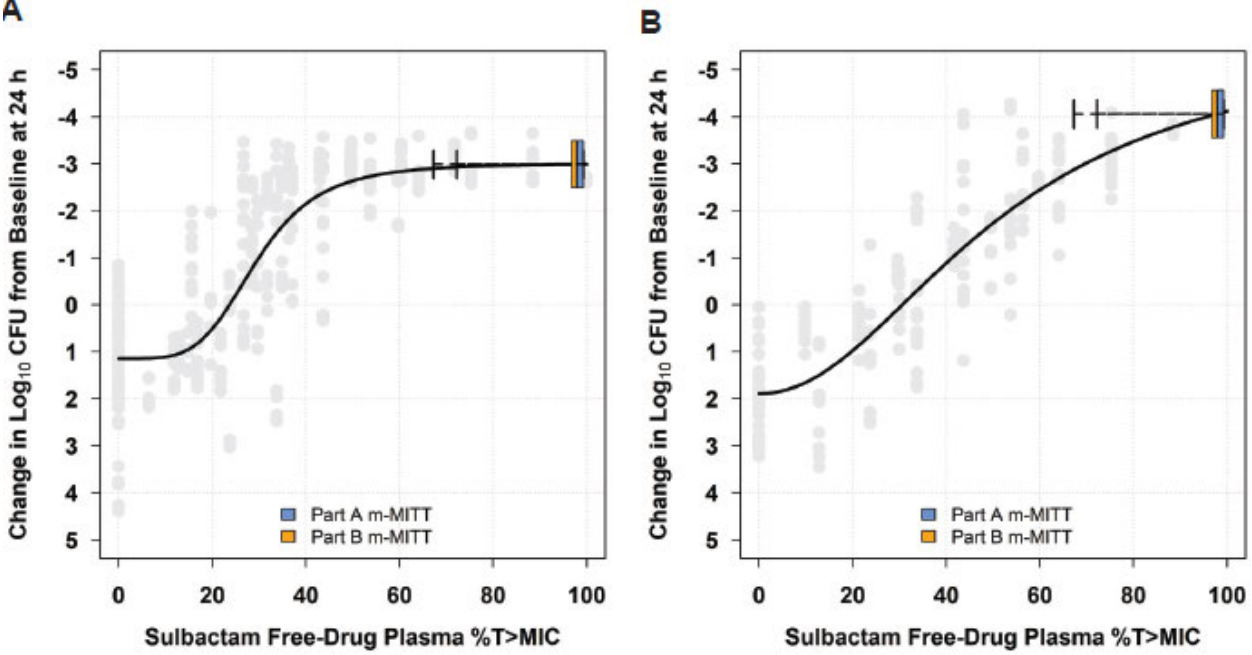
### 14.5.2.3. Results

**Nonclinical PK/PD Relationships**

The distributions of free-drug plasma PK/PD indices for SUL and DUR among subjects in the Part A and Part B microbiologically modified intent-to-treat (m-MITT) Analysis Populations were assessed relative to nonclinical PK/PD relationships for each agent against *A. baumannii* efficacy based on data from neutropenic murine infection models. Figure 25 and Figure 26

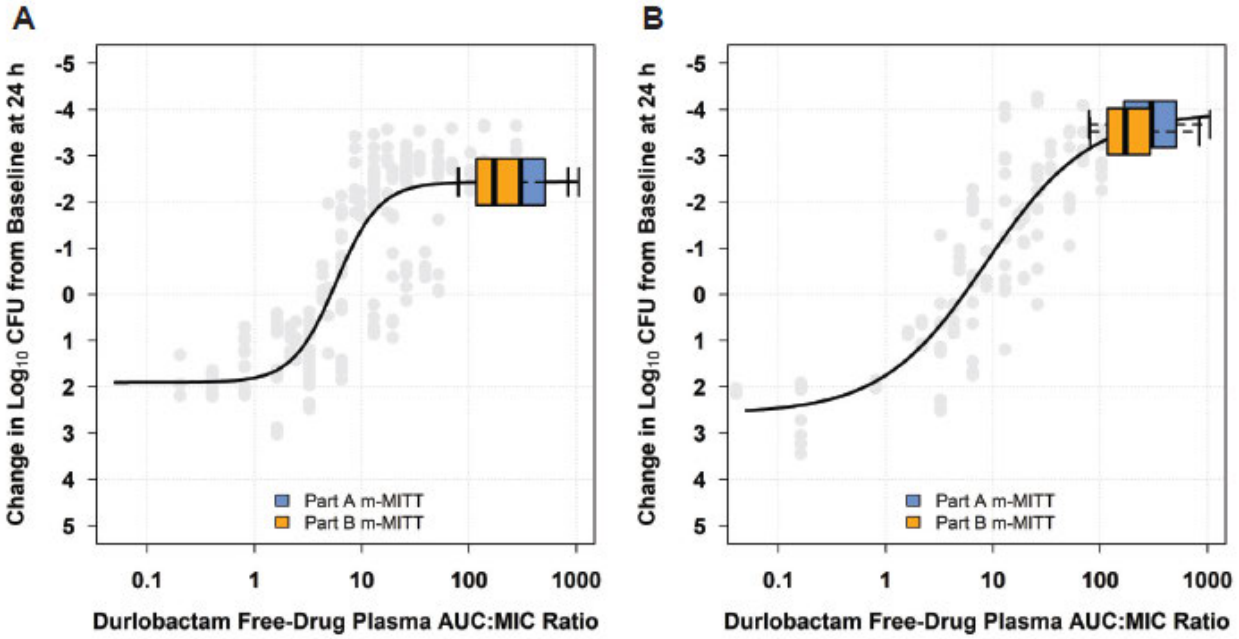
demonstrate that majority of patients achieved PK/PD indices that were on the plateau of the nonclinical PK/PD relationships for efficacy.

**Figure 25. Nonclinical PK/PD Relationships for SUL Efficacy Based on Data From Neutropenic Murine-Thigh (A) and -Lung (B) Infection Models**




Source: PK/PD Study Report 2022-0008, Figure 5. Page 83.
Note: Horizontal box-and-whisker plots of the SUL free-drug plasma %T > MIC over Days 1 to 3 among patients in the Part A and Part B m-MITT Analysis Populations from Study 2017-0004 after administration of SUL 1 g/ DUR 1 g IV q6h or dosing regimens adjusted for renal function are shown overlaid on PK/PD relationships for *A. baumannii* efficacy based on data from neutropenic murine-thigh and -lung infection models. For each boxplot, the vertical edge of the box represents the 25th to the 75th percentiles of the distribution for SUL free-drug plasma %T > MIC. The vertical line within the box represents with median SUL free-drug plasma %T > MIC. The whiskers extend to the 5th and 95th percentiles.
Abbreviations: CFU, colony forming units; DUR, durlobactam; m-MITT, microbiologically modified intent-to-treat population; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; q6h, every 6 hours; SUL, sulbactam; %T > MIC; percent of time free drug remains above the minimum inh bitory concentration

**Figure 26. Nonclinical PK/PD Relationships for DUR Efficacy for *A. baumannii*, Based on Data From Neutropenic Murine-Thigh (A) and -Lung (B) Infection Models**




Source: PK/PD Study Report 2022-0008, Figure 6. Page 84.
Note: Horizontal box-and-whisker plots of the average of Days 1 to 3 DUR free-drug plasma AUC:MIC ratio among patients in the Part A and Part B m-MITT Analysis Populations after administration of SUL 1 g/ DUR 1 g IV q6h or dosing regimens adjusted for renal function are shown overlaid on PK/PD relationships for *A. baumannii* efficacy based on data from neutropenic murine-thigh and -lung infection models. For each boxplot, the vertical edge of the box represents the 25th to the 75th percentiles of the distribution for DUR free-drug plasma AUC:MIC ratio. The vertical line within the box represents with median DUR free-drug plasma AUC:MIC ratio. The whiskers extend to the 5th and 95th percentiles.
Abbreviations: AUC, area under the curve; CFU, colony forming units; DUR, durlobactam; m-MITT, microbiologically modified intent-to-treat population; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; q6h, every 6 hours; SUL, sulbactam

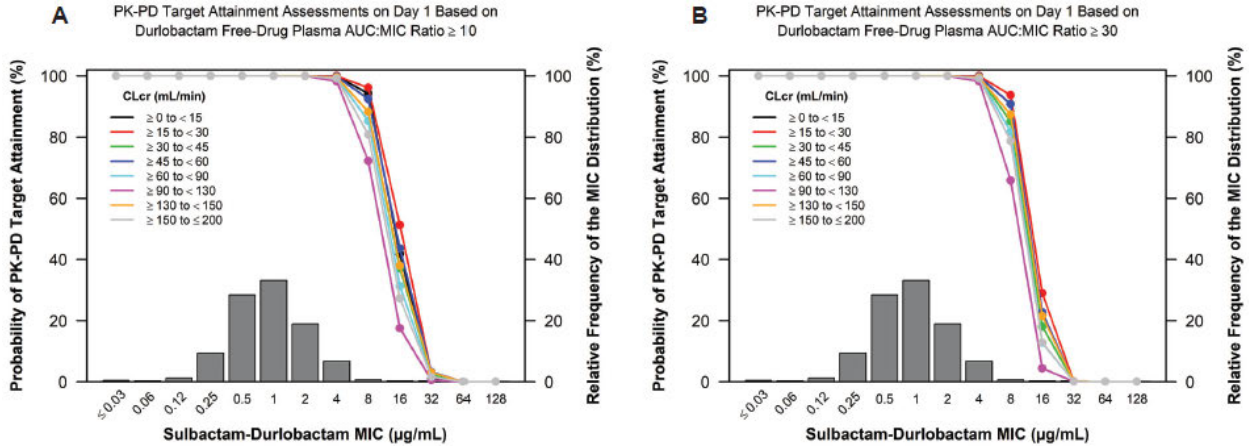
## PK/PD Target Attainment Analyses for Efficacy

The data for CLcr groups based on free-drug plasma PK/PD targets is shown graphically up to a SUL-DUR MIC value of 128 µg/mL in Figure 27, overlaid upon the MIC distribution for the collection of 7,026 *Acinetobacter* isolates. The data for CLcr groups based on total-drug ELF PK/PD targets is shown graphically up to a SUL-DUR MIC value of 128 µg/mL in Figure 28, overlaid upon the MIC distribution for *Acinetobacter* isolates.

As shown in Figure 27, percent probabilities of PK/PD target attainment associated with a DUR free-drug plasma AUC:MIC ratio target ≥10 ranged from 98.3 to 99.9% at an MIC value of 4 µg/mL (the MIC value inhibiting 98.4% of the collection of ABC isolates) among simulated patients by CLcr group. Percent probabilities of PK/PD target attainment associated with a DUR free-drug plasma AUC:MIC ratio target ≥30 ranged from 98.3 to 99.9% at an MIC value of 4 µg/mL among simulated patients by CLcr group.

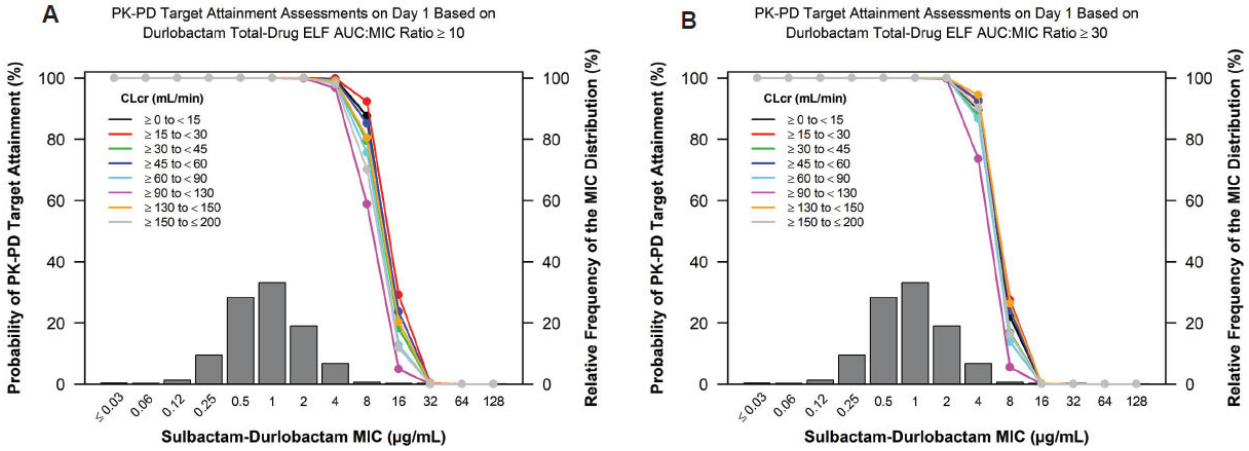
As shown in Figure 28, percent probabilities of PK/PD target attainment associated with a DUR total-drug ELF AUC:MIC ratio target ≥10 ranged from 96.8 to 99.8% at an MIC value of 4 µg/mL among simulated subjects by CLcr group. Percent probabilities of PK/PD target attainment associated with a total-drug ELF plasma AUC:MIC ratio target ≥30 ranged from 99.7 to 100% at an MIC value of 4 µg/mL among simulated subjects by CLcr group.

**Figure 27. Percent Probabilities of PK/PD Target Attainment by MIC on Day 1 Based on the Assessment of SUL Free-Drug Plasma %T > MIC ≥50% and DUR Free-Drug Plasma AUC:MIC Ratio ≥10 (A) and ≥30 (B) Targets Simulated Patients by CLcr Group After Administration of Sulbactam 1 g/ Durlobactam 1 g IV q6h and Dosing Regimens Adjusted for Renal Impairment and Augmented Renal Function, Overlaid Upon the MIC Distribution for 7,026 *Acinetobacter* Isolates**




Source: PK/PD study report 2022-0008. Figure 15. Page 120.
Abbreviations: AUC, area under the concentration time curve; CLcr, creatinine clearance; DUR, durlobactam; IV, intravenous; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; q6h, every 6 hours; SUL, sulbactam; %T > MIC; percent of time free drug remains above the minimum inhibitory concentration

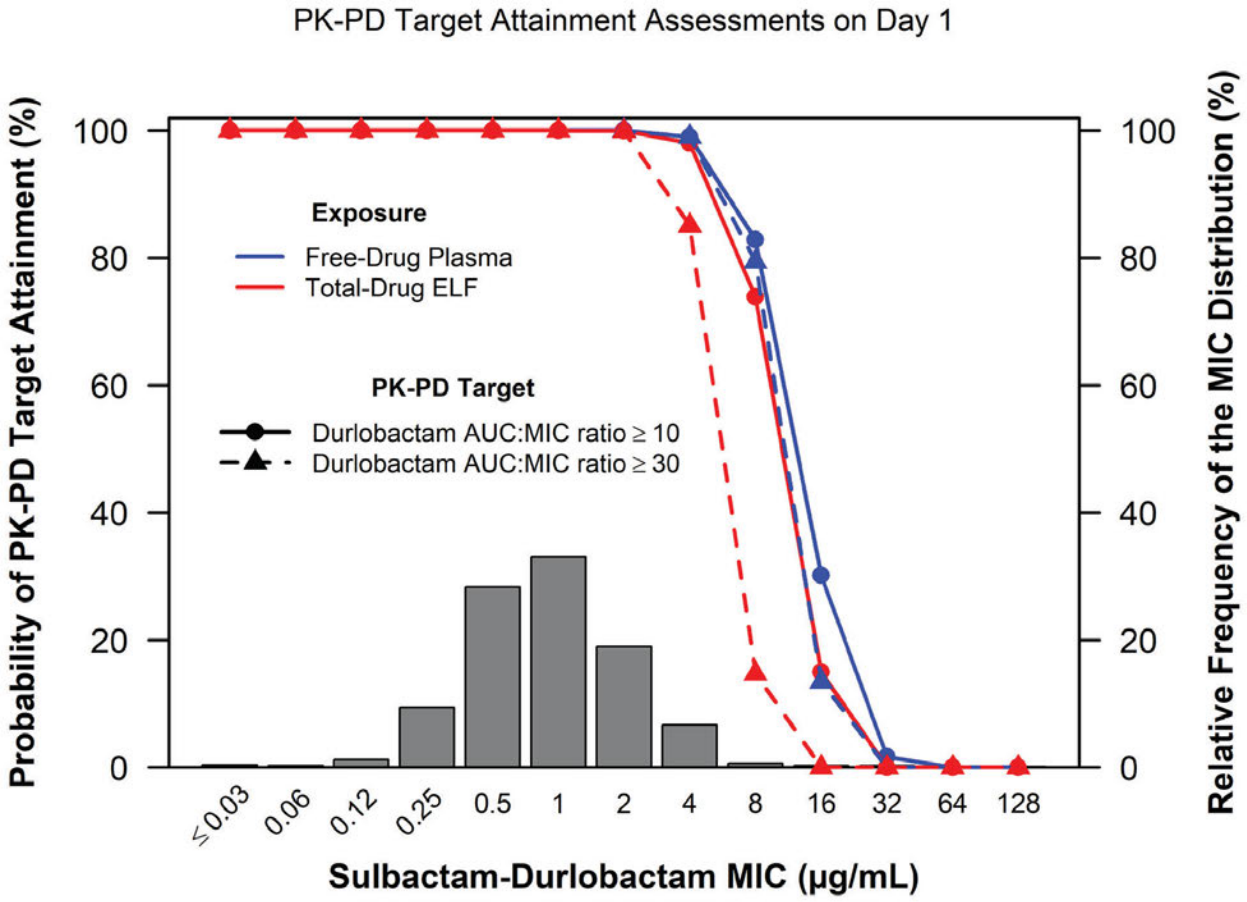
**Figure 28. Percent Probabilities of PK/PD Target Attainment by MIC on Day 1 Based on the Assessment of SUL Free-Drug Plasma %T > MIC ≥50% and DUR Free-Drug Plasma ELF AUC:MIC Ratio ≥10 (A) and ≥30 (B) Targets Simulated Patients by CLcr Group After Administration of SUL 1 g/ DUR 1 g IV q6h and Dosing Regimens Adjusted for Renal Impairment and Augmented Renal Function, Overlaid Upon the MIC Distribution for 7,026 *Acinetobacter* Isolates**




Source: PK/PD study report 2022-0008. Figure 16. Page 123.
Abbreviations: AUC, area under the concentration time curve; CLcr, creatinine clearance; DUR, durlobactam; ELF, epithelium lining fluid; IV, intravenous; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; q6h, every 6 hours; SUL, sulbactam; %T > MIC; percent of time free drug remains above the minimum inhibitory concentration

Data for the clinical study population based on both free-drug plasma and total-drug ELF PK/PD targets is shown graphically in Figure 29.

**Figure 29. Percent Probabilities of PK/PD Target Attainment by MIC on Day 1 Based on the Assessment of SUL-DUR PK/PD Targets for Efficacy Among Simulated Patients Resembling the Clinical Study Population After Administration of SUL 1 g/ DUR 1 g IV q6h and Dosing Regimens Adjusted for Renal Impairment and Augmented Renal Function, Overlaid Upon the MIC Distribution for 7,026 *Acinetobacter* Isolates**




Source: PK/PD study report 2022-0008. Figure 17. Page 124.
Abbreviations: AUC, area under the concentration time curve; DUR, durlobactam; ELF, epithelium lining fluid; IV, intravenous; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; q6h, every 6 hours; SUL, sulbactam

Across all CLcr groups and the simulated subjects resembling the clinical study population, percent probabilities of PK/PD target attainment ≥90% were achieved on Day 1 based on all evaluated DUR free-drug plasma and total-drug ELF AUC:MIC ratio targets at an MIC value of 2 µg/mL. At an MIC of 4 µg/mL, percent probabilities of PK/PD target attainment ≥90% were achieved on Day 1 for all simulated subject groups, except for percent probabilities of PK/PD target attainment based on a DUR total-drug ELF AUC:MIC ratio target ≥30 for simulated patients in CLcr ≥0 to <15 mL/min, ≥30 to <45 mL/min, ≥60 to <90 mL/min, ≥90 to <130 mL/min groups, and the simulated subjects resembling the clinical study population.

*Reviewer's Comments: Additional questions to be addressed:*

*(1) Appropriateness of dosing for subjects with high body weight ≥120 kg.*

*(2) Whether we should recommend dose of SUL/DUR 1.5 g /1.5 g every 6 hours versus 1.0 g /1.0 g every 4 hours for in patients with augmented renal function (CLcr ≥130 mL/min)?*

*(3) Please justify the use of CLcr (mL/min) for the proposed label rather than eGFR (mL/min/1.73m2) criteria.*

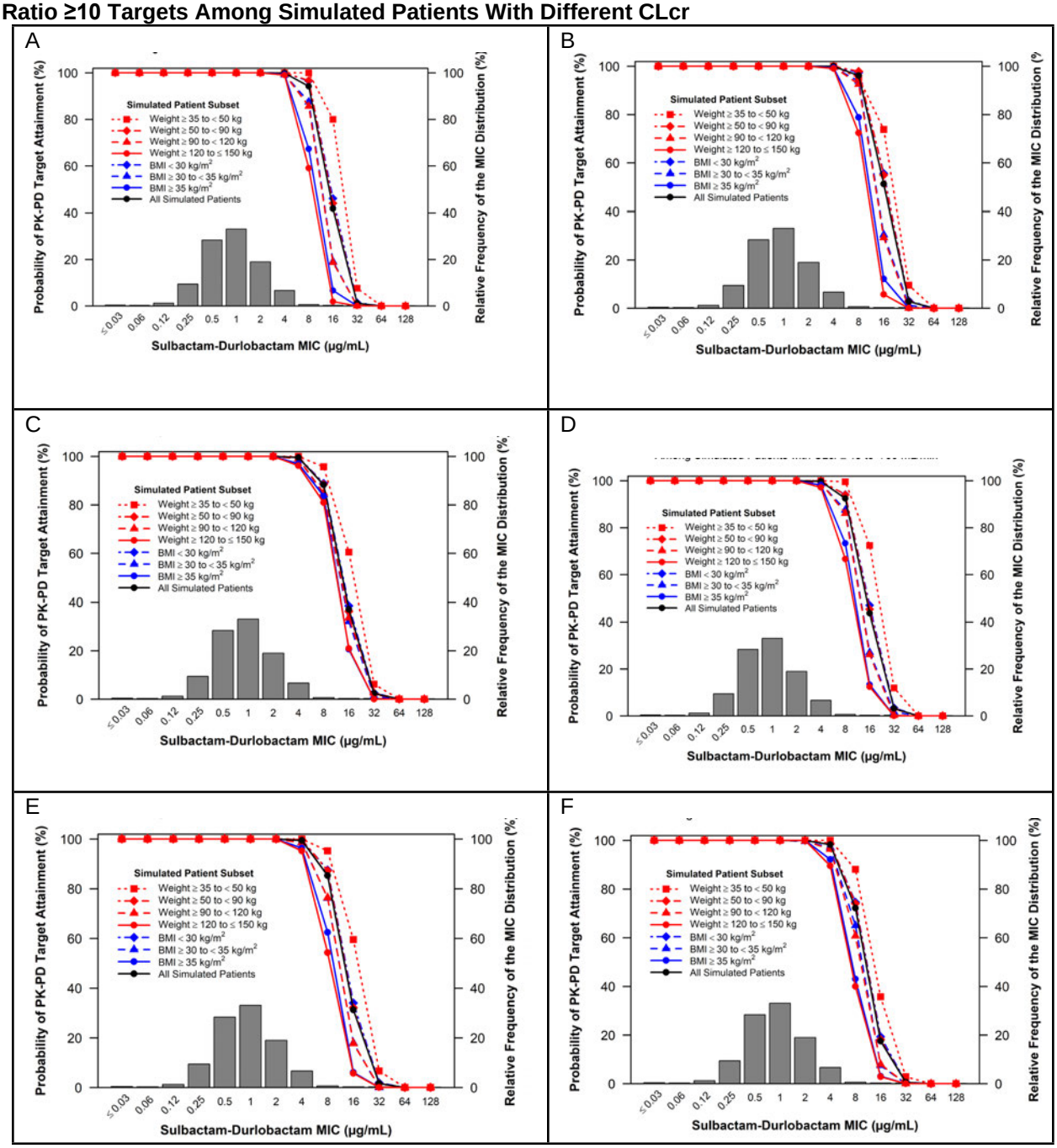
***Comment 1. Appropriateness of Dosing for Subjects With High Body Weight ≥120 kg***

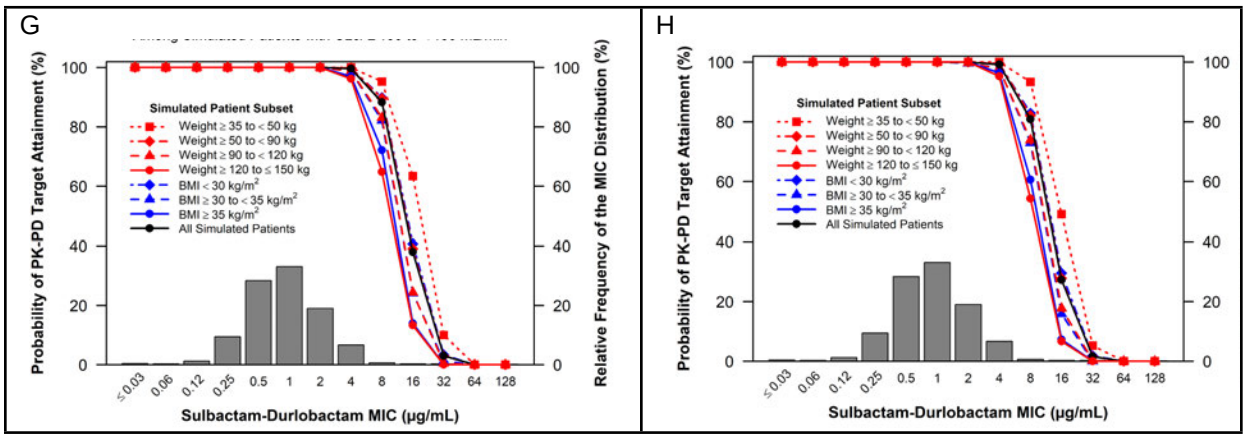
*Since body weight was identified as a statistically significant predictor of the variability in CL and Vc for SUL and DUR, lower drug exposures were observed in subjects with high body weights and this trend is expected to be more significant at body weight ≥120 kg. In order to gain more insights into the efficacy in these subgroups at the proposed dose regimens for subjects with high body weight (≥120 kg), an information request was sent to the Applicant on 01/19/2023 requesting additional %PTA analyses among simulated patients at the following body weight bands: 35 to 50 kg, 51 to 90 kg, 91 to 120 kg and 121 to 150 kg.*

*The results show that at the doses and using unbound plasma PK/PD targets associated with a 1-$log_{10}$ CFU reduction, a PTA of ≥90% for an MIC of 4 µg/mL is achieved at steady-state (Day 3) in all simulated patients, including those in the highest weight category (≥120 kg to ≤150 kg). Similar results were observed on Day 1, with the exception of patients with creatinine clearance of ≥90 to <130 mL/min and who weighed ≥120 to ≤150 kg, where the %PTA was 89.5% at an MIC of 4 µg/mL. Based on total-drug ELF targets, in patients with creatinine clearance of ≥90 to <130 mL/min and who weighed ≥120 to ≤150 kg, the Day 1 and Day 3%PTA was 85.7% and 89.5%, respectively for an MIC of 4 µg/mL.*

*Based on these results, the reviewer determined that the proposed dose for subjects with high body weight ≥120 kg is appropriate.*

**Figure 30. Percent Probabilities of PK/PD Target Attainment by MIC on Days 1 Based on the Assessment of SUL Free-Drug Plasma %T > MIC ≥50% and DUR Free-Drug Plasma AUC:MIC Ratio ≥10 Targets Among Simulated Patients With Different CLcr**






Source: Applicant's IR response NDA 216974 SDN 25, Figures 1-16 for Question 1
Note: A) Patients with CLcr ⩾0 to <15 mL/min; B) Patients with CLcr ⩾15 to <30 mL/min; C) Patients with CLcr ⩾30 to <45 mL/min; D) Patients with CLcr ⩾45 to <60 mL/min; E) Patients with CLcr ⩾60 to <90 mL/min; F) Patients with CLcr ⩾90 to <130 mL/min; G) Patients with CLcr ⩾130 to <150 mL/min; H: Patients with CLcr ⩾150 mL/min)
Abbreviations: AUC, area under the concentration time curve; BMI, body mass index; CLcr, creatinine clearance; DUR, durlobactam; MIC, minimum inh bitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; SUL, sulbactam; %T > MIC; percent of time free drug remains above the minimum inhibitory concentration

**Table 138. Percent Probabilities of PK/PD Target Attainment at MIC Values of 4 and 8 µg/mL on Days 1 and 3 Based on the Assessment of SUL and DUR Free-Drug Plasma and Total-Drug ELF PK/PD Targets Associated With a 1-log10 CFU Reduction From Baseline[a] and MIC Data for 7,026 ABC Isolates Collected Worldwide Among Simulated Patients by CLcr and Weight or BMI Groups After Administration of SUL 1 g/ DUR 1 g IV q6h and Dosing Regimens Adjusted for Renal Impairment and Augmented Renal Function[a]**

| Exposure | CLcr group (mL/min) | MIC (µg/mL)[b] | Day | Percent probabilities of PK-PD target attainment[b] by MIC and CLcr (mL/min) and weight or BMI groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Weight (kg) | | | | BMI (kg/m$^2$) | | | All simulated patients |
| | | | | ≥ 35 to < 50 | ≥ 50 to < 90 | ≥ 90 to < 120 | ≥ 120 to ≤ 150 | <30 | ≥30 to <35 | ≥35 | |
| Free-drug plasma | ≥ 0 to < 15 | 4 | 1 | 100 | 100 | 99.5 | 99.0 | 100 | 99.2 | 99.4 | >99.9 |
| | | | 3 | 100 | >99.9 | 99.0 | 96.2 | >99.9 | 98.8 | 97.6 | 99.7 |
| | | 8 | 1 | 100 | 96.7 | 85.6 | 59.0 | 96.5 | 87.5 | 67.3 | 94.2 |
| | | | 3 | 99.5 | 95.6 | 89.5 | 71.4 | 95.6 | 91.2 | 77.0 | 94.3 |
| | ≥ 15 to < 30 | 4 | 1 | 100 | 100 | 99.7 | 99.0 | 100 | 99.6 | 99.4 | >99.9 |
| | | | 3 | 99.5 | >99.9 | 99.5 | 100 | >99.9 | 99.2 | 100 | 99.9 |
| | | 8 | 1 | 95.2 | 97.9 | 92.6 | 72.4 | 97.4 | 93.8 | 78.8 | 96.1 |
| | | | 3 | 92.4 | 97.7 | 94.4 | 86.7 | 97.1 | 95.0 | 89.7 | 96.6 |
| | ≥ 30 to < 45 | 4 | 1 | 100 | 99.7 | 99.0 | 96.2 | 99.7 | 99.2 | 97.0 | 99.5 |
| | | | 3 | 100 | 99.7 | 99.0 | 97.1 | 99.7 | 99.2 | 97.6 | 99.6 |
| | | 8 | 1 | 95.7 | 88.5 | 84.9 | 81.0 | 88.9 | 84.2 | 83.6 | 88.2 |
| | | | 3 | 97.1 | 92.6 | 91.5 | 91.4 | 93.0 | 90.0 | 92.7 | 92.7 |
| | ≥ 45 to < 60 | 4 | 1 | 100 | >99.9 | 99.0 | 97.1 | >99.9 | 98.8 | 98.2 | 99.7 |
| | | | 3 | 100 | >99.9 | 99.0 | 98.1 | >99.9 | 98.8 | 98.8 | 99.8 |
| | | 8 | 1 | 99.5 | 94.0 | 86.2 | 66.7 | 94.1 | 87.5 | 73.3 | 92.4 |
| | | | 3 | 99.5 | 95.9 | 90.5 | 80.0 | 95.9 | 92.1 | 83.0 | 94.9 |
| | ≥ 60 to < 90 | 4 | 1 | 100 | 99.7 | 98.5 | 95.2 | 99.7 | 98.8 | 96.4 | 99.4 |
| | | | 3 | 100 | 99.8 | 98.5 | 96.2 | 99.7 | 98.8 | 97.0 | 99.5 |
| | | 8 | 1 | 95.2 | 87.3 | 76.4 | 54.3 | 87.5 | 76.2 | 62.4 | 85.3 |
| | | | 3 | 97.1 | 91.0 | 84.4 | 67.6 | 91.3 | 83.3 | 73.9 | 89.8 |
| | ≥ 90 to < 130 | 4 | 1 | 100 | 98.8 | 96.4 | 89.5 | 98.8 | 97.1 | 92.1 | 98.3 |
| | | | 3 | 100 | 98.9 | 96.7 | 93.3 | 98.9 | 97.5 | 94.5 | 98.5 |
| | | 8 | 1 | 88.1 | 74.1 | 60.8 | 40.0 | 74.6 | 65.0 | 43.0 | 72.2 |
| | | | 3 | 90.5 | 79.1 | 70.5 | 51.4 | 79.8 | 69.6 | 58.8 | 77.9 |
| | ≥ 130 to < 150 | 4 | 1 | 100 | 99.8 | 98.7 | 96.2 | 99.8 | 98.8 | 97.0 | 99.6 |
| | | | 3 | 100 | 99.9 | 98.7 | 97.1 | 99.8 | 98.8 | 97.6 | 99.6 |
| | | 8 | 1 | 95.2 | 89.6 | 83.1 | 64.8 | 89.8 | 82.1 | 72.1 | 88.3 |
| | | | 3 | 96.2 | 91.2 | 86.4 | 69.5 | 91.4 | 87.5 | 75.2 | 90.2 |
| | ≥ 150 to ≤ 200 | 4 | 1 | 100 | 99.5 | 97.7 | 95.2 | 99.4 | 97.9 | 96.4 | 99.1 |
| | | | 3 | 100 | 99.5 | 97.7 | 95.2 | 99.4 | 97.9 | 96.4 | 99.1 |
| | | 8 | 1 | 93.3 | 82.1 | 73.8 | 54.3 | 82.8 | 72.9 | 60.6 | 80.9 |
| | | | 3 | 93.3 | 84.0 | 76.7 | 60.0 | 84.7 | 75.0 | 66.1 | 82.9 |

Source: Applicant's IR response NDA 216974, SDN 25, Table 2 for Question 1. Page 21.
[a] Based on the sulbactam free-drug plasma and total-drug ELF %T > MIC target ≥50 and durlobactam free-drug plasma and total-drug ELF AUC:MIC ratio target ≥10.
[b] Represents the sulbactam-durlobactam MIC value.
Note: Shaded cells indicate probabilities of PK/PD target attainment ≥90%.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; AUC, area under the curve'; BMI, body mass index; CFU, colony forming units; CLcr, creatinine clearance; DUR, durlobactam; ELF, epithelium lining fluid; IV, intravenous; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; q6h, every 6 hours; SUL, sulbactam; %T > MIC; percent of time free drug remains above the minimum inhibitory concentration

**Table 139. Percent Probabilities of PK/PD Target Attainment at MIC Values of 4 and 8 µg/mL on Days 1 and 3 Based on the Assessment of SUL and DUR Free-Drug Plasma and Total-Drug ELF PK/PD Targets Associated With a 1-log10 CFU Reduction From Baseline[a] and MIC Data for 7,026 ABC Isolates Collected Worldwide Among Simulated Patients by CLcr and Weight or BMI Groups After Administration of SUL 1 g/ DUR 1 g IV q6h and Dosing Regimens Adjusted for Renal Impairment and Augmented Renal Function[a]**

| Exposure | CLcr group (mL/min) | MIC (µg/mL)[b] | Day | Percent probabilities of PK-PD target attainment[b] by MIC and CLcr (mL/min) and weight or BMI groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Weight (kg) | | | | BMI (kg/m²) | | | All simulated patients |
| | | | | ≥ 35 to < 50 | ≥ 50 to < 90 | ≥ 90 to < 120 | ≥ 120 to ≤ 150 | <30 | ≥30 to <35 | ≥35 | |
| Total-drug ELF | ≥ 0 to < 15 | 4 | 1 | 100 | 100 | 99.0 | 95.2 | >99.9 | 98.8 | 97.0 | 99.7 |
| | | | 3 | 100 | 99.8 | 98.5 | 95.2 | 99.7 | 98.8 | 96.4 | 99.5 |
| | | 8 | 1 | 99.5 | 91.7 | 70.5 | 33.3 | 91.6 | 74.6 | 41.2 | 87.5 |
| | | | 3 | 98.6 | 91.6 | 80.0 | 54.3 | 91.7 | 79.6 | 65.5 | 89.3 |
| | ≥ 15 to < 30 | 4 | 1 | 100 | >99.9 | 99.5 | 98.1 | >99.9 | 99.2 | 98.8 | 99.8 |
| | | | 3 | 99.5 | 99.9 | 99.0 | 98.1 | 99.8 | 98.8 | 98.8 | 99.7 |
| | | 8 | 1 | 93.3 | 95.2 | 84.1 | 55.2 | 94.5 | 87.1 | 63.0 | 92.2 |
| | | | 3 | 90.0 | 95.1 | 90.3 | 76.2 | 94.4 | 92.1 | 80.6 | 93.5 |
| | ≥ 30 to < 45 | 4 | 1 | 100 | 99.3 | 97.7 | 95.2 | 99.2 | 97.9 | 96.4 | 99.0 |
| | | | 3 | 100 | 99.5 | 97.7 | 96.2 | 99.4 | 97.9 | 97.0 | 99.2 |
| | | 8 | 1 | 92.4 | 79.3 | 75.4 | 72.4 | 80.3 | 74.2 | 72.7 | 79.4 |
| | | | 3 | 94.8 | 86.7 | 83.8 | 87.6 | 87.3 | 81.2 | 88.5 | 86.9 |
| | ≥ 45 to < 60 | 4 | 1 | 100 | 99.8 | 98.5 | 95.2 | 99.8 | 98.8 | 96.4 | 99.5 |
| | | | 3 | 100 | 99.9 | 99.0 | 96.2 | 99.8 | 98.8 | 97.6 | 99.6 |
| | | 8 | 1 | 95.7 | 87.5 | 74.9 | 52.4 | 87.8 | 75.0 | 60.0 | 85.3 |
| | | | 3 | 97.1 | 92.3 | 85.6 | 66.7 | 92.4 | 86.7 | 73.3 | 90.9 |
| | ≥ 60 to < 90 | 4 | 1 | 100 | 99.3 | 97.2 | 91.4 | 99.2 | 97.9 | 93.3 | 98.8 |
| | | | 3 | 100 | 99.4 | 97.4 | 94.3 | 99.4 | 97.9 | 95.8 | 99.0 |
| | | 8 | 1 | 91.4 | 77.7 | 63.8 | 41.0 | 78.4 | 66.2 | 44.8 | 75.6 |
| | | | 3 | 93.8 | 83.8 | 74.4 | 55.2 | 84.4 | 72.9 | 63.0 | 82.3 |
| | ≥ 90 to < 130 | 4 | 1 | 99.5 | 97.7 | 92.6 | 85.7 | 97.6 | 94.6 | 87.3 | 96.8 |
| | | | 3 | 99.5 | 98.2 | 94.9 | 89.5 | 98.1 | 95.8 | 91.5 | 97.5 |
| | | 8 | 1 | 82.9 | 61.0 | 43.6 | 20.0 | 62.3 | 43.3 | 25.5 | 58.9 |
| | | | 3 | 85.2 | 68.7 | 57.2 | 37.1 | 69.9 | 57.1 | 40.6 | 67.3 |
| | ≥ 130 to < 150 | 4 | 1 | 100 | 99.4 | 98.2 | 95.2 | 99.4 | 98.8 | 96.4 | 99.2 |
| | | | 3 | 100 | 99.4 | 98.2 | 95.2 | 99.4 | 98.8 | 96.4 | 99.2 |
| | | 8 | 1 | 92.4 | 82.1 | 72.3 | 51.4 | 82.7 | 72.5 | 57.6 | 80.5 |
| | | | 3 | 94.3 | 84.6 | 77.7 | 59.0 | 85.2 | 76.2 | 66.1 | 83.5 |
| | ≥ 150 to ≤ 200 | 4 | 1 | 100 | 98.6 | 95.9 | 89.5 | 98.5 | 97.1 | 91.5 | 98.0 |
| | | | 3 | 100 | 98.6 | 96.2 | 90.5 | 98.5 | 97.1 | 92.7 | 98.1 |
| | | 8 | 1 | 85.7 | 71.9 | 58.7 | 41.9 | 72.6 | 61.2 | 43.0 | 70.1 |
| | | | 3 | 86.7 | 74.7 | 65.6 | 49.5 | 75.3 | 66.2 | 53.9 | 73.5 |

Source: Applicant's IR response NDA 216974, SDN 25, Table 2 for Question 1. Page 22.
[a] Based on the sulbactam free-drug plasma and total-drug ELF %T > MIC target ≥50 and durlobactam free-drug plasma and total-drug ELF AUC:MIC ratio target ≥10.
[b] Represents the sulbactam-durlobactam MIC value.
Note: Shaded cells indicate probabilities of PK/PD target attainment ≥90%.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; AUC, area under the curve; BMI, body mass index; CFU, colony forming units; CLcr, creatinine clearance; DUR, durlobactam; ELF, epithelium lining fluid; IV, intravenous; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; q6h, every 6 hours; SUL, sulbactam; %T > MIC; percent of time free drug remains above the minimum inhibitory concentration

### *Comment 2. SUL/DUR 1.5 g /1.5 g (Every 6 Hours) Versus SUL/DUR 1.0 g /1.0 g (every 4 hours) for in Patients With Augmented Renal Function (CLcr ≥130 mL/min)*

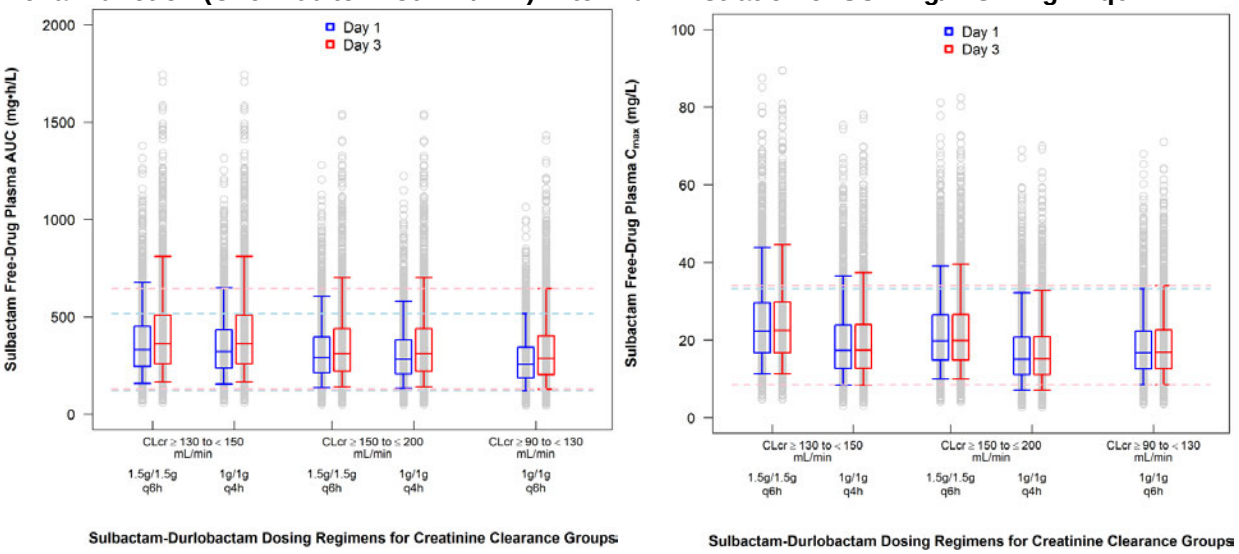
*The Applicant proposed to adjust the dosing regimen of SUL-DUR to 1.5 g /1.5 g every 6 hours in patients with augmented renal function (CLcr ≥130 mL/min). This dose will require using two XACDURO kits. Since each kit includes one SUL 1 g single dose vial and two DUR 0.5 g single use vials, the proposed 1.5 g SUL /1.5 g DUR dose will result in one 0.5 g DUR vial being leftover, which may lead to medication errors. An information request was sent to the Applicant on 01/19/2023 requesting investigating the alternative dosing regimen by using population PK modeling and PTA analysis for patients with augmented renal function, e.g., 1.0 g /1.0 g every 4 hours in order to avoid the potential medication error and achieve drug exposures similar to those in patients with normal renal function.*

*Based on the IR responses, using the population PK analysis, exposures (Day 1 and Day 3 $AUC_{0-24}$ and $C_{max}$) with the 1.0 g SUL /1.0 g DUR q4h were similar to exposures achieved with the 1.5 g SUL/1.5 g DUR q6h. In addition, both dosing regimens, 1.0 g SUL/1.0 g DUR q4h and*

*1.5 g SUL /1.5 g DUR q6h, in subjects with CLcr ≥130 mL/min achieved a PTA ≥90% for an MIC of 4 µg/mL.*

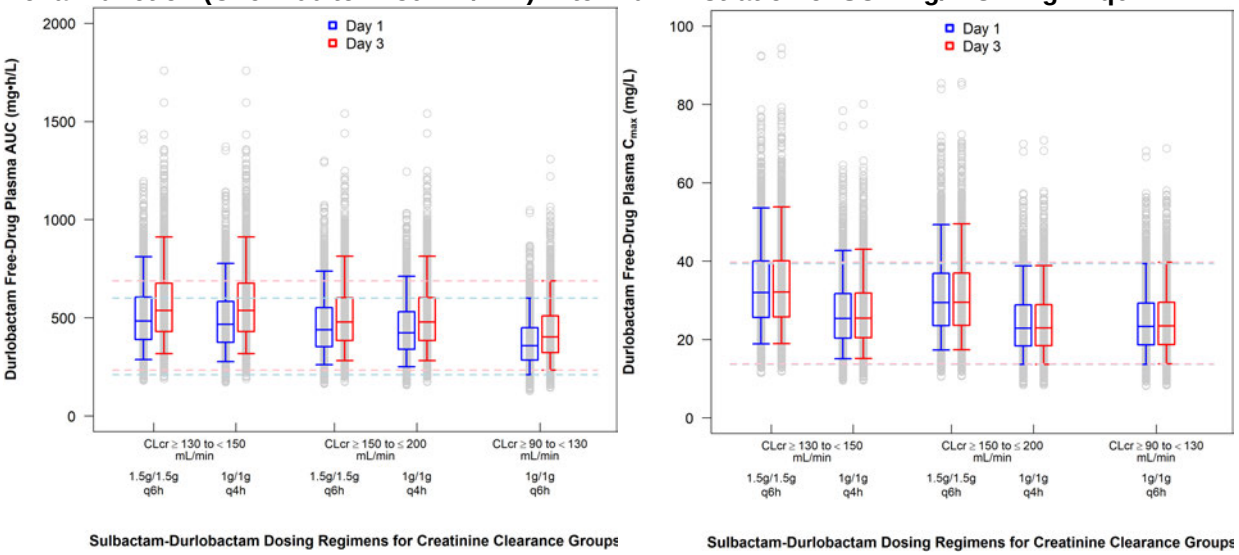
*Given the comparable exposures and a PTA ≥90% for an MIC of 4 µg/mL across both the 1.0 g SUL/1.0 g DUR q4h and the 1.5 g SUL/1.5 g DUR q6h regimens, we determine that both the 1.0 g SUL/1.0 g DUR q4h and 1.5 g SUL/1.5 g DUR q6h dosing regimen are acceptable for patients with CLcr ≥130 mL/min. The dosing of 1.0 g SUL/1.0 g DUR q4h may provide additional benefit to avoid potential medication error.*

**Figure 31. Box-and-Whisker Plots by CLcr Group of Sulbactam Free-Drug Plasma (Right) AUC and (Left) $C_{max}$ on Days 1 and 3 Among Simulated Patients With CLcr ≥130 to ≤200 mL/min After Administration of Two SUL-DUR Dosing Regimens and Among Simulated Patients With Normal Renal Function (CLcr ≥90 to <130 mL/min) After Administration of SUL 1 g/ DUR 1 g IV q6h**




Source: Applicant's IR response NDA 216974, SDN 25, Figure 1 and Figure 2 for Question 2. Pages 24 - 27.
Note: The horizontal dashed lines represent the 90% prediction interval of the ≥90 to <130 mL/min group, defined as the 5th and 95th percentiles for su bactam free-drug plasma AUC and $C_{max}$ on Days 1 and 3.
Abbreviations: AUC, area under the curve; CLcr; creatinine clearance; $C_{max}$, maximum plasma concentration; DUR, durlobactam; IV, intravenous; q4h, every 4 hours; q6h, every 6 hours; SUL, su bactam

**Figure 32. Box-and-Whisker Plots by CLcr Group of DUL Free-Drug Plasma (Right) AUC and (Left) $C_{max}$ on Days 1 and 3 Among Simulated Patients With CLcr ≥130 to ≤200 mL/min After Administration of Two SUL-DUR Dosing Regimens and Among Simulated Patients With Normal Renal Function (CLcr ≥90 to <130 mL/min) After Administration of SUL 1 g/ DUR 1 g IV q6h**




Source: Applicant's IR response NDA 216974, SDN 25, Figure 3 and Figure 4 for Question 2. Pages 28 - 31.
Note: The horizontal dashed lines represent the 90% prediction interval of the ≥90 to <130 mL/min group, defined as the 5th and 95th percentiles for su bactam free-drug plasma AUC and $C_{max}$ on Days 1 and 3.
Abbreviations: AUC, area under the curve; CLcr; creatinine clearance; $C_{max}$, maximum plasma concentration; DUR, durlobactam; IV, intravenous; q4h, every 4 hours; q6h, every 6 hours; SUL, su bactam

**Table 140. Percent Probabilities of PK/PD Target Attainment on Days 1 and 3 at MIC Values of 4 and 8 µg/mL Based on the Assessment of SUL and DUR Free-Drug Plasma and Total-Drug ELF PK/PD Targets Associated With a 1-log10 CFU Reduction From Baseline[a] and MIC Data for 7,026 *Acinetobacter* Isolates Collected Worldwide Among Simulated Patients With CLcr ≥130 to ≤200 mL/min After Administration of Two SUL-DUR Dosing Regimens and Among Simulated Patients With Normal Renal Function (CLcr ≥90 to <130 mL/min) After Administration of SUL 1 g/ DUR 1 g IV q6h**

| Exposure measure | Percent probabilities of PK-PD target attainment[a] by MIC and CLcr (mL/min) group on Days 1 or 3 | | | | | | |
|---|---|---|---|---|---|---|---|
| | MIC (µg/mL) | Day | CLcr ≥ 130 to < 150 mL/min | | CLcr ≥ 150 to ≤ 200 mL/min | | CLcr ≥ 90 to < 130 mL/min |
| | | | Sulbactam 1.5 g/ durlobactam 1.5 g IV q6h | Sulbactam 1 g/ durlobactam 1 g IV q4h | Sulbactam 1.5 g/ durlobactam 1.5 g IV q6h | Sulbactam 1 g/ durlobactam 1 g IV q4h | Sulbactam 1 g/ durlobactam 1 g IV q6h |
| Free-drug plasma | 4 | 1 | 99.6 | 99.7 | 99.1 | 99.3 | 98.3 |
| | | 3 | 99.6 | 99.7 | 99.1 | 99.4 | 98.5 |
| | 8 | 1 | 88.3 | 89.3 | 80.9 | 82.8 | 72.2 |
| | | 3 | 90.2 | 91.6 | 82.9 | 84.9 | 77.9 |
| Total-drug ELF | 4 | 1 | 99.2 | 99.2 | 98.0 | 98.4 | 96.8 |
| | | 3 | 99.2 | 99.3 | 98.1 | 98.7 | 97.5 |
| | 8 | 1 | 80.5 | 81.9 | 70.1 | 72.0 | 58.9 |
| | | 3 | 83.5 | 85.1 | 73.5 | 76.3 | 67.3 |

Source: Applicant's IR response NDA 216974, SDN 25, Table 1 for Question 2. Pages 36.
[a] Based on the sulbactam free-drug plasma and total-drug ELF %T > MIC target ≥50 and durlobactam free-drug plasma and total-drug ELF AUC:MIC ratio target ≥10 associated with a 1-$log_{10}$ CFU reduction from baseline.
Note: Shaded cells indicate percent probabilities of PK/PD target attainment ≥90%.
Abbreviations: AUC, area under the curve; CFU, colony forming units; CLcr, creatinine clearance; DUR, durlobactam; ELF, epithelium lining fluid; IV, intravenous; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; q4h, every 4 hours; q6h, every 6 hours; SUL, sulbactam; %T > MIC; percent of time free drug remains above the minimum inhibitory concentration

***Comment 3. Please justify the use of CLcr (mL/min) for the proposed label rather than eGFR (mL/min/1.73m2) criteria.***

*The Applicant proposed to adjust the dosing regimen of SUL-DUR for patients with renal impairment based on CLcr (mL/min) sub-groups. An information request was sent to the Applicant on 01/19/2023 requesting justification for using CLcr as the criterion rather than eGFR as for this subgroup population. According to the Applicant, eGFR values (mL/min/1.73m$^2$) were used to categorize subjects with different degrees of renal impairment in the renal impairment study. While in the population PK analyses, CLcr was calculated using the Cockcroft-Gault equation to determine renal function for all subjects included in the model. Since CLcr is used in the population PK model for deriving SUL-DUR exposures, as well as subsequent PTA analyses, the reviewer determined that using CLcr as the criterion for dosage adjustment by degree of renal impairment is acceptable.*

## 14.6. Pharmacogenetics

N/A

# 15. Study/Trial Design

This section provides additional details on the design of study CS2514-2017-0004 that are not included in Section 6 of the review.

**Part A-Specific Inclusion Criteria**

In addition to the general inclusion criteria above, patients may enroll in Part A if they meet the criteria below. All patients must be categorized in 1 infection type that is judged to be the primary infection by the Investigator:

Diagnosed with HABP, VABP, VP, and/or bacteremia, defined as:

**Table 141. HABP With ABC in Sputum/Respiratory Sample**

| All of the Following | And Signs or Symptoms Evidenced by at Least Two of the Following | And at Least One of the Following |
|---|---|---|
| • Onset of symptoms >48 hours after admission or ≥7 days after discharge from an inpatient acute or chronic care facility (e.g., LTAC, rehabilitation center, hospital, or skilled nursing home);<br>OR<br>• Admission from LTAC or rehabilitation center, or admission from home <7 days after discharge from an LTAC or rehabilitation center;<br>AND<br>• New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours. | • A new onset of cough (or worsening of baseline cough);<br>• Auscultatory findings consistent with pneumonia/pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony);<br>• Dyspnea, tachypnea, or respiratory rate >25 breaths/minute;<br>OR<br>• Hypoxemia (oxygen saturation <90% or pO2<60 mmHg while breathing room air, or worsening of the oxygen saturation/ FiO2);<br>OR the following alone:<br>• New onset need for mechanical ventilation. | • Fever[1] (oral or tympanic temperature ≥38$^0$C<br>• [≥100.4$^0$F] or rectal/core temperature ≥38.3°C [≥100.9°F]);<br>OR<br>• Hypothermia (rectal/core temperature <35°C [<95°F]);<br>• Elevated total peripheral WBC count (>10,000/mm$^3$);<br>• >15% 15% immature neutrophils (bands) regardless of total peripheral WBC count;<br>OR<br>• Leukopenia (total WBC count <4500/mm$^3$). |

Source: Table under Section 4.1.2 of protocol amendment 3, version 4.0.
[1] Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; CT, computed tomography; FiO2, fraction of inspired oxygen; HABP, hospital-acquired bacterial pneumonia; LTAC, long-term acute care; MRI, magnetic resonance imaging; pO2, partial pressure of oxygen; WBC, white blood cell

**Table 142. VABP With ABC in Sputum/Respiratory Sample**

| All of the Following | And Signs or Symptoms Evidenced by at Least Two of the Following | And at Least One of the Following |
|---|---|---|
| • Onset of symptoms >48 hours after receiving ventilator support via an endotracheal (or nasotracheal) tube;<br>• Requires ventilator support;<br>AND<br>• New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization.<br><br>Note: If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours. | • Auscultatory findings consistent with pneumonia/pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony);<br>• An acute change in the ventilator support system to enhance oxygenation, as determined by a worsening oxygen saturation/$FiO_2$ ratio;<br>• Increased suctioning;<br>OR<br>• Tracheal aspirate change to purulence. | • Fever[1] (oral or tympanic temperature ≥$38^0$C<br>• [≥$100.4^0$F] or rectal/core temperature ≥$38.3^0$C [≥100.9°F])<br>OR<br>• Hypothermia (rectal/core temperature <35°C [<95°F]);<br><br>• Elevated total peripheral WBC (>10,000/$mm^3$);<br>• >15% immature neutrophils (bands) regardless of total peripheral WBC count;<br><br>OR<br>• Leukopenia (total WBC <4500/$mm^3$). |

Source: Table under Section 4.1.2 of protocol amendment 3, version 4.0.
[1] Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; CT, computed tomography; FiO2, fraction of inspired oxygen; MRI, magnetic resonance imaging; VABP, ventilator-associated bacterial pneumonia; WBC, white blood cell

**Table 143. VP With ABC in Respiratory Sample**

| All of the Following | And Signs or Symptoms Evidenced by at Least Two of the Following | And at Least One of the Following |
|---|---|---|
| • Requires ventilator support;<br>AND<br>• New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization.<br><br>Note: If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours. | • Auscultatory findings consistent with pneumonia/pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony);<br>• An acute change in the ventilator support system to enhance oxygenation;<br>• Increased suctioning;<br>OR<br>• Tracheal aspirate change to purulence. | • Fever[1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F])<br>OR<br>• Hypothermia (rectal/core temperature <35°C [<95°F]);<br><br>• Elevated total peripheral WBC count (>10,000/mm$^3$);<br>• >15% immature neutrophils (bands) regardless of total peripheral WBC count;<br>OR<br>• Leukopenia (total WBC count <4500/mm$^3$). |

Source: Table under Section 4.1.2 of protocol amendment 3, version 4.0.
[1] Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; CT, computed tomography; MRI, magnetic resonance imaging; Vp, ventilator pneumonia; WBC, white blood cell

**Table 144. Bacteremia With ABC**

| All of the Following | And at Least One of the Following |
|---|---|
| • Isolation of ABC from at least 1 blood culture collected from a peripheral vein OR newly placed intravenous line. | • Fever[1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]);<br>• Elevated total peripheral WBC count (>10,000/mm$^3$);<br>• >15% immature neutrophils (bands) regardless of total peripheral WBC count;<br>• Leukopenia (total WBC count <4500/mm$^3$);<br>• Tachycardia >100 bpm;<br>• Tachypnea >25 breaths/minute;<br>OR<br>• Hypotension, systolic <90 mmHg. |

Source: Table under Section 4.1.2 of protocol amendment 3, version 4.0.
[1] Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; bpm, beats per minute; WBC, white blood cell.

Enrollment of HABP, VP, and bacteremia patients will be limited to a total of no more than 40% of patients in Part A, regardless of resistance.

**Part B-Specific Inclusion Criteria**

Part B is an open label portion of the study that includes patients with the following ABC infections: HABP, VABP, VP, or bacteremia who do not qualify for Part A, and cUTI/AP or surgical or post-traumatic wound infections.

- Patients with HABP, VABP, VP, or bacteremia should be considered for enrollment in Part B if they meet ANY of the following criteria (*a*, *b*, *c,* OR *d*), in addition to the general inclusion criteria above:

  (a) Has an infection caused by ABC organisms known to be resistant to colistin or polymyxin B (defined as MIC ≥4 mg/L by a nonagar-based method);

  - For known colistin- or polymyxin B-resistant infections, the following must be satisfied:
  - Has a known resistant infection based on evidence from culture and susceptibility testing by a nonagar-based method within 72 hours prior to randomization, alone or as a single organism of a polymicrobial infection; AND has received no more than 48 hours of an antimicrobial agent to which the ABC is susceptible prior to the first dose of study drug; or
  - Has documented clinical evidence of failure (i.e., clinical deterioration or failure to improve that is attributable to ABC infection) after at least 48 hours of treatment with colistin or polymyxin B; OR

  (b) Has known intolerance to colistin;

  - Note: Patients whom the Investigator feels may have a potential intolerance to colistin can be enrolled in Part B on a case-by-case basis after discussion with the Medical Monitor; OR

  (c) Has myasthenia gravis or another neuromuscular syndrome(s) that contraindicates colistin and is not ventilated;

  - Note: Ventilated patients with myasthenia gravis or other neuromuscular syndromes where, in the opinion of the Investigator, colistin administration is reasonable are permitted for consideration for the study; OR

  (d) Has acute kidney injury and is receiving renal replacement therapy at study entry;

- Patients diagnosed with cUTI, AP, or surgical or post-traumatic wound infections may enroll in Part B if they meet the general inclusion criteria as well as either *a*, *b*, *c*, *d*, OR *e* in addition to the indication requirements for *f*:

  (a) Has an infection caused by ABC organisms known to be resistant to colistin or polymyxin B (defined as MIC ≥4 mg/L by a nonagar-based method); OR

  (b) Has known intolerance to colistin;

- Note: Patients whom the Investigator feels may have a potential intolerance to colistin can be enrolled in Part B on a case-by-case basis after discussion with the Medical Monitor; OR

(c) Has myasthenia gravis or another neuromuscular syndrome(s) that contraindicates colistin; OR

(d) Has acute kidney injury and is receiving renal replacement therapy at study entry; OR

(e) Has documented clinical evidence of failure (i.e., clinical deterioration or failure to improve) after at least 48 hours of treatment with a polymyxin-based regimen; AND

(f) Is diagnosed with cUTI, AP, or surgical or post-traumatic wound infection, defined as:

**Table 145. cUTI With ABC**

| At Least 1 of the Following | And at Least 2 of the Following Signs and Symptoms | And at Least 1 of the Following |
|---|---|---|
| • Indwelling urinary catheter or intermittent bladder catheterization;<br>• Neurogenic bladder with presence or history of urine residual volume of ≥100 mL;<br>• Obstructive uropathy (e.g., nephrolithiasis, tumor, fibrosis) that is expected to be medically or surgically treated within 48 hours postrandomization;<br>• Azotemia due to intrinsic renal disease;<br>OR<br>• Urinary retention in men due to previously diagnosed benign hypertrophy. | • Chills, rigors, or fever[1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]);<br>• Elevated WBC count (>10,000/mm$^3$) or left shift (>15% immature PMNs);<br>• Nausea or vomiting;<br>• Dysuria, increased urinary frequency, or urinary urgency;<br>OR<br>• Lower abdominal pain or pelvic pain. | • Positive LCE on urinalysis;<br>• WBC count ≥10 cells/mm$^3$ in unspun urine;<br>OR<br>• WBC count ≥10 cells/hpf in urine sediment. |

Source: Table under Section 4.1.3 of protocol amendment 3, version 4.0.
[1] Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; cUTI, complicated urinary tract infection; hpf, high-power field; LCE, leukocyte esterase; PMN, polymorphonuclear leukocyte; WBC, white blood cell

**Table 146. AP With ABC**

| Presence of an Ascending Tract Infection Including at Least 2 of the Following Signs or Symptoms | And at Least 1 of the Following |
|---|---|
| • Chills, rigors, or fever[1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]);<br>• Elevated WBC count (>10,000/mm$^3$) or left shift (>15% immature PMNs);<br>• Nausea or vomiting;<br>• Dysuria, increased urinary frequency, or urinary urgency;<br>• Flank pain;<br>OR<br>• Costovertebral angle tenderness on physical examination. | • Positive LCE on urinalysis;<br>• WBC count ≥10 cells/mm$^3$ in unspun urine;<br>OR<br>• WBC count ≥10 cells/hpf in urine sediment. |

Source: Table under Section 4.1.3 of protocol amendment 3, version 4.0.
[1] Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; AP, acute pyelonephritis; hpf, high-power field; LCE, leukocyte esterase; PMN, polymorphonuclear leukocyte; WBC, white blood cell

**Table 147. Surgical Wound Infection With ABC**

| Superficial SSI Meeting all of the Following Criteria | And at Least 1 of the Following Regional or Systemic Signs of Infection |
|---|---|
| • Follows clean surgery (elective, not emergency, nontraumatic, primarily closed, no acute inflammation; no break in technique; respiratory, gastrointestinal, biliary, and genitourinary tracts not entered);<br>• Involves only the skin or subcutaneous tissue around the incision, does not involve fascia;<br>• Occurs within 30 days after procedure;<br>• Original surgical incision ≥3 cm;<br>AND<br>• Purulent drainage (spontaneous or therapeutic) that is positive for ABC by culture with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 $cm^2$. | • Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI;<br>• Fever[1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]);<br>OR<br>• Hypothermia (rectal/core temperature <35°C [<95°F]);<br>• WBC count >10,000/$mm^3$ or <4000/$mm^3$;<br>OR<br>• >15% immature neutrophils. |

Source: Table under Section 4.1.3 of protocol amendment 3, version 4.0.
[1] Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; ABSSSI, acute bacterial skin and skin structure infection; SSI, systemic sign of infection; WBC, white blood cell

**Table 148. Post-Traumatic Wound Infection With ABC**

| Post-Traumatic Wound (Including Penetrating Trauma) Characterized by the Following Within 24 Hours of Screening | And at Least 1 of the Following Regional or Systemic Signs of Infection |
|---|---|
| • Purulent drainage (spontaneous or therapeutic) that is positive for ABC by culture with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 $cm^2$. | • Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI;<br>• Fever[1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]);<br>OR<br>• Hypothermia (rectal/core temperature <35°C [<95°F]);<br>• WBC count >10,000/$mm^3$ or <4000/$mm^3$;<br>OR<br>• >15% immature neutrophils. |

Source: Table under Section 4.1.3 of protocol amendment 3, version 4.0.
[1] Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; ABSSSI, acute bacterial skin and skin structure infection; WBC, white blood cell

**Efficacy Variables**

The primary efficacy endpoint for the study is 28-day all-cause mortality in the CRABC m-MITT Population in Part A.

The secondary efficacy endpoints for Part A and Part B include the following:

- 28-day all-cause mortality in the intent-to-treat (ITT) Population;
- Clinical cure at TOC in the CRABC m-MITT Population;
- OC in the m-MITT, clinical evaluable (CE), microbiologic evaluable (ME), and CRABC ME Populations;
- Clinical cure at Day 5, Day 7, EOT, and LFU in the m-MITT, CRABC m-MITT, CE, ME, and CRABC ME Populations;
- Microbiological favorable assessment at Day 5, Day 7, EOT, TOC, and LFU in the m-MITT, CRABC m-MITT, ME, and CRABC ME Populations;
- 14-day all-cause mortality in the CRABC m-MITT and m-MITT Populations;
- 28-day all-cause mortality in the m-MITT and CRABC ME Populations; and
- PK exposure of ETX2514 and sulbactam in the PK population.

The exploratory efficacy endpoints include the following:

- Clinical cure based on PK exposure;
- Clinical cure based on MIC distribution of ETX2514SUL;
- Clinical cure based on baseline resistance to ETX2514SUL, carbapenems, or colistin;
- Number of days in the intensive care unit;
- Number of patients transferred to the intensive care unit;
- For patients with VABP, VP, or ventilated HABP, number of days on ventilators;
- Number of days in the hospital; and
- Number of days on study drug treatment.

**Outcome Definitions**

Clinical Outcome

Clinical outcome will be used to determine a response of clinical success for all patients. Based on the assessment of signs and symptoms, the unblinded Investigator will choose 1 of the following clinical outcomes at the Day 5, Day 7, EOT Visit, TOC Visit, LFU Visit, and early termination Visit, if applicable. In Part A, in addition to the unblinded Investigator, a blinded assessor will also determine clinical outcome. If there is a discrepancy between the assessment of the blinded assessor and unblinded Investigator, the assessment from the blinded assessor will be used. If there is a missing assessment from either the blinded assessor or unblinded Investigator, the other available assessment will be used. An adjudication committee may be organized for endpoint adjudication should it be deemed necessary by the DSMB. In such a case, a charter will be developed that describes their activities.

Clinical cure: Complete resolution or significant improvement of signs and symptoms that were present at baseline and no new symptoms, such that no additional gram-negative antimicrobial therapy is warranted.

Clinical failure: Symptoms present at study entry have not significantly improved or completely resolved, or new symptoms have developed and require the initiation of a nonstudy Gram negative antibacterial drug therapy, death, or intolerance to study drug leading to discontinuation from the study treatment.

Clinical indeterminate: Determination cannot be made because of missing data, or the subject is lost to follow-up.

Microbiologic Outcome

*Microbiologic outcome for bacteremia, complicated urinary tract infection, or acute pyelonephritis:*

For subjects with bacteremia, cUTI, or AP, per-patient microbiological response will be determined programmatically as 1 of the following outcomes based on the results of blood and/or urine cultures at the Day 5, Day 7, EOT, TOC, and LFU Visits. A microbiological favorable assessment will include eradication and presumed eradications, as detailed below.

Microbiologic eradication:

- For subjects with cUTI or AP: the baseline strain of ABC is reduced to <103 CFU/mL on urine culture and negative on repeat blood culture (if positive at baseline); or
- For subjects with bacteremia: absence of the baseline strain of ABC on culture.

Microbiologic presumed eradication: No culture was done, and the patient meets clinical criteria for clinical cure.

Microbiologic persistence:

- For subjects with cUTI or AP: the demonstration that the urine culture grew $\geq 10^3$ CFU/mL of the baseline strain of ABC identified at study entry and/or a blood culture demonstrates the same baseline pathogen(s); or
- For patients with bacteremia: presence of the baseline strain of ABC on repeat culture. Subjects who are a persistence at EOT will be considered a persistence at TOC.

Microbiologic presumed persistence: No culture was done, and the patient meets clinical criteria for clinical failure.

Microbiologic indeterminate: if clinically indicated (for cUTI and bacteremia only), no follow-up culture is available, the culture cannot be interpreted for any reason, or the culture is considered contaminated.

Microbiologic recurrence:

- For subjects with cUTI or AP: the demonstration that the urine culture grew $\geq 10^3$ CFU/mL of the baseline strain of ABC identified at study entry at any time after documented eradication at the TOC Visit up to and including the LFU Visit; or
- For subjects with bacteremia: a positive blood culture for ABC at any time after documented eradication at the TOC Visit up to and including the LFU Visit.

*Microbiologic outcome for hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, ventilated pneumonia, or surgical or post-traumatic wound infections:*

Microbiologic presumed eradication: No culture was done, and the patient meets clinical criteria for clinical cure. For patients with HABP/VABP/VP or surgical or post-traumatic wound infections, where repeat culture samples may not be indicated, presumed eradication based on clinical improvement will be inferred.

Microbiologic presumed persistence: No culture was done, and the subject meets clinical criteria for clinical failure.

**Safety Variables**

The safety parameters include the incidence, severity, causality, and seriousness of treatment-emergent adverse events (TEAEs) and adverse events of special interest, including nephrotoxicity as measured by RIFLE criteria, and the evaluation of changes from baseline in safety laboratory test results, electrocardiograms (ECGs), vital signs, physical examinations, and chest X-ray/radiology/ultrasound and mechanical ventilator assessments for patients with HABP, VABP, or VP. Newly emergent infections that appear after baseline will be reported as adverse events and summarized separately.

**Analyses Populations**

The ITT Population will include all subjects randomized to study drug treatment (ETX2514SUL plus imipenem/cilastatin or colistin plus imipenem/cilastatin) in Part A or enrolled in Part B, regardless of whether the subject actually receives study drug.

The Modified ITT (MITT) Population will include subjects in Parts A and B who meet ITT criteria and receive any amount of study drug. The MITT Population will be considered the Safety Population. Subjects with HABP/VABP/VP who were randomized to Part A on the basis of a BPP rapid test result but were subsequently withdrawn due to a lack of a culture growing ABC will be counted in the MITT and Safety Populations.

The m-MITT Population will include patients who meet MITT criteria and have an ABC organism isolated as the qualifying culture specimen, as confirmed by the central and/or local microbiology laboratory. If an isolate for testing at the central laboratory is not available, the local laboratory data can be used to confirm the presence of ABC organism, as long as the local laboratory uses modern methods of diagnosis such as molecular-based tests, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, Vitek, Phoenix, etc. (i.e., not conventional biochemical or manual phenotypic methods). Patients with HABP/VABP/VP who are enrolled based upon a positive BPP rapid test for ABC, but subsequently are found to have respiratory sample cultures that do not grow ABC (by the local laboratory), will be withdrawn from the study drug treatment. These subjects will not be included in the m-MITT Population but will remain in the MITT Population.

The CRABC m-MITT Population will include subjects who meet m-MITT criteria and have a baseline ABC organism that is confirmed to be carbapenem-resistant (MIC to

imipenem/meropenem ≥8 mg/L) by the central laboratory or by the local laboratory if the central laboratory is not able to identify the isolate for any reason. Subjects will be excluded from the CRABC m-MITT Population if they have isolates that are deemed by the central laboratory to be resistant to ETX2514SUL (MIC >4 mg/L) or colistin (MIC ≥4 mg/L), if their blood culture or respiratory samples are collected more than 72 hours prior to randomization, if they are transferred from Part A to Part B, or if they are enrolled with infections other than ABC pneumonia or bloodstream infection (i.e., ABC infections other than HABP, VABP, VP, and bacteremia). A sensitivity analysis for the primary efficacy endpoint will be performed for patients whose eligible culture is >48 hours from the first dose of study drug, as well as for all patients with and without evidence of nonsusceptibility to colistin and ETX2514SUL at baseline.

The CE Population will include patients who meet m-MITT criteria and meet evaluability criteria (meet key inclusion criteria, do not have key exclusion criteria, received at least 72 hours of study drug [i.e., 12 doses of ETX2514SUL plus 12 doses of imipenem/cilastatin or 6 doses of colistin plus 12 doses of imipenem/cilastatin in patients without dose adjustments] to be a clinical cure, received at least 48 hours of study drug [i.e., 8 doses of ETX2514SUL plus 8 doses of imipenem/cilastatin or 4 doses of colistin plus 8 doses of imipenem/cilastatin in subjects without dose adjustments] to be a clinical failure, received ≥80% of anticipated doses, and did not have a clinical response of indeterminate at the TOC Visit).

The ME Population will include subjects who meet m-MITT criteria and CE criteria and have an appropriately collected culture specimen and interpretable culture result when specimen collection is clinically indicated at the TOC Visit.

The CRABC ME Population will include subjects who meet ME criteria and who have a baseline ABC organism that is confirmed to be carbapenem-resistant (and susceptible to ETX2514SUL for Parts A and B and susceptible to colistin for Part A).

The PK Population will include subjects who receive any amount of study drug and have evaluable PK data.

**Efficacy**

The primary efficacy endpoint for the study is 28-day all-cause mortality in the CRABC m-MITT Population in Part A. Subjects in the CRABC m-MITT Population who discontinue study drug prematurely in Part A for any reason will be included in the assessment of 28-day all-cause mortality, provided consent has not been withdrawn.

A sensitivity analysis for the primary efficacy endpoint will be performed for subjects whose eligible culture is >48 hours from the first dose of study drug, as well as for all subjects with and without evidence of nonsusceptibility to colistin and ETX2514SUL at baseline.

The noninferiority assessment will be based on the 2-sided 95% confidence intervals (CIs) for the difference ([ETX2514SUL + imipenem/cilastatin] – [colistin + imipenem/cilastatin]) in 28-day all-cause mortality rates between the treatment groups. Noninferiority will be concluded if the upper limit of the 2-sided 95% CI is less than +20%.

If noninferiority is achieved, a test of superiority will be performed.

The analysis of the primary efficacy endpoint 28-day all-cause mortality will also be performed in the ITT Population.

The number and percentage of subjects in each response category for the secondary efficacy endpoints will be summarized by treatment group for the populations defined earlier. Two-sided 95% CIs for the difference in outcome rates between the treatment groups in Part A will be provided.

Part B data will be analyzed separately from Part A using descriptive statistics.

Further subgroup analyses will be conducted, and details of the analysis will be described in the Statistical Analysis Plan.

Exploratory endpoint analysis will be described in the Statistical Analysis Plan. Exploratory endpoints for health resource utilization difference between treatment groups (such as length of ventilation, intensive care unit stay, hospitalization, additional antibiotic use, etc.) will be reported separately. Efficacy analysis for subjects with HABP/VABP/VP who are identified as positive for ABC by BPP molecular methodology will be explored.

**Pharmacokinetics**

Descriptive statistics will be provided for PK concentration data and PK parameters. All PK analyses will be performed using the PK Population.

For the intense PK group, PK samples will be obtained from the first approximately 30 subjects randomized in Part A. The PK samples will be collected for both treatment groups in Part A to keep the study data blinded. The PK samples obtained from the ETX2514SUL group will be analyzed for ETX2514 and sulbactam concentrations using a validated assay by a central bioanalytical laboratory. Pharmacokinetic assessment of the initial 15 subjects on ETX2514SUL in Part A will be performed by an independent PK assessor, prior to the opening of enrollment in Part B. The independent PK assessor will conduct sequential PK analysis from patients as they are enrolled. An initial aggregate assessment of PK parameters will be done after enrollment of the first 8 HABP/VABP/VP subjects randomized to ETX2514SUL. The independent PK assessor will report results to the DSMB, relative to concentrations projected in the population PK model, once data from all 15 subjects on ETX2514SUL is available. However, if the preliminary analysis of the first 8 subjects with HABP/VABP/VP on ETX2514SUL reveals evidence of inadequate exposure this will be escalated to the DSMB.

The intense PK sampling will also be performed on the first approximately 20 subjects randomized in Part A from China Mainland sites. The PK samples obtained from subjects who have received the ETX2514SUL treatment will be analyzed for ETX2514 and sulbactam concentrations, which will be applied to build the population PK model combined with data from the sparse PK group.

For the sparse PK group, PK samples will be obtained from all other subjects enrolled in the study (Parts A and B), which will be used to better inform the population PK model.

Analysis of the PK data and incorporation into the population PK analysis and PK/ /pharmacodynamic model will be described in a separate PK Analysis Plan.

**Safety**

All subjects who receive any amount of study drug (MITT Population) will be included in the safety analyses. Subjects who received the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received.

A primary analysis of safety will be performed for Part A to assess the proportion of subjects with nephrotoxicity, as measured by the RIFLE criteria based on the Safety and CE Populations.

Overall safety will be assessed for Part A and Part B in the Safety Population. The number and percentage of subjects in each treatment group reporting at least 1 occurrence of a TEAE for each unique system organ class and preferred term will be tabulated. A TEAE is defined as an adverse event occurring on or after the administration of the first dose of study drug. Treatment-emergent adverse events will also be tabulated by treatment group, severity, and the relationship to study drug as assessed by the Investigator. The number and percentage of subjects in each treatment group reporting at least 1 occurrence of a treatment-emergent serious adverse event will be tabulated. The number and percentage of subjects (in each treatment group) prematurely discontinuing study drug treatment due to a TEAE will be tabulated by system organ class and preferred term. Adverse events of special interest in Part A will be summarized for all subjects by treatment.

Safety laboratory data will be presented by descriptive statistics of the postbaseline value and the change from baseline, as well as the number and percentage of subjects with potentially clinically significant laboratory values. Descriptive statistics of vital signs and electrocardiogram parameters and the change from baseline will also be presented. An outlier analysis of the electrocardiogram parameters will be conducted.

**Sample Size Determination**

Subjects will be enrolled until there are 120 subjects in the CRABC m-MITT Population in Part A. The study will have 80% power to demonstrate noninferiority between Group 1 and Group 2 using a 20% noninferiority margin and a 2-sided 95% CI. This assumes a mortality rate in the comparator group (Group 2) of 41% and in the ETX2514SUL group (Group 1) of 36%. To have 120 patients in the CRABC m-MITT Population, Part A will need to enroll approximately 200 subjects, assuming 60% of ABC clinical isolates are carbapenem-resistant. Patient enrollment in Part B (Group 3) will continue until Part A enrollment in the CRABC m-MITT Population is complete. Rates of carbapenem resistance among isolates from Part A patients will be monitored by the unblinded data manager/designee at the Clinical Research Organization on an ongoing basis.

Sites: Approximately 100 global sites

# 16. Efficacy

This section includes additional information on assessment of efficacy for study CS2514-2017-0004.

The numbers of subjects in each analysis population and the reasons for their exclusion from the ITT population are displayed in Table 149.

**Table 149. Analysis Populations and Reasons for Exclusion From ITT Population, CS2514-2017-0004 Part A**

| Analysis Populations and Reasons for Exclusion From ITT Population | SUL-DUR N (%) | Colistin N (%) | Total N (%) |
|---|---|---|---|
| *ITT population* | 92 (100) | 89 (100) | 181 (100) |
| *MITT population* | 91 (98.9) | 86 (96.6) | 177 (97.8) |
| Subjects in ITT excluded from MITT population | 1 (1.1) | 3 (3.4) | 4 (2.2) |
| Not receiving study drug | 1 (1.1) | 3 (3.4) | 4 (2.2) |
| *m-MITT population* | 78 (84.8) | 79 (88.8) | 157 (86.7) |
| Subjects in ITT excluded from m-MITT population | 14 (15.2) | 10 (11.2) | 24 (13.2) |
| Not receiving study drug (not in MITT population) | 1 (1.1) | 3 (3.4) | 4 (2.2) |
| No baseline ABC organism from qualifying culture specimen | 13 (14.1) | 7 (7.9) | 20 (11.0) |
| BPP positive but culture negative | 12 (13.0) | 5 (5.6) | 17 (9.4) |
| ABC isolates outside 72-hour window prior to randomization | 3 (3.3) | 0 (0) | 3 (1.7) |
| *CRABC m-MITT population* | 64 (69.6) | 64 (71.9) | 128 (70.7) |
| Subjects in ITT excluded from CRABC m-MITT population | 28 (30.4) | 25 (28.1) | 53 (29.3) |
| Not in MITT population | 14 (15.2) | 10 (11.2) | 24 (13.3) |
| Baseline ABC organism not carbapenem-resistant | 4 (4.3) | 4 (4.5) | 8 (4.4) |
| Baseline ABC organism resistant to SUL/DUR | 2 (2.2) | 4 (4.5) | 6 (3.3) |
| Baseline ABC organism resistant to colistin | 8 (8.7) | 7 (7.9) | 15 (8.3) |
| Transferred from Part A to Part B | 1 (1.1) | 1 (1.1) | 2 (1.1) |
| *CE population* | 68 (73.9) | 59 (66.3) | 127 (70.2) |
| Subjects in ITT excluded from CE population | 24 (26.1) | 30 (33.7) | 54 (29.8) |
| Not in m-MITT population | 14 (15.2) | 10 (11.2) | 34 (18.8) |
| Received <72 hours of study drug for clinical cure or <48 hours of study drug for clinical failure | 3 (3.3) | 7 (7.9) | 10 (5.5) |
| Received <80% of anticipated doses | 4 (4.3) | 11 (12.4) | 15 (8.3) |
| Clinical response of indeterminate at TOC visit | 4 (4.3) | 3 (3.4) | 7 (3.9) |
| *ME population* | 59 (64.1) | 52 (58.4) | 111 (61.3) |
| Subjects in ITT excluded from ME population | 33 (35.9) | 37 (41.6) | 70 (38.7) |
| Not in m-MITT population | 14 (15.2) | 10 (11.2) | 24 (13.3) |
| Not in CE population | 24 (26.1) | 30 (33.7) | 54 (29.8) |
| No appropriately collected culture specimen at TOC visit | 7 (7.6) | 6 (6.7) | 13 (7.2) |
| Did not have an interpretable culture result at TOC visit | 3 (3.3) | 2 (2.2) | 5 (2.8) |
| *CRABC ME population* | 46 (50.0) | 44 (49.4) | 90 (49.7) |
| Subjects in ITT excluded from CRABC ME population | 46 (50.0) | 45 (50.6) | 91 (50.3) |
| Not in CRABC m-MITT population | 28 (30.4) | 25 (28.1) | 53 (29.3) |
| Not in ME population | 33 (35.9) | 37 (41.6) | 70 (38.7) |

Source: Tables 11 and 14.1.3.2 in the CS2514-2017-0004 Clinical Study Report.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; BPP, Biofire FilmArray 2.0 Pneumonia Panel; CE, clinically evaluable; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; ME, microbiologically evaluable; MITT, modified intent-to-treat; m-MITT, microbiologically modified intent-to-treat; N, number of subjects; SUL, sulbactam; TOC, test-of-cure

# 16.1. Demographic and Baseline Characteristics

**Table 150. Demographic and Baseline Characteristics, CS2514-2017-0004 Part A CRABC m-MITT Population**

| Characteristic | SUL-DUR (N=64) | Colistin (N=64) | All (N=128) |
|---|---|---|---|
| Age | | | |
| Mean (SD) | 61.6 (16.1) | 65.1 (17.0) | 63.4 (16.6) |
| Median | 62 | 66 | 63 |
| Minimum, maximum | 25, 91 | 19, 98 | 19, 98 |
| Age group, n (%) | | | |
| <65 years | 36 (56.3) | 31 (48.4) | 67 (52.3) |
| 65 to 75 years | 16 (25.0) | 12 (18.8) | 28 (21.9) |
| >75 years | 12 (18.8) | 21 (32.8) | 33 (25.8) |
| Gender, n (%) | | | |
| Male | 46 (71.9) | 49 (76.6) | 95 (74.2) |
| Female | 18 (28.1) | 15 (23.4) | 33 (25.8) |
| Race, n (%) | | | |
| American Indian or Alaska Native[1] | 4 (6.3) | 2 (3.1) | 6 (4.7) |
| Asian | 23 (35.9) | 34 (53.1) | 57 (44.5) |
| Chinese | 22 (34.4) | 29 (45.3) | 51 (39.8) |
| Non-Chinese | 1 (1.6) | 4 (6.3) | 5 (3.9) |
| Black or African American | 0 (0.0) | 1 (1.6) | 1 (0.8) |
| White | 36 (56.3) | 27 (42.2) | 63 (49.2) |
| Other | 1 (1.6) | 0 (0.0) | 1 (0.8) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 9 (14.1) | 9 (14.1) | 18 (14.1) |
| Not Hispanic or Latino | 54 (84.4) | 55 (85.9) | 109 (85.2) |
| Not reported | 1 (1.6) | 0 (0.0) | 1 (0.8) |
| Region (a stratification factor at randomization), n (%) | | | |
| Mainland China | 15 (23.4) | 19 (29.7) | 34 (26.6) |
| Rest of the world | 49 (76.6) | 45 (70.3) | 94 (73.4) |
| United States | 1 (1.6) | 0 (0.0) | 1 (0.8) |
| Europe | 31 (48.4) | 21 (32.8) | 52 (40.6) |
| Latin America | 9 (14.1) | 9 (14.1) | 18 (14.1) |
| Asia–Pacific | 8 (12.5) | 15 (23.4) | 23 (18.0) |
| Type of infection (a stratification factor at randomization), n (%) | | | |
| Bacteremia | 2 (3.1) | 1 (1.6) | 3 (2.3) |
| HABP | 24 (37.5) | 31 (48.4) | 55 (43.0) |
| VABP | 38 (59.4) | 30 (46.9) | 68 (53.1) |
| VP | 0 (0.0) | 2 (3.1) | 2 (1.6) |
| Baseline BPP test and culture results for ABC in subjects infected with HABP/VABP/VP, n (%) | | | |
| Subjects infected with HABP/VABP/VP | 62 (96.9) | 63 (98.4) | 125 (97.7) |
| BPP positive and culture positive | 42 (65.6) | 42 (65.6) | 84 (65.6) |
| BPP positive and culture negative | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Culture positive only | 20 (31.3) | 21 (32.8) | 41 (32.0) |
| Subjects infected with bacteremia | 2 (3.1) | 1 (1.6) | 3 (2.3) |
| Baseline APACHE II score | | | |
| N | 59 | 57 | 116 |
| Mean (SD) | 16.4 (5.1) | 17.2 (5.2) | 16.8 (5.2) |
| Median | 16 | 16 | 16 |
| Minimum, maximum | 9, 28 | 5, 30 | 5, 30 |

| Characteristic | SUL-DUR (N=64) | Colistin (N=64) | All (N=128) |
|---|---|---|---|
| Baseline APACHE II score group, n (%) | | | |
| <10 | 1 (1.6) | 1 (1.6) | 2 (1.6) |
| 10-19 | 43 (67.2) | 37 (57.8) | 80 (62.5) |
| 20-30 | 15 (23.4) | 19 (29.7) | 34 (26.6) |
| Not available | 5 (7.8) | 7 (10.9) | 12 (9.4) |
| Baseline SOFA score, n (%) | | | |
| <7 | 5 (7.8) | 3 (4.7) | 8 (6.3) |
| 7-9 | 1 (1.6) | 6 (9.4) | 7 (5.5) |
| ≥10 | 2 (3.1) | 2 (3.1) | 4 (3.1) |
| Not available | 56 (87.5) | 53 (82.8) | 109 (85.2) |
| Baseline qSOFA score, n (%) | | | |
| <2 | 1 (1.6) | 0 (0.0) | 1 (0.8) |
| 2 | 7 (10.9) | 10 (15.6) | 17 (13.3) |
| 3 | 1 (1.6) | 1 (1.6) | 2 (1.6) |
| Not available | 55 (85.9) | 53 (82.8) | 108 (84.4) |
| Baseline APACHE II, SOFA, and qSOFA scores (a stratification factor at randomization), n (%) | | | |
| APACHE II score 10-19/SOFA score 7-9/ qSOFA score 2 | 47 (73.4) | 44 (68.8) | 91 (71.1) |
| APACHE II score 20-30/SOFA score ≥10/ qSOFA score 3 | 16 (25.0) | 20 (31.3) | 36 (28.1) |
| Not available | 1 (1.6) | 0 (0) | 1 (0.8) |
| Baseline mechanical ventilation status, n (%) | | | |
| Yes | 47 (73.4) | 50 (78.1) | 97 (75.8) |
| No | 17 (26.6) | 14 (21.9) | 31 (24.2) |
| Baseline creatinine clearance (mL/min) | | | |
| Mean (SD) | 127.52 (87.85) | 111.53 (68.70) | 119.52 (78.96) |
| Median | 114.0 | 104.5 | 107.5 |
| Minimum, maximum | 10.86, 397 | 20, 322 | 10.86, 397 |
| Baseline creatinine clearance (mL/min) group, n (%) | | | |
| <15 | 1 (1.6) | 0 (0.0) | 1 (0.8) |
| 15 to <30 | 5 (7.8) | 4 (6.3) | 9 (7.0) |
| 30 to <60 | 10 (15.6) | 13 (20.3) | 23 (18.0) |
| 60 to <90 | 9 (14.1) | 9 (14.1) | 18 (14.1) |
| ≥90 | 39 (60.9) | 38 (59.4) | 77 (60.2) |
| Baseline Charlson Comorbidity Index score | | | |
| Mean (SD) | 4.6 (3.2) | 4.8 (3.3) | 4.7 (3.3) |
| Median | 5.0 | 4.0 | 4.5 |
| Minimum, maximum | 0, 15 | 0, 16 | 0, 15 |
| Baseline Charlson Comorbidity Index group, n (%) | | | |
| <3 | 21 (32.8) | 19 (29.7) | 40 (31.3) |
| ≥3 | 43 (67.2) | 45 (70.3) | 88 (68.8) |
| Baseline septic shock status, n (%) | | | |
| Yes | 7 (10.9) | 12 (18.8) | 19 (14.8) |
| No | 57 (89.1) | 52 (81.3) | 109 (85.2) |
| Duration of ICU stay at baseline (days), n (%) | | | |
| No ICU stay | 21 (32.8) | 19 (29.7) | 40 (31.3) |
| <5 | 2 (3.1) | 3 (4.7) | 5 (3.9) |
| 5-14 | 23 (35.9) | 24 (37.5) | 47 (36.7) |
| >14 | 18 (28.1) | 18 (28.1) | 36 (28.1) |

| Characteristic | SUL-DUR (N=64) | Colistin (N=64) | All (N=128) |
|---|---|---|---|
| Received antibiotics within 24 hours prior to the first dose of study drug, n (%) | | | |
| Yes | 54 (84.6) | 60 (93.8) | 114 (89.1) |
| No | 10 (15.6) | 4 (6.3) | 14 (10.9) |
| Received antibiotics prior to the first dose of study drug, n (%) | | | |
| Yes | 62 (96.9) | 64 (100) | 126 (98.4) |
| No | 2 (3.1) | 0 (0.0) | 2 (1.6) |

Source: Table 12 in the CS2514-2017-0004 Clinical Study Report and the Statistical Reviewer.
[1]American Indian or Alaska Native referred to a person having origins in any of the original people of North, South, or Central America and who maintained tribal affiliation or community attachment. These subjects were identified as American Indian or Alaska Native, but they were in Peru rather than the United States.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; APACHE II, Acute Physiology and Chronic Health Evaluation II; BPP, Biofire FilmArray 2.0 Pneumonia Panel; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; m-MITT; microbiologically modified intent-to-treat; N, number of subjects; qSOFA, quick Sequential Organ Failure Assessment; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SUL, su bactam; VABP, ventilator-associated bacterial pneumonia; VP, ventilator pneumonia

Of note, the primary efficacy analysis included 125 subjects in the CRABC m-MITT population who did not withdraw consent prior to assessment of Day 28 survival status. The demographic and baseline characteristics for these 125 subjects will be presented in Section 14 of the labeling as follows:

The demographic and baseline characteristics were comparable between treatment groups among 125 subjects in the analysis: 74% male, 50% White, 44% Asian, and the mean age was 63 (±17) years. The majority of subjects had pneumonia as the baseline infection (53% VABP and 43% HABP); 2% had bacteremia. The mean APACHE II score at baseline was 17 and 26% of subjects had an APACHE II score ≥20. At randomization, 64% of subjects had been in the intensive care unit (ICU) ≥5 days; 26% of patients had been in the ICU for >14 days, and 75% were mechanically ventilated. Approximately 39% of patients had CLcr less than 90 mL/min at baseline. The mean duration of treatment was 9 days for the XACDURO group and 8 days for the colistin group.

## 16.2. FDA's Sensitivity Analyses for the Primary Efficacy Endpoint

Sensitivity analyses using the most conservative imputation were conducted in the CRABC m-MITT, m-MITT, and ITT populations. The imputation approach was that subjects who missed the survival status assessment at Day 28 or received a prohibited medication before Day 28 were considered events in the SUL-DUR group and nonevents in the colistin group. The imputation in each analysis population is detailed below:

- In the CRABC m-MITT population, two subjects with missing survival status at Day 28 due to withdrawal of consent or receipt of a prohibited medication were considered events in the SUL-DUR group, and two subjects with missing survival status at Day 28 due to withdrawal of consent in the colistin group were considered nonevents
- In the m-MITT population, two subjects with missing survival status at Day 28 due to withdrawal of consent or receipt of a prohibited medication were considered events in the

SUL-DUR group, and two subjects with missing survival status at Day 28 due to withdrawal of consent in the colistin group were considered nonevents

- In the ITT population, two subjects with missing survival status at Day 28 due to withdrawal of consent or receipt of a prohibited medication were considered events in the SUL-DUR group, and four subjects with missing survival status at Day 28 due to withdrawal of consent or loss to follow-up in the colistin group were considered nonevents

The results of the sensitivity analyses are displayed in Table 151. The upper limits of 95% CIs for treatment difference in the 28-day mortality rates were below 10% in all three populations, meeting both 20% and 10% NI margins.

**Table 151. Results of Sensitivity Analysis for 28-Day All-Cause Mortality in ITT, m-MITT, and CRABC ME Populations, CS2514-2017-0004 Part A**

| Analysis Population | SUL+DUR n/N (%) | Colistin n/N (%) | Treatment Comparison | |
|---|---|---|---|---|
| | | | Difference (%) | 95% CI[1] |
| CRABC m-MITT | 14/64 (21.9) | 20/64 (31.3) | −9.4 | (−26.2, 7.4) |
| m-MITT excluding two subjects transferred to Part B | 17/77 (22.1) | 25/78 (32.1) | −10.0 | (−25.2, 5.2) |
| m-MITT including two subjects transferred to Part B | 17/78 (21.8) | 25/79 (31.6) | −9.9 | (−24.9, 5.2) |
| ITT excluding two subjects transferred to Part B | 21/91 (23.1) | 27/88 (30.7) | −7.6 | (−21.7, 6.5) |
| ITT including two subjects transferred to Part B | 21/92 (22.8) | 27/89 (30.3) | −7.5 | (−21.5, 6.4) |

Source: Statistical Reviewer's analyses using ADSL.XPT, SS.XPT and ADTTE.XPT
[1] The 95% CI was calculated using continuity-corrected Z-statistics.
Abbreviations: CI, confidence interval; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; ITT, intent-to-treat; ME, microbiologically evaluable; m-MITT; microbiologically modified intent-to-treat; n, number of observed or imputed all-cause mortalities by Day 28; N, number of subjects in analysis; SUL, sulbactam

# 17. Clinical Safety

### Safety in Phase 1 Studies

A total of 209 subjects were exposed to SUL alone or in combination with DUR in phase 1 studies, including 123 subjects in the DUR only group and 72 subjects in the SUL-DUR group, Table 152.

**Table 152. Phase 1 Sulbactam and Durlobactam Studies**

| Study ID, Location, Dates | Design | Dosing Regimens | Population | No of Subjects |
|---|---|---|---|---|
| CS2514-2016-0001<br>Australia<br>12 Sep 2016 – 03 Aug 2017 | Single-center, randomized, double-blind, and placebo-controlled study in 4 parts (A, B, C, and D); SAD and MAD of DUR in combination with SUL and/or IMI/CIL | Part A: 8 cohorts with 8 subjects, 6 DUR and 2 placebo; DUR doses: 0.25 g, 0.5 g, 1.0 g, 2.0 g, 4.0 g, and 8.0 g IV over 3 h, (except 1 cohort receiving 1.0 g over 2 h)<br>Part B: 4 cohorts with 8 subjects, 6 given DUR and 2 placebo, DUR doses: 0.25 g, 0.5 g, 1.0 g, and 2.0 g over 3 h q6h for 8 days.<br>Part C: 2 cohorts with 8 subjects, 6 DUR and 2 placebo;<br>• DUR 1.0 g or placebo over 3 h on D1, SUL 1.0 g over 3 h on D3, and DUR 1.0 g or placebo plus SUL 1.0 g over 3 h at D5.<br>• DUR 1.0 g or placebo over 3 h on D1, IMI/CIL 0.5 g over 30 minutes on D3, DUR 1.0 g or placebo plus IMI/CIL 0.5 g over 30 minutes on D5, and DUR 1.0 g or placebo plus SUL 1.0 g over 3 h plus IMI/CIL 0.5 g over 30 min on D8.<br>Part D: 1 cohort with 12 subjects, 10 given DUR and 2 placebo; DUR 1.0 g or placebo plus SUL 1.0 g over 3 h plus IMI/CIL 0.5 g over 30 m q6h for 10 days with 1 dose administered on D11 | Healthy M and F subjects 18-55 years of age, with 8 subjects 65 or older also enrolled in Part A | 124<br>Part A: 64<br>Part B: 32<br>Part C: 16<br>Part D: 12 |
| CS2514-2017-0001<br>USA<br>21 Aug 2017 – 26 Oct 2017 | Multiple dose, open-label PK study to compare plasma, ELF, and AM concentrations of DUR and SUL | 3 doses of DUR 1.0 g and SUL 1.0 g infused over 3 h q6h with BAL samples taken at 1.0, 2.0, 2.5, 3.25, 4.0, or 6.0 h after the start of the third dose infusion. | Healthy M and F subjects 18-55 years of age | 30 |
| CS2514-2017-0002<br>USA<br>18 Sep 2017 – 29 May 2018 | Open-label, nonrandomized study evaluating PK of a single dose SUL-DUR in subjects with varying degrees of RI | Cohorts 1-3: Single dose of SUL 1.0 g and DUR 1.0 g infused over 3 h<br>Cohort 4: Single dose SUL 0.5 g and DUR 0.5 g infused over 3 h<br>Cohort 5: Two doses of SUL 0.5 g and DUR 0.5 g infused over 3 h with a week between doses | M and F subjects 18-70 years of age, BMI between 18-40 kg/m$^2$ that are healthy (Cohort 1) or have mild (Cohort 2), moderate (Cohort 3), severe (Cohort 4) RI, or ESRD on HD (Cohort 5) | 34<br>Cohort 1: 8<br>Cohort 2: 6<br>Cohort 3: 6<br>Cohort 4: 8<br>Cohort 5: 6 |

| Study ID, Location, Dates | Design | Dosing Regimens | Population | No of Subjects |
|---|---|---|---|---|
| CS2514-2018-0002<br>USA<br>28 Jun 2019 – 26 Jul 2019 | Open-label, single-dose, PK study to determine routes and excretion rates of radiolabel from 14C-DUR | Single IV dose of 1 g of nonlabeled DUR and 1 µCi of 14C-labeled DUR infused over 3 h | Healthy males, 18-55 years of age | 8 |
| CS2514-2018-0003<br>USA<br>10 Jun 2019 – 24 Jul 2019 | Phase 1, partially double-blind study conducted as placebo and active-controlled, single-infusion, 3-way crossover study to evaluate effects of supratherapeutic DUR plasma concentrations on QTc | Treatments in 6 randomized cohort sequences: ABC, ACB, BAC, BCA, CAB, and CBA.<br>Treatment A: Single IV dose of DUR 4 g infused over 3 h<br>Treatment B: Single IV dose of placebo for DUR infused over 3 h<br>Treatment C: Single IV dose of placebo for DUR infused over 3 h and a single oral dose of 400 mg open-label moxifloxacin given at the end of the infusion | Healthy M and F 18-55 years of age | 32 enrolled<br>ABC: 4, 1 subject discontinued<br>ACB: 5<br>BAC: 5<br>BCA: 5<br>CAB: 6<br>CBA: 5, 1 subject discontinued |
| ZL-2402-001<br>China<br>11 Aug 2020 – 26 Aug 2020 | Single-dose, open-label study to evaluate PK of SUL-DUR in Chinese subjects | All subjects received DUR 1.0 g and SUL 1.0 g as 3 h infusion in the morning on D1 | Healthy adult Chinese M and F 18-45 years of age | 12 |

Source: Adapted from 5.2 tabular listing of clinical studies, module 5, NDA 216974
Abbreviations: AM, alveolar macrophage; BAL, bronchoalveolar lavage; BMI, body mass index; DUR, Durlobactam; ELF, epithelial lining fluid; ESRD, end-stage renal disease; F, female; HD, hemodialysis; IMI/CIL, imipenem/cilastatin; IV, intravenous; M, male; MAD, multiple-ascending dose; PK, pharmacokinetics; QTc, corrected QT interval; q6h, every 6 hours; RI, resistive index; SAD, single-ascending dose; SUL, sulbactam

The mean age of subjects across groups in phase 1 studies was 31-36 years; the subjects were mostly males. In the DUR only group, serious adverse events (SAEs) and TEAEs leading to study discontinuation each were reported in 1 (0.8%) subject, and TEAEs leading to study drug discontinuation were reported in 3 (12.4%) subjects (anaphylaxis due to Brazil nuts, nausea with somnolence, nausea and infusion reaction). No subjects in the SUL-DUR or comparator groups had serious TEAEs or TEAEs leading to study or study drug discontinuation. No TEAEs leading to death occurred in healthy volunteers.

**Table 153. TEAE in Phase 1 Sulbactam and Durlobactam Studies**

| TEAE Category | DUR Only (N=123) n (%) | SUL-DUR (N=72) n (%) | Comparators (N=91) n (%) |
|---|---|---|---|
| TEAE | 56 (45.5) | 17 (23.6) | 33 (36.3) |
| Treatment-related TEAE | 39 (31.7) | 9 (12.5) | 20 (22.0) |
| Severe TEAE | 1 (0.8) | 0 | 0 |
| Treatment-related severe TEAE | 0 | 0 | 0 |
| Serious TEAE | 1 (0.8) | 0 | 0 |
| Serious treatment-related TEAE | 0 | 0 | 0 |
| TEAE leading to discontinuation from study drug | 3 (2.4) | 0 | 0 |
| TEAE leading to study discontinuation | 1 (0.8) | 0 | 0 |
| TEAE leading to death | 0 | 0 | 0 |

Source: Adapted from Table 10 Clinical Safety Summary, NDA 216974
Abbreviations: SUL-DUR, sulbactam-durlobactam; TEAE, treatment-emergent adverse event; n, number of subjects in category; N, number of subjects

Table 154 presents TEAE reported in ≥2% of subjects in phase 1 studies.

**Table 154. Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects in Any Durlobactam or Sulbactam-Durlobactam Treatment Group – All Phase 1 Healthy Volunteers Pool**

| System Organ Class<br>Preferred Term | DUR Only (N=123) n (%) | SUL-DUR (N=72) n (%) | Comparators (N=91) n (%) |
|---|---|---|---|
| Any TEAE | 56 (45.5) | 17 (23.6) | 33 (36.3) |
| Nervous system disorders | 21 (17.1) | 6 (8.3) | 14 (15.4) |
| Headache | 14 (11.4) | 3 (4.2) | 10 (11.0) |
| Dizziness | 5 (4.1) | 1 (1.4) | 1 (1.1) |
| Somnolence | 3 (2.4) | 0 | 1 (1.1) |
| Dysgeusia | 0 | 3 (4.2) | 0 |
| General disorders and administration site conditions | 19 (15.4) | 6 (8.3) | 9 (9.9) |
| Catheter site phlebitis | 10 (8.1) | 0 | 1 (1.1) |
| Catheter site pain | 2 (1.6) | 2 (2.8) | 0 |
| Fatigue | 2 (1.6) | 2 (2.8) | 4 (4.4) |
| Infusion site pain | 0 | 2 (2.8) | 1 (1.1) |
| Infections and infestations | 10 (8.1) | 5 (6.9) | 3 (3.3) |
| Upper respiratory tract infection | 5 (4.1) | 3 (4.2) | 2 (2.2) |
| Respiratory, thoracic, and mediastinal disorders | 9 (7.3) | 2 (2.8) | 2 (2.2) |
| Oropharyngeal pain | 3 (2.4) | 2 (2.8) | 2 (2.2) |
| Nasal congestion | 4 (3.3) | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 9 (7.3) | 3 (4.2) | 6 (6.6) |
| Back pain | 3 (2.4) | 0 | 1 (1.1) |
| Musculoskeletal pain | 0 | 2 (2.8) | 0 |

| System Organ Class<br>Preferred Term | DUR Only (N=123)<br>n (%) | SUL-DUR (N=72)<br>n (%) | Comparators (N=91)<br>n (%) |
|---|---|---|---|
| Skin and subcutaneous tissue disorders | 7 (5.7) | 3 (4.2) | 1 (1.1) |
| Rash | 2 (1.6) | 2 (2.8) | 0 |
| Vascular disorders | 5 (4.1) | 3 (4.2) | 1 (1.1) |
| Phlebitis | 4 (3.3) | 2 (2.8) | 1 (1.1) |

Source: Adapted from Table 15 Clinical Safety Summary, NDA 216974
Abbreviations: SUL-DUR, sulbactam-durlobactam; TEAE, treatment-emergent adverse event; n, number of subjects in category; N, number of subjects

The most commonly reported TEAEs in healthy volunteers treated with DUR or SUL-DUR were headache (9.3%), catheter site phlebitis (5.5%), upper respiratory tract infection (4.4%), and dizziness and phlebitis (each 3.3%). Headache was less common in the SUL-DUR group (4.2%) compared with the DUR only (11.4%). Catheter site phlebitis was not reported in the SUL-DUR group and was reported in 8.1% of subjects in the DUR only group and in 1.1% of subjects in the placebo group. Among, the adverse events of special interests, one subject in the SUL-DUR group had a TEAE based on the acute renal failure SMQ (mild protein urine present) and one subject in the SUL-DUR group (multidose) had TEAEs based on the drug-related hepatic disorders SMQ (mild hepatic enzyme increased), and one subject in the DUR only group and one subject in the SUL-DUR group had events in the pseudomembranous colitis SMQ (mild diarrhea).

**Safety in Phase 2 Study**

A phase 2 double-blind, randomized, placebo-controlled study evaluating SUL-DUR in the treatment of cUTI was conducted from January to May 2018. All subjects received background therapy with imipenem-cilastatin. The study enrolled 80 adult subjects, 53 in the SUL-DUR group and 27 in the placebo group. Because no subjects with *A. baumannii* were enrolled, and only one subject in the SUL-DUR group had an isolate resistant to imipenem, the data from this study did not inform the efficacy. Table 155 summarizes phase 2 study.

**Table 155. Phase 2 Sulbactam and Durlobactam Study**

| Study ID, Location, Dates | Design | Dosing Regimen | Population |
|---|---|---|---|
| CS2514-2017-0003<br>Bulgaria, Belarus, Russia, Ukraine<br>30 Jan 2018 - 17 May 2018 | Phase 2, double-blind, randomized, placebo-controlled study | SUL 1.0 g and DUR 1.0 g or placebo infused over 3 h q6h for 7 days with a background therapy of IMI/CIL infused over 30 min q6h in both study arms | M and F 18-90 years of age with cUTI including AP |

Source: Adapted from 5.2 tabular listing of clinical studies, module 5, NDA 216974
Abbreviations: AP, acute pyelonephritis; cUTI, complicated urinary tract infections; DUR, durlobactam; F, female; IMI/CIL, imipenem/cilastatin; M, male; q6h, every 6 hours; SUL, sulbactam; SUL-DUR, su bactam-durlobactam

The incidence of TEAEs in the phase 2 study is presented in Table 156. Overall, the incidence of treatment-related TEAEs was higher in the SUL-DUR in the phase 2 study (22.6%) than in the phase 3 study (13.2%). In the phase 2 study no subject in either group had an SAE or TEAE leading to death.

**Table 156. Incidence of TEAEs in the Phase 2 Sulbactam and Durlobactam Study**

| | Phase 2 (cUTI) | |
|---|---|---|
| **TEAE Category** | **SUL-DUR (N=53) n (%)** | **Placebo (N=27) n (%)** |
| TEAE | 20 (37.7) | 8 (29.6) |
| Treatment-related TEAE | 12 (22.6) | 4 (14.8) |
| Severe TEAE | 1 (1.9) | 0 |
| Treatment-related severe TEAE | 1 (1.9) | 0 |
| Serious TEAE | 0 | 0 |
| Serious treatment-related TEAE | 0 | 0 |
| TEAE leading to discontinuation from study drug | 2 (3.8) | 0 |
| TEAE leading to study discontinuation | 1 (1.9) | 0 |
| TEAE leading to death | 0 | 0 |

Source: Table 9, Summary of Clinical Safety, NDA 216974
Abbreviations: cUTI, complicated urinary tract infections; n, number of subjects in category; N, number of subjects; SUL-DUR, sulbactam-durlobactam; TEAE, treatment-emergent adverse event

Table 157 below lists the TEAEs in the phase 2 study. No deaths or serious adverse events were noted. Two subjects on SUL-DUR had treatment discontinuations due to increased creatinine and urticaria. Headache and phlebitis were noted in >5% of subjects on sulbactam-durlobactam.

**Table 157. Patients With TEAEs Occurring in >2 Subjects, Safety Population, Phase 2**

| **Preferred Term** | **SUL-DUR N=53 n (%)** | **Placebo + IMI/CIL N=27 n (%)** | **SUL-DUR vs Placebo + IMI/CIL Risk Difference (%) (95% CI)** |
|---|---|---|---|
| Any AE | 20 (37.7) | 8 (29.6) | 8.1 (-13.5, 29.7) |
| Diarrhea | 2 (3.8) | 0 | 3.8 (-1.4, 8.9) |
| Vascular pain | 2 (3.8) | 0 | 3.8 (-1.4, 8.9) |
| Vomiting | 2 (3.8) | 0 | 3.8 (-1.4, 8.9) |
| Headache | 5 (9.4) | 2 (7.4) | 2.0 (-10.6, 14.7) |
| Phlebitis | 3 (5.7) | 1 (3.7) | 2.0 (-7.5, 11.4) |
| Nausea | 2 (3.8) | 1 (3.7) | 0.1 (-8.7, 8.8) |

Source: FDA Analysis
Abbreviations: AE, adverse event; CI, confidence interval; DUR, durlobactam; IMI/CIL, imipenem/cilastatin; N, number of subjects; n, number of subjects in category; SUL, su bactam, TEAE, treatment-emergent adverse event

**Table 158. Safety Explorations by Creatinine Clearance, Phase 3 Study**

| **Renal Group** | **Event Category** | **Part A: SUL-DUR N=91 n (%)** | **Part A: Colistin N=86 n (%)** |
|---|---|---|---|
| <15 mL/min | Any AE | 2/2 (100) | 0 |
| <15 mL/min | Any TEAE | 2/2 (100) | 0 |
| <15 mL/min | Any Treatment-emergent SAE | 1/2 (50) | 0 |
| <15 mL/min | TEAE leading to permanent discontinuation of study drug | 1/2 (50) | 0 |
| 15-<30 mL/min | Any AE | 7/7 (100) | 7/7 (100) |
| 15-<30 mL/min | Any TEAE | 7/7 (100) | 7/7 (100) |
| 15-<30 mL/min | Any Treatment-emergent SAE | 6/7 (85.7) | 3/7 (42.9) |
| 15-<30 mL/min | TEAE leading to permanent discontinuation of study drug | 1/7 (14.3) | 1/7 (14.3) |
| 30-<60 mL/min | Any AE | 18/19 (94.7) | 16/16 (100) |
| 30-<60 mL/min | Any TEAE | 18/19 (94.7) | 16/16 (100) |

| Renal Group | Event Category | Part A: SUL-DUR N=91 n (%) | Part A: Colistin N=86 n (%) |
|---|---|---|---|
| 30-<60 mL/min | Any Treatment-emergent SAE | 8/19 (42.1) | 8/16 (50) |
| 30-<60 mL/min | TEAE leading to permanent discontinuation of study drug | 2/19 (10.5) | 3/16 (18.8) |
| 60-<90 mL/min | Any AE | 12/14 (85.7) | 18/19 (94.7) |
| 60-<90 mL/min | Any TEAE | 12/14 (85.7) | 18/19 (94.7) |
| 60-<90 mL/min | Any Treatment-emergent SAE | 9/14 (64.3) | 8/19 (42.1) |
| 60-<90 mL/min | TEAE leading to permanent discontinuation of study drug | 1/14 (7.1) | 2/19 (10.5) |
| >=90 mL/min | Any AE | 41/49 (83.7) | 40/44 (90.9) |
| >=90 mL/min | Any TEAE | 41/49 (83.7) | 40/44 (90.9) |
| >=90 mL/min | Any Treatment-emergent SAE | 12/49 (24.5) | 23/44 (52.3) |
| >=90 mL/min | TEAE leading to permanent discontinuation of study drug | 5/49 (10.2) | 8/44 (18.2) |

Source: FDA Analysis
Abbreviations: AE, adverse event; DUR, durlobactam; N, number of subjects; n, number of subjects in category; SAE, serious adverse event; SUL, sulbactam, TEAE, treatment-emergent adverse event

### Subjects With Bacteremia

Table 159 discusses characteristics of the bacteremia subjects in Part B and Part A. The subjects with bacteremia (N = 17) in part B were not noted to have HABP/VABP/VP with positive ABC. Infections were mostly monomicrobial, most subjects received prior therapy. Their baseline APACHE II scores were 10 to 21, duration of ICU stay mean 14 days. Subjects (b) (6) and (b) (6) had septic shock at baseline. Two subjects did not complete Part B of the study. One subject had a baseline ABC organism resistant to colistin (b) (6) and the other subject died at day 24 (b) (6).

**Table 159. Characteristics of Subjects With Bacteremia in the Phase 3 Study – Part A**

| Subject ID | Age | Sex | Reason to Exclude From CRABC m-MITT | Reason Study is Not Completed | Treatment Arm | Baseline Pathogens | Prior Antibacterials Within 24 Hours | Concomitant Antibacterials |
|---|---|---|---|---|---|---|---|---|
| (b) (6) | 67 | M | Baseline ABC organism is not carbapenem-resistant | N/A | SUL-DUR | Monomicrobial ABC | Yes | Vancomycin, ceftriaxone, ceftazidime |
| | 47 | M | N/A | N/A | Colistin | Monomicrobial ABC | Yes | None |
| | 75 | M | Imipenem-S, meropenem-R and colistin non tested | Death[1] | SUL-DUR | Monomicrobial ABC | Yes | Colistin |
| | 91 | F | Imipenem-S, meropenem-R and colistin NT | N/A | SUL-DUR | Monomicrobial ABC | Yes | None |
| | 21 | F | N/A | N/A | Colistin | Polymicrobial: ABC + other gram-negative pathogens | No | Levofloxacin |

Source: FDA Analysis
[1] To complete the study, a subject should receive study drug for seven days, complete 14 days of follow-up and die between Days 21 and 28.
[2] Catheter related bloodstream infection on day 1 (variable facat in sdtm fa.xpt)
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; F, female; M, male; m-MITT, microbiologically modified intent-to-treat; N/A, not applicable; R, resistant; S, suscept ble; SUL, sulbactam

**Table 160. Characteristics of Subjects With Bacteremia in the Phase 3 Study – Part B**

| Subject ID | Age | Sex | Reason to Exclude From CRABC m-MITT | Reason Study is Not Completed | Baseline Pathogens | Negative Blood Cultures at Randomization | Prior Antibacterial Within 24 Hours | Concomitant Antibacterials | Duration of Hosp. (Days) | Selected TEAE |
|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | 53 | M | Colistin-R by the local laboratory and S by central laboratory | N/A | Monomicrobial ABC | Y | Y | Cefoperazone, sulbactam | 18 | NR |
| | 76 | M | Baseline ABC organism resistant to colistin | N/A | Monomicrobial ABC | Y | Y | Ampicillin/ sulbactam, meropenem, metronidazole | 26 | Peripancreatic effusion, ascites |

| Subject ID | Age | Sex | Reason to Exclude From CRABC m-MITT | Reason Study is Not Completed | Baseline Pathogens | Negative Blood Cultures at Randomization | Prior Antibacterial Within 24 Hours | Concomitant Antibacterials | Duration of Hosp. (Days) | Selected TEAE |
|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | 44 | M | Baseline ABC organism resistant to colistin | N/A | Monomicrobial ABC | N/A | Y | Ampicillin/ sulbactam, ciprofloxacin, colistin, meropenem, gentamicin | 28 | VABP due to *Pseudomonas* |
| | 65 | M | Baseline ABC organism resistant to colistin | N/A | Monomicrobial ABC | Y | Y | Ampicillin/ sulbactam, colistin, vancomycin, amikacin | 28 | Neutropenia |
| | 75 | M | Baseline ABC organism resistant to colistin | Death | Monomicrobial ABC | N/A | Y | Colistin, daptomycin, metronidazole, ceftazidime/ avibactam, tigecycline, linezolid | 24 | *Enterococcus faecium* blood stream infection, cardiac arrest, multiorgan failure |
| | 46 | M | ABC isolate was not carbapenem resistant (i.e., imipenem-S and meropenem-S) | N/A | Monomicrobial ABC | N/A | Y | Colistin, tigecycline | 30 | NR |
| | 52 | M | Baseline ABC organism resistant to colistin | N/A | Monomicrobial ABC | Y | Y | Tigecycline, vancomycin | 23 | NR |
| | 60 | F | Baseline ABC organism resistant to colistin | N/A | Monomicrobial ABC | N/A | Y | Imipenem | 24 | NR |
| | 60 | M | ABC isolate was not carbapenem resistant | N/A | Monomicrobial ABC | Y | Y | None | 9 | NR |

| Subject ID | Age | Sex | Reason to Exclude From CRABC m-MITT | Reason Study is Not Completed | Baseline Pathogens | Negative Blood Cultures at Randomization | Prior Antibacterial Within 24 Hours | Concomitant Antibacterials | Duration of Hosp. (Days) | Selected TEAE |
|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | 62 | M | Baseline ABC organism resistant to colistin | N/A | Monomicrobial ABC | N/A | Y | Colistin | 0 | NR |
| | 24 | M | Baseline ABC organism resistant to colistin | N/A | Monomicrobial ABC | N/A | Y | Amikacin, colistin | 29 | NR |
| | 59 | F | Baseline ABC organism resistant to colistin | N/A | Monomicrobial ABC | Y | Y | Metronidazole | 29 | NR |
| | 54 | M | Baseline ABC organism resistant to colistin | N/A | Monomicrobial ABC | Y | Y | Amikacin, colistin | 12 | NR |
| | 44 | M | Baseline ABC organism resistant to colistin | N/A | Monomicrobial ABC | N/A | Y | Imipenem, linezolid | 28 | NR |
| | 55 | M | Imipenem-R and meropenem-R; at the central laboratory colistin-S, Imipenem-S and Meropenem-S | N/A | Monomicrobial ABC | Y | Y | Amoxicillin, colistin | 30 | NR |
| | 46 | M | Baseline ABC organism resistant to colistin | N/A | Polymicrobial: ABC + Gram-Positive Pathogens | Y | Y | Colistin | 24 | NR |

| Subject ID | Age | Sex | Reason to Exclude From CRABC m-MITT | Reason Study is Not Completed | Baseline Pathogens | Negative Blood Cultures at Randomization | Prior Antibacterial Within 24 Hours | Concomitant Antibacterials | Duration of Hosp. (Days) | Selected TEAE |
|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | 59 | M | Imipenem-R, meropenem-R and colistin susceptible | Other: did not complete treatment because the patient was ineligible for Part B enrollment | Monomicrobial ABC Pathogens | N/A | Y | None | 0 | NR |

Source: FDA Analysis
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; Hosp, hospitalization; m-MITT, microbiologically modified intent-to-treat; N/A, not applicable; NR, not reported; R, resistant; S, susceptible; TEAE, treatment-emergent adverse effect; VABP, ventilator-associated bacterial pneumonia

**Safety Data From Expanded-Access Patients**

Twelve subjects received SUL-DUR under the expanded access program in the United States and under the Italian Medicines Agency compassionate-use program. The subjects were critically ill, some on renal replacement therapy, treated for CRABC pneumonia with or without bacteremia, empyema, sternal wound infection, COVID-19 pneumonia complicated by secondary infection with CRABC or MDR *Acinetobacter*, burn wound infection, and surgical site infection. The treatment duration with SUL-DUR ranged from 1 to 42 days. Although eight subjects cleared their infection, six subjects died. Of the subjects with fatal outcomes, two died from COVID-19. Before treatment with SUL-DUR, the subjects generally failed multiple salvage regimens with combinations of antibacterials such as tigecycline and cefiderocol; cefiderocol and polymyxin B; meropenem, high-dose ampicillin-sulbactam and polymyxin B; meropenem; eravacycline and polymyxin B; meropenem and minocycline; cefiderocol, tigecycline, and polymyxin B. Most isolates were MDR and CRABC, notably with cefiderocol resistance and SUL-DUR MICs ranging from 2 to 8 mg/L.

**Safety Explorations by Body Weight, Phase 3 Study**

According to clinical pharmacology analysis, higher drug exposures were observed in patients with body weight 35 to 50 kg, which was found to be not covered by the exposure from the tested highest dose for DUR and the high dose recommended for SUL from literature. Therefore, safety analyses were conducted to justify the high exposures in the low body weight patients. The safety profile for SAEs and discontinuations due to adverse events appeared similar in those <50 and >50 kg, as outlined in Table 161 below.

**Table 161. AEs by Body Weight, Phase 3 Study**

| AEs by Body Weight | ETX2514SUL + IMI (Part A) | Colistin + IMI (Part A) |
|---|---|---|
| Body weight <50 kg | N=7 | N=7 |
| Number of subjects with at least 1 AE | 7 | 7 |
| Serious AE, all unrelated | 4(57%) | 3(42.8%) |
| AEs leading to treatment discontinuation | 1 | 1 |
| Body weight >50 kg | N=84 | N=79 |
| Number of subjects with at least 1 AE | 74(88%) | 74(93.6%) |
| Serious AE, | 32(38%) | 38(48%) |
| Serious AE, related | 1(1.2%) | 2(2.5%) |
| AEs leading to treatment discontinuation | 9(10.7%) | 13(16.4%) |

Source: FDA Analysis
Abbreviations: AE, adverse event; ETX2514, durlobactam; IMI, imipenem; N, number of subjects; SUL, sulbactam

**Safety Explorations by Creatinine Clearance, Phase 3 Study**

According to clinical pharmacology analysis, the predicted drug exposures at the Applicant's proposed new dose (1.0 g sulbactam/1.0 g durlobactam administered q12h) to mitigate medication errors for CrCL group of 15-30 were approximately 2-fold higher than that from patients with normal renal function, but were still covered by the exposure limits from the patients who received a higher dose regimen in the phase 3 study (1.0 g sulbactam/1.0 g durlobactam q8h). Safety analyses were conducted in the different groups of CrCL in the phase 3 study. The safety profile for AEs, TEAEs, SAEs and treatment discontinuations due to adverse events appeared similar between study drug groups and between the CrCL groups, as outlined in Table 158.

# 18. Clinical Virology

Not applicable.

# 19. Clinical Microbiology

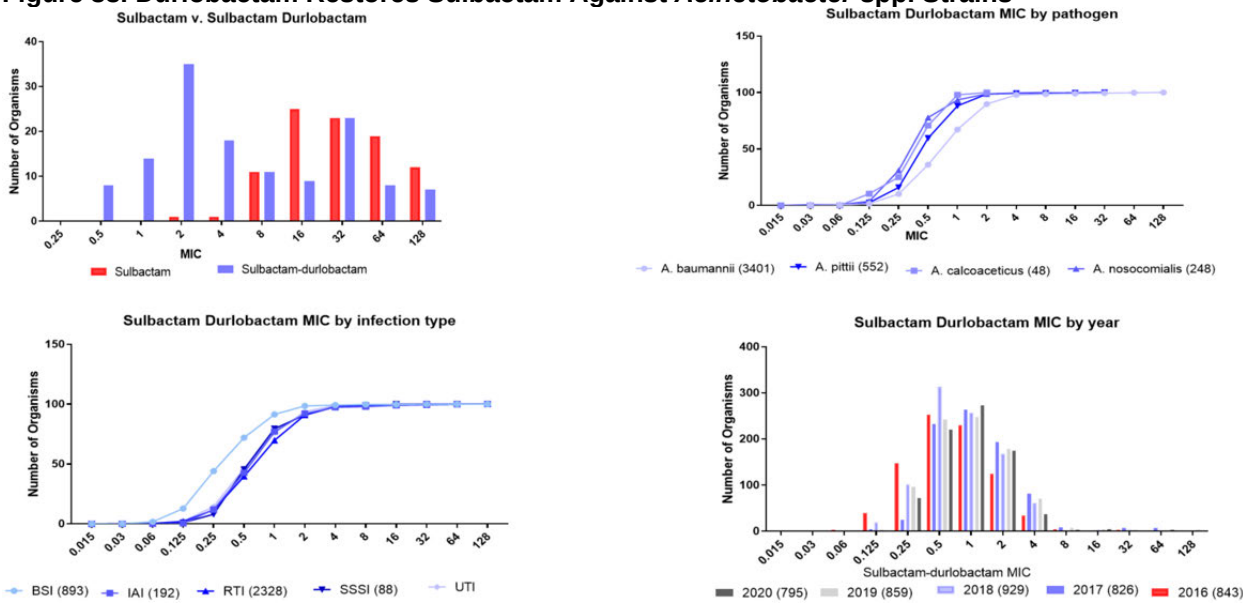
## 19.1. Nonclinical Microbiology

**Antimicrobial Spectrum of Activity**

Surveillance studies (2011 to 2021) collected over 7000 *Acinetobacter baumannii-calcoaceticus* complex isolates from 250 centers worldwide. Isolates were sourced from community-associated as well as hospital-associated infections and included respiratory tract, intra-abdominal, urinary tract, skin and skin structure and blood. Isolates also included important resistance phenotypes (e.g., carbapenem-resistant, colistin-resistant, MDR, extensively-resistant [XDR] and pan-drug resistant [PDR]). Isolates were collected from Europe, North America, Asia-South Pacific, Latin America, and India. The MIC was determined by broth microdilution method in freshly prepared or frozen cation-adjusted Mueller-Hinton broth following Clinical Laboratory and Standards Institute (CLSI) guidelines (2018 to 2019) (CLSI 2018). Sulbactam-durlobactam MICs were determined as 2-fold dilutions of sulbactam in the presence of durlobactam at a fixed concentration of 4 mg/L. The addition of durlobactam at a fixed concentration of 4 mg/L lowered the sulbactam $MIC_{90}$ from >32 mg/L to 2 - 4 mg/L with 98.2% of isolates having sulbactam-durlobactam MIC values ≤4 mg/L. (**Note**: For the purposes of the review the sulbactam-durlobactam MIC values are provided as sulbactam MIC values which are based on a fixed durlobactam dose of 4 mg/L). Figure 33 shows the in vitro activity of sulbactam-durlobactam against the following:

- There was no difference in sulbactam-durlobactam activity against ABC subspecies showing $MIC_{50/90}$ values of 1 and 2 mg/L, respectively with 98.8% of the isolates having sulbactam-durlobactam MICs at or below 4 mg/L. Most of the clinical isolates tested were *A. baumannii* (81.7%), 11.0% were *A. pittii*, 6.2% *A. nosocomialis*, 0.9% *A. calcoaceticus*, 0.1% *A. dijkshoorniae*, and 0.1% *Acinetobacter* spp (PC2514-2021-0002, PC2514-2021-0016, PC2514-2016-0035) (Yang et al. 2020).
- Sulbactam-durlobactam MIC values did not vary by infection source showing ≤4 mg/L in all isolates from bloodstream, intra-abdominal, skin and skin structure and urinary isolates. Approximately 96.3% of the isolates from the respiratory tract had MICs ≤4 mg/L (PC2514-2021-0002, PC2514-2021-0016, PC2514-2020-0005, PC2514-2021-0021) (Yang et al. 2020).
- Sulbactam-durlobactam MIC values remained stable globally over time with $MIC_{90}$ values ranging from 2 mg/L to 4 mg/L for the period 2011 through 2020 (PC2514-2021-0002, 2514-2020-0005).

**Figure 33. Durlobactam Restores Sulbactam Against *Acinetobacter* spp. Strains**

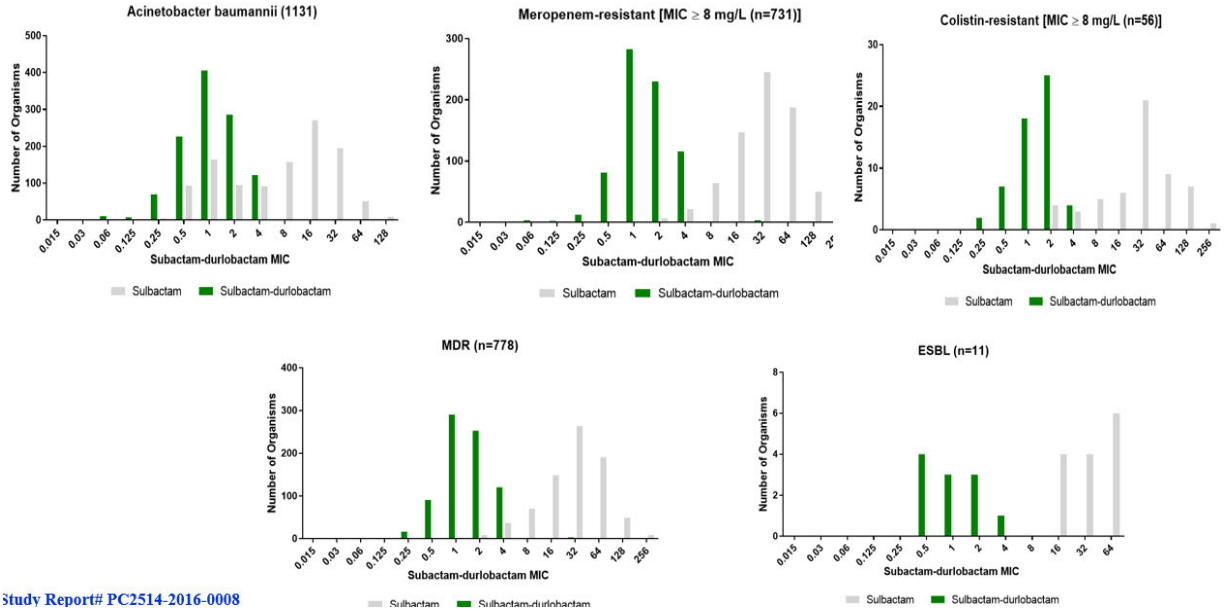



Source: Study Report# PC2514-2021-0012; PC2514-2022-0017; PC2514-(2016-2020)-0008
Abbreviations: MIC, minimum inhibitory concentration

Sulbactam-durlobactam maintained activity against resistant subsets of *A. baumannii-calcoaceticus* complex isolates in comparison to sulbactam alone (Figure 34). Among sulbactam-resistant isolates, the sulbactam-durlobactam MIC values were ≤4 mg/L in 96.9% of amikacin-resistant, 97.4% of ciprofloxacin-resistant, 98.9% of colistin-resistant, 96.6% of meropenem-resistant and 97.3% of minocycline resistant isolates. Activity was also maintained against MDR ABC isolates (defined as resistance to three or more classes of antimicrobials) with 96.7% having sulbactam-durlobactam MICs ≤4 mg/L and 90.2% against XDR ABC isolates (defined as isolate that remain susceptible to one or two antimicrobial categories) (PC2514-2021-0002, PC2514-2021-0016, PC2514-2022-0001) (Seifert et al. 2020; Nodari et al. 2021; Petropoulou et al. 2021).

Durlobactam restored sulbactam activity against well characterized *A. baumannii-calcoaceticus* complex isolates expressing class A enzymes (CTX-M, TEM, PER and SHV-type extended β-lactamases [ESBLs], KPC), Class C enzymes (ADC-30, ADC-25, ADC-52-like, ADC-63-like, ADC-26, ADC-56, ADC-79) and Class D (OXA-58, OXA-51, OXA-23 and OXA-24/40) showing 2-fold to 16-fold shift in sulbactam MICs depending on the β-lactamase. However, isolates that encoded for Class B metallo- β-lactamases (NDM-1 and variants) had sulbactam-durlobactam values greater than 4 mg/L (PC2514-2020-0006, PC2514-2021-0003, PC2514-2021-0005, PC2514-2021-0012) (Durand-Reville et al. 2017; Seifert et al. 2020; Petropoulou et al. 2021).

**Figure 34. Durlobactam Restores Sulbactam Activity Against Resistant Sub-Types**




Study Report# PC2514-2016-0008

Abbreviations: ESBL, extended-spectrum β-lactamase; MDR, multi-drug resistant; MIC, minimum inhibitory concentration; n, number of subjects in category

Global studies showed that sulbactam-durlobactam $MIC_{90}$ values against MDR *A. baumannii-calcoaceticus* complex spp. ranged from 1 to 4 mg/L with no notable differences in sulbactam-durlobactam MIC values in isolates obtained from North America, Latin America, Europe, Middle-East, Asia-South Pacific or China (Table 162). Sulbactam-durlobactam showed higher MICs against isolates from India which showed a predominance of NDM-producing *A. baumannii*, which are consistent with the finding that durlobactam does not inhibit metallo-β-lactamases (NDM-producing isolates) (PC2514-2018-0010, PC2514-2020-0005, PC2514-2020-0006, PC2514-2021-0002, PC2514-2021-0003, PC2514-2021-0004, PC2514-2021-0006, PC2514-2021-0012, PC2514-2021-0016, PC2514-2021-0021) (Seifert et al. 2020; Yang et al. 2020; Nodari et al. 2021; Petropoulou et al. 2021).

**Table 162. Activity of Sulbactam in Combination With Durlobactam at Fixed Concentration of 4 mg/L Against *Acinetobacter spp*. Isolates**

| Species | Number Tested | $MIC_{50}$ | $MIC_{90}$ | MIC Range[1] | Country | Reference |
|---|---|---|---|---|---|---|
| ***Region (2016–2020)*** | | | | | | |
| Asia | 456 | 1 | 2 | ≤0.03 – >64 | -- | Study Report# PC2514-2021-0002 |
| Europe | 1776 | 1 | 2 | ≤0.03 – >64 | -- | Study Report# PC2514-2021-0002 |
| Latin America | 532 | 1 | 4 | ≤0.03 – >64 | -- | Study Report# PC2514-2021-0002 |
| Middle East | 88 | 1 | 2 | 0.25 – 32 | -- | Study Report# PC2514-2021-0002 |
| North America | 1271 | 0.5 | 2 | ≤0.03 – >64 | -- | Study Report# PC2514-2021-0002 |
| South Pacific | 129 | 0.5 | 2 | 0.06 – 64 | -- | Study Report# PC2514-2021-0002 |
| India | 121 | 2 | >64 | 0.25 - >64 | -- | Study Report# PC2514-2020-0006 |
| ***Publications*** | | | | | | |
| *Acinetobacter* spp. | 195 | 1 | 4 | ≤0.06 - 32 | Global | (Durand-Reville et al. 2017) |
| *Acinetobacter* spp. | 72 | 1 | 2 | 0.25 - 32 | US | (Barnes et al. 2019) |
| *Acinetobacter* spp. | 982 | 1 | 2 | ≤0.03 - >64 | China | (Yang et al. 2020) |
| *Acinetobacter* spp. | 1722 | 1 | 2 | ≤0.03 - >64 | Global | (McLeod et al. 2020) |
| *Acinetobacter baumannii* (carbapenem-resistant)[2] | 112 | 1 | 1 | ≤0.25 - 4 | Brazil | (Nodari et al. 2021) |
| *Acinetobacter baumannii* (carbapenem-resistant) | 190 | 4 | 8 | 0.5 - >64 | Greece | (Petropoulou et al. 2021) |
| *Acinetobacter baumannii* (carbapenem-resistant) | 246 | 1 | 2 | 0.25 - 128 | Global | (Seifert et al. 2020) |
| *Acinetobacter baumannii* | 1420 | 1 | 4 | ≤0.03 - >64 | Global | (McLeod et al. 2020) |
| *Acinetobacter calcoaceticus* | 10 | 0.5 | 1 | 0.12 - 1 | Global | (McLeod et al. 2020) |
| *Acinetobacter nosocomialis* | 60 | 0.5 | 1 | 0.12 - 4 | Global | (McLeod et al. 2020) |
| *Acinetobacter pittii* | 232 | 0.5 | 2 | 0.12 - 4 | Global | (McLeod et al. 2020) |

[1] Susceptibility Testing Interpretive Criteria as published by Clinical Laboratory Standards Institute (CLSI) 2021 unless stated otherwise
Note: The MICs are expressed based on the sulbactam MIC value only in the presence of durlobactam tested at a fixed concentration of 4 mg/L
Abbreviations: MIC, minimum inhibitory concentration

Both sulbactam alone and with durlobactam showed bactericidal activity against *A. baumannii* isolates; however, the bactericidal activity of sulbactam-durlobactam was achieved at lower MICs compared to sulbactam alone (PC2514-2016-0009, PC2514-2017-0006). Time-kill studies showed time-dependent bactericidal killing (≥3 $\log_{10}$ killing) at 8x sulbactam MIC in combination with 4 mg/L durlobactam (PC2514-2017-0009).

While *A. baumannii* is generally viewed as an extracellular pathogen, recent studies have described the organism's ability to invade and replicate within macrophages and epithelial cells. Intracellular sulbactam and durlobactam concentrations within macrophages were approximately 40% and 10% of the extracellular concentration, respectively. The intracellular concentrations of durlobactam in murine macrophages (1.0 - 3.04 mg/L) were comparable to those observed in human macrophages (1.31 mg/L); while the sulbactam concentrations were slightly higher (4.5 - 16.0 mg/L) but still within range of human macrophages (1.01 mg/L). Exposure to sulbactam-durlobactam (2:2; 10:10 or 20:20 mg/L) resulted in concentration- and time-dependent reduction in intracellular bacterial counts of AbCA1 isolate. The highest concentration of sulbactam-durlobactam (20:20 mg/L) resulted in a reduction in bacterial burden that was nearly at the limit of detection at all time points relative to no drug control at 0 hours. Sulbactam-durlobactam at 10:10 mg/L and 2:2 mg/L reduced the bacterial burden to LOD after 4 and 6 hours of incubation. Taken together, the data suggest that sulbactam-durlobactam has activity against intracellular *A. baumannii* actively replicating in macrophages (PC2514-2020-0014).

**Interaction With Other Antimicrobials**

Against 10 *A. baumannii* clinical isolates in checkerboard assays, no antagonism was reported for sulbactam-durlobactam in combination with other antimicrobial agents including amikacin, colistin, meropenem, imipenem, ciprofloxacin, cefepime, ceftazidime-avibactam, rifampicin, linezolid, vancomycin, daptomycin, oritavancin, tedizolid, dalbavancin, rifaximin, fidaxomicin, metronidazole or fluconazole. There were a few instances of synergy observed but these were strain- and drug-dependent. In vitro studies showed that the sulbactam-durlobactam combination was more active than sulbactam-imipenem or imipenem-durlobactam. There was no difference in the sulbactam-durlobactam activity compared to sulbactam-durlobactam in combination with meropenem or imipenem (PC2514-2017-0007, PC2514-2021-0001).

No postantibiotic effect was observed after testing with 4x or 8x MIC of sulbactam-durlobactam consistent with other cephalosporins such as ceftazidime, ceftaroline or aztreonam tested in combination with avibactam against gram-negative organisms (PC2514-2017-0001, PC2514-2017-0010, PC2514-2019-0005).

Sulbactam-durlobactam prevents the formation of biofilm; however, it does not eliminate established biofilms in *A. baumannii* clinical isolates (PC2514-2010-0005).

**Susceptibility Testing Methods**

The MIC values for sulbactam-durlobactam were determined by broth microdilution method in accordance with CLSI guidelines (M07-A10).

- In vitro experiments support that the optimal condition for susceptibility testing by the broth microdilution method is by holding the concentration of durlobactam constant at 4 mg/L while varying the sulbactam concentration in two-fold increments. The 4 mg/L concentration of durlobactam was selected because of its ability to correctly separate the "predicted sensitive" from "predicted resistant" isolates by applying the known β-lactamase spectrum of sulbactam (class A) and durlobactam (Class A, Class C and some Class D enzymes). Sulbactam titrations in the presence of lower concentrations of durlobactam (≤2 mg/L) resulted in larger numbers of "predicted sensitive/inhibited"

strains testing as resistant, suggesting that there was insufficient β-lactamase inhibition by durlobactam at these concentrations to fully restore sulbactam to wild-type activity levels (PC2514-2017-0008).

- Stability studies showed no variation in MIC beyond one dilution from the modal MIC over a six-month period, suggesting panels may be stored frozen (-80°C) up to 6 months with no loss of activity (PC2514-2017-0002).
- Varying the starting inoculum, incubation temperature, atmospheric conditions, concentration of divalent cations, presence of surfactant or presence of human serum or human albumin did not significantly affect sulbactam-durlobactam MIC determination. The exception was that changes in pH altered sulbactam-durlobactam MICs, especially in the presence of urine. Four- to eight-fold increases in sulbactam-durlobactam MIC values in the presence of 50% urine at pH 5.0 was observed for most of the isolates tested, similar to what has been reported for ceftazidime avibactam. (PC2514-2017-0006). The activity of sulbactam-durlobactam showed little (2-fold increase in $MIC_{90}$) to no change when tested in iron depleted media; however, the $MIC_{90}$ values were 8-fold lower in RPMI +10% fetal calf serum. The reason for increased activity of sulbactam-durlobactam in RPMI +10% FCS is unknown (PC2514-2021-0012).
- A multi-center, tier 2 quality control (QC) study was conducted in accordance with CLSI M23 guidelines (CLSI 2018), performed at eight independent laboratories using three different lots of either cation-adjusted Mueller Hinton broth of (b) (4) (Lot#5257869, (b) (4) (Lot#1743805, (b) (4) (Lot#4045151 (b) (4) Each laboratory tested 10 replicates of *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *A. baumannii* NCTC 13304 or *Escherichia coli* NCTC13353 (PC2514-2017-0001). The results showed that:
  - Routine QC testing for sulbactam-durlobactam by broth microdilution method is recommended using the QC strain *Acinetobacter baumannii* NCTC 13304.
  - Routine QC testing for sulbactam alone by broth microdilution is recommended using the QC strain, *Klebsiella pneumoniae* ATCC 700603, the QC strains *Escherichia coli* ATC 25922 and *Acinetobacter baumannii* NCTC 13304 will be used as alternatives. Sulbactam alone should be tested to ensure that the QC strains are resistant.
  - These criteria have been published by CLSI in M100-Ed32 (2022) tables (Table 163).

**Table 163. Broth Microdilution QC Ranges for Sulbactam-Durlobactam**

| | Sulbactam | | SUL-DUR | |
|---|---|---|---|---|
| Organism | MIC Range (µg/mL) | % in Range | MIC Range (µg/mL) | % in Range |
| *Escherichia coli* ATCC 25922 | 16 - 64 | 100% | NR | -- |
| *Klebsiella pneumoniae* ATCC 700603 | 32 – 128 | 99.6% | NR | -- |
| *Acinetobacter baumannii* NCTC 13304 | 16 - 64 | 98.8% | 0.5/4 – 2/4 | 99.6% |

Source: Study Report# PC2514-2017-0001
Abbreviations: DUR, durlobactam; MIC, minimum inh bitory concentration; NR, not reported; SUL, su bactam; QC, quality control

For the disk diffusion method:

- The optimal disk mass of sulbactam-durlobactam for disk diffusion testing was determined to be 10 µg sulbactam and 10 µg durlobactam which corresponded acceptably with in vitro broth microdilution susceptibility method of sulbactam-durlobactam (at a fixed concentration of 4 µg/mL). Based on the error-rate bounding analysis, the 10/10 µg demonstrated acceptable error rates, with no very major or major errors with minor categorical errors of 32.5% (below the recommended minor error rate of 40%). In addition, using the 10/10 µg resulted, on average, in susceptible zone diameters ≥18 mm which is consistent with CLSI M23 (CLSI 2018) recommendations of an optimal susceptible zone diameter breakpoint starting at 15 to 25 mm to correlate with susceptible MIC values (PC2514-2017-0003; PC2514-2017-0004).
- No information was provided on disk stability studies or the various parameters that affect in vitro susceptibility testing by the disk diffusion method.
- A multi-center, tier 2 QC study of the 10/10 µg disk was conducted in accordance with CLSI M23 guidelines, performed at eight independent laboratories using 3 different agar media lots from (b) (4) (Lot# 191341), (b) (4) (Lot# 7173648; (b) (4) (Lot# 17212). The sulbactam-durlobactam 10/10 µg disk were obtained from (b) (4) (Lot# 392472) and (b) (4) (Lot#3011). Each laboratory tested 3 different media lots of 10 replicates (2 x 3 x 10 = 60 zone diameter determinations) at 8 independent testing sites (480 total zone diameter values per reference strain). The average colony counts for *E. coli* ATCC 25922 was 9.6 x $10^8$ CFU/mL and 7.3 x $10^8$ CFU/mL for *A. baumannii* NCTC 13304 strain. (Study Report# PC2514-2018-0008). The results showed that:
  - Routine QC testing for sulbactam-durlobactam by the disk diffusion method is recommended using the QC strain *Acinetobacter baumannii* NCTC 13304. Escherichia *coli* ATCC 25922 can be used as an alternative QC strain.
  - These criteria have been published by CLSI in M100-Ed32 (CLSI 2022) tables (Table 164).

**Table 164. Disk Diffusion QC Ranges for Sulbactam-Durlobactam**

| QC Strain | Sulbactam-Durlobactam Zone Diameters (mm) | Percent in Range |
|---|---|---|
| *A. baumannii* NCTC 13304 | 24 – 30 (7mm range) | 100% |
| *E. coli* ATCC 25922 | 26 – 32 (7 mm range) | 99.8% |

Source: Study Report# PC2514-2018-0008
Abbreviations: QC, quality control

- No information provided on the agar dilution method.

**Animal Models of Infection**

Durlobactam restored activity of sulbactam in animal models of infection including neutropenic mouse thigh and pneumonia infections. Many of the isolates tested that produced clinically relevant β-lactamases had sulbactam-durlobactam MIC values ranging from 0.5 to 16 mg/L, and 2 to 64 mg/L for sulbactam.

- In a neutropenic thigh infection model sulbactam was assessed (Table 165):
  - When administered in the presence of durlobactam at a constant ratio of 4:1. The sulbactam-durlobactam 50% effective dose ($ED_{50}$) against sulbactam-resistant isolates ranged from 5.93 to 7.54 mg/kg given every 3 hours (q3h) or 35.3 to 100 mg/kg given q6h. Although sulbactam treatment alone was not evaluated against resistant strains, sulbactam activity was restored in the presence of durlobactam against sulbactam-resistant strains (PC2514-2016-0020, PC2514-2022-0006).
  - Similarly, when sulbactam was administered at a fixed dose of 15 mg/kg and varying concentrations of durlobactam. Treatment with sulbactam alone at 15 mg/kg q3h showed minimal to no activity with 0.55 to 1.70 $\log_{10}$ CFU/g increase in growth against 3 sulbactam-resistant strains tested. This ineffective dose of sulbactam was selected to allow for a full dose response of durlobactam. The addition of durlobactam restored the activity of sulbactam in a dose proportional manner with durlobactam $ED_{50}$ ranging from 10 to 25 mg/kg q3h, consistent with data generated with 4:1 fixed ratio dosing (PC2514-2016-0022, PC2514-2022-0006).
  - Durlobactam demonstrated poor activity when administered alone (50 mg/kg) showing minimal to no activity with 0.82 to 2.21 $\log_{10}$ CFU/g increase in growth. The addition of durlobactam at a dose range of 12.5 to 200 mg/kg q3h to sulbactam at 75 or 150 mg/kg q3h resulted in a dose proportional reduction in bacterial burden with durlobactam $ED_{50}$ values ranging from 2.30 to 15.3 mg/kg q3h (PC2514-2017-0013, PC2514-2022-0006).

**Table 165. Activity of Sulbactam in Combination With Durlobactam in a Neutropenic Murine Thigh Infection Model Against Sulbactam-Resistant *A. baumannii* Strains**

| Strain | β-lactamases | Minimum Inhibitory Concentration (mg/L) | | Sulbactam-Durlobactam $ED_{50}$ (mg/kg) | Maximum 24-hour $\log_{10}$ CFU/g change |
|---|---|---|---|---|---|
| | | SUL | SUL-DUR | | |
| Sulbactam-durlobactam (4:1 ratio) | | | | | |
| ARC2058 | ADC-3-like (AmpC); OXA-259 (OXA-95) | 2 | 1 | ND | -3.12 |
| ARC3484 | OXA-23, OXA-64, TEM-1 | 16 | 0.5 | 7.54[1] | -2.66 |
| ARC3486 | OXA-66, OXA-75, TEM-1 | 32 | 0.5 | 5.93[1] | -3.17 |
| ARC5079 | OXA-65, OXA-72 | 32 | 1 | 100[2] | -2.58 |
| ARC5081 | OXA-23, OXA-66 | 8 | 2 | 97.5[2] | -2.89 |
| ARC5091 | OXA-23, OXA-78 | 8 | 1 | 35.3[2] | -2.93 |
| Sulbactam-durlobactam (15 mg sulbactam [fixed]; durlobactam range 12.5 – 200 mg/kg) | | | | | |
| ARC3486 | OXA-66, OXA-75, TEM-1 | 32 | 0.5 | 6.86[3] | -2.59 |
| ARC5079 | OXA-65, OXA-72 | 32 | 1 | 21.5[3] | -1.79 |
| ARC5081 | OXA-23, OXA-66 | 8 | 2 | 11.1[3] | -2.86 |

| Strain | β-lactamases | Minimum Inhibitory Concentration (mg/L) SUL | SUL-DUR | Sulbactam-Durlobactam $ED_{50}$ (mg/kg) | Maximum 24-hour $log_{10}$ CFU/g change |
|---|---|---|---|---|---|
| Sulbactam-durlobactam (fixed sulbactam of 75 or 150 mg; durlobactam range 12.5 – 200 mg/kg) | | | | | |
| ARC5077 | ADC-82; OXA-72 | 16 | 4 | 10.6[3] | -2.14 |
| ARC5950 | ADC-11, OXA-23, OXA-69 | 64 | 8 | 11.8[3] | -4.42 |
| ARC5954 | TEM-1, OXA-83, ADC-30 | 32 | 16 | 11.1[3] | -2.27 |
| ARC5955 | TEM-1, OXA-23, OXA-66, ADC-82 | 64 | 8 | 11.6[3] | -1.51 |

Source: Study Report# PC2514-2016-0020, PC2514-2016-0022; PC2514-2017-0013; PC2514-2022-0006
[1] q3h regimen
[2] q6h regimen
[3] For durlobactam q3h regimen
Abbreviations: ADC, ambler class C β-lactamase; CFU, colony forming units; DUR, durlobactam; $ED_{50}$, 50% effective dose; ND, not determined; OXA, ambler class D β-lactamase; q3h, every 3 hours; q6h, every 6 hours; SUL, sulbactam; TEM, ambler class A β-lactamase

In a neutropenic murine lung infection model sulbactam was assessed when administered in the presence of durlobactam at a constant ratio of 4:1 (Table 166). The sulbactam-durlobactam $ED_{50}$ ranged from 11.9 to 36.4 mg/kg when given q3h in mice; demonstrated slightly higher dose requirements compared to thigh infection model (PC2514-2016-2020, PC2514-2022-0006).

**Table 166. Activity of Sulbactam and Sulbactam-Durlobactam (4:1) Against Sulbactam-Resistant *A. baumannii* Isolates in a Neutropenic Lung Infection Model**

| Strain ID | β-lactamase | Minimum Inhibitory Concentration (µg/mL) SUL | SUL-DUR | $ED_{50}$ (mg/kg) SUL | SUL-DUR | Maximum 24 hour $log_{10}$ CFU/g Change |
|---|---|---|---|---|---|---|
| ARC2058 | OXA-95 | 2 | 1 | 27.5 | ND | -2.64 |
| ARC3484 | OXA-23; OXA-64; TEM-1 | 16 | 1 | ND | 23.2 | -3.85 |
| ARC3486 | OXA-66; OXA-72; TEM-1 | 32 | 0.7 | ND | 11.9 | -3.67 |
| ARC5079 | OXA-65; OXA-72 | 32 | 1 | ND | 15.4 | -3.43 |
| ARC5081 | OXA-23; OXA-94 | 16 | 4 | ND | 36.4 | -4.24 |

Abbreviations: CFU = colony forming units; DUR = durlobactam; $ED_{50}$ = 50% effective dose (based on sulbactam dose); ID = identifier; MDR = multi-drug resistant; ND = not determined; SUL = sulbactam.
Source: Study Report# PC2514-2016-0020; PC2514-2022-0006
Abbreviations: OXA, ambler class D β-lactamase; TEM, ambler class A β-lactamase

## Pharmacokinetics and Pharmacodynamics

Based on studies conducted in vitro (hollow-fiber infection and chemostat models) and animal models of infection (thigh and lung infection), the Applicant proposed that the PK/PD drivers best associated with antibacterial activity are the percentage of the free-drug concentration above the MIC over a 24-hour period (%*f*T > MIC) for sulbactam and the free-drug $AUC_{0-24}$/MIC ratio for durlobactam (PC2514-2015-0020, PC2514-2016-0021, PC2514-2016-0023, PC2514-2017-0011). The studies showed that:

- When sulbactam was administered in the presence of durlobactam at a ratio of 4:1 in a murine neutropenic thigh infection model, the mean %*f*T > MIC magnitudes for sulbactam were 34.3% (range, 26.2 to 45.7%) to achieve a 1-$log_{10}$ kill and 38.6% (range, 28.8 to 52.9%) for a 2-$log_{10}$ kill, respectively, against 5 sulbactam-resistant *A. baumannii* isolates (PC2514-2016-2020).

- When sulbactam was administered in the presence of durlobactam at a ratio of 4:1 in a murine neutropenic lung infection model, the mean %*f*T > MIC magnitudes for sulbactam were 45.5% (range, 37.1 to 58.1%) to achieve a 1-$\log_{10}$ kill and 55.5% (range, 43.9 to 90.9%) for a 2-$\log_{10}$ kill, respectively, against 4 sulbactam-resistant *A. baumannii* isolates (PC2514-2016-0021).
- When fixed doses of sulbactam and varied doses of durlobactam were administered in a mouse thigh infection model against 6 sulbactam-resistant *A. baumannii* isolate, the daily *f*AUC/MIC values associated with 1-$\log_{10}$ kill and 2-$\log_{10}$ kill were 7.5 and 31.8, respectively (PC2514-2016-0022). These results were consistent with *f*AUC/MIC values obtained in the neutropenic thigh and lung infection studies using 4:1 sulbactam-durlobactam fixed ratio dose (PC2514-2016-2020, PC2514-2016-0021).

Based on the above results, the Applicant proposed PK/PD targets of 50%*f*T > MIC for sulbactam and $f\text{AUC}_{0\text{-}24}$/MIC of 10 to achieve 1-$\log_{10}$ kill against sulbactam-resistant *A. baumannii* strains. Greater than 2-$\log_{10}$ kill requires $f\text{AUC}_{0\text{-}24}$/MIC of 30. PTA analyses for both plasma and ELF exposures using these PK/PD targets support the clinical dose selection of 1g sulbactam and 1 g durlobactam. PTA results showed that the free plasma drug exposure will be achieved in more than 98 to 100% of subjects with normal to severe renal impairment with isolates having sulbactam-durlobactam MIC values ≤4 mg/L. Similar PK/PD targets were observed for ELF exposure (see Section 5.1 and Section 14.5.1.)

## 19.2. Microbiology Data From Clinical Studies

One phase 3 pivotal clinical study (CS2514-2017-0004) evaluated the efficacy and safety of sulbactam-durlobactam compared to colistin in subjects with infections caused by CRABC isolates. The phase 3 study design and results are described elsewhere in the review (see Section 15). The m-MITT population was the primary evaluable population and included all randomized subjects that received any amount of study drug and had CRABC organisms isolated at baseline. The study was conducted in two parts, in which Part A was the pivotal, randomized, assessor-blind, comparative, noninferiority study which included subjects with HABP, VABP, ventilated pneumonia or bacteremia. Part B was the open-label, single-arm study that included subjects who did not qualify for Part A. The following summary of efficacy assesses only included subjects from Part A.

**Baseline Isolates**

Table 167 shows the CRABC isolates that were identified in 125 subjects (63 subjects in the sulbactam-durlobactam arm and 62 subjects in the colistin arm).

- The most prevalent CRABC isolate was *A. baumannii* (80.5%) with 22 isolates (17.2%) not identified beyond ABC or *Acinetobacter* spp., 2 isolates (1.6%) were *A. nosocomialis* and 1 isolate (0.8%) *A. dijkshoorniae*.
- Most of the infections were monomicrobial (63.2%), the proportion of subjects with monomicrobial infections was higher in the colistin arm than in sulbactam-durlobactam arm (69.4% v. 57.1%). Of those CRABC isolates that were polymicrobial, 33.6% were mixed with other gram-negative isolates, few were mixed with gram-positive isolates

(2.4%) and only one subject had CRABC with fungal isolate. Of the subjects that had ABC plus one or more co-infecting gram-negative pathogens, the most common were *Klebsiella* spp. (n = 33 [78.6%]), *Pseudomonas aeruginosa* (n = 16, [38.1%]), *E. coli* (n = 9 [21.4%]), *Proteus mirabilis* (n = 9 [21.4%]), *Stenotrophomonas maltophilia* (n = 4 [9.5%]), *Serratia marcescens* (n = 3 [7.1%]), *Enterobacter* spp. (n = 2 [4.8%]), *Achromobacter* (n = 1 [2.4%]), *Elizabethkingia anopheles* (n = 1 [2.4%]), *Haemophilus influenzae* (n = 1 [2.4%]). Although the relative number of monomicrobial infections was consistently higher than polymicrobial ABC infections across regions, there were fewer monomicrobial infections in Latin America (55%) and more in China (77%).

**Table 167. Baseline Pathogens Isolated in Subjects in Part A of Phase 3 Clinical Study, CS2514-2017- 0004**

| Baseline Pathogen | Sulbactam-Durlobactam N=63 N (%) | Colistin N=62 N (%) | Total N=125 N (%) |
|---|---|---|---|
| *Acinetobacter baumannii* | 50 (79.3) | 51 (82.3) | 101 (80.8) |
| Acinetobacter baumannii-calcoaceticus complex | 9 (14.1) | 6 (9.7) | 15 (12.0) |
| *Acinetobacter dijkshoorniae* | 1 (1.6) | 0 (0.0) | 7 (5.6) |
| *Acinetobacter nosocomialis* | 0 (0.0) | 2 (3.2) | 1 (0.8) |
| *Acinetobacter* spp. | 3 (4.7) | 4 (6.2) | 2 (1.6) |
| Monomicrobial | 36 (57.1) | 43 (69.4) | 79 (63.2) |
| Polymicrobial | 27 (42.9) | 19 (30.6) | 46 (36.8) |
| ABC + gram negative isolates | 24 (38.1) | 18 (29.0) | 42 (33.6) |
| ABC + gram positive isolates | 2 (3.2) | 1 (1.6) | 3 (2.4) |
| ABC + fungal isolates | 1 (1.6) | 0 (0.0) | 1 (0.8) |

Source: Clinical Study Report CS2514-2017-0004
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; N, number of subjects

## Per-Pathogen Response

Analyses of 28-day all-cause mortality, clinical cure and microbiological favorable response by baseline isolate showed that (Table 168):

- Subjects in the sulbactam-durlobactam arm had lower mortality rates than in the colistin arm due to CRABC. The proportion of subjects infected with *A. baumannii* who died by day 28 was lower in the sulbactam-durlobactam arm than in the colistin arm (20% versus 33%). This difference was also observed in subjects infected with other *Acinetobacter* spp. in the sulbactam-durlobactam arm compared to colistin (15.4% versus 27.3%).
- A higher proportion of subjects with ABC isolates experienced clinical cure in the sulbactam-durlobactam arm than in the colistin arm at EOT, TOC and LFU. The single subject in the sulbactam-durlobactam arm whose baseline isolate was identified as *A. dijkshoorniae* experienced clinical cure at all time points. Of the two subjects in the colistin arm whose baseline isolate was identified as *A. nosocomialis*, one experienced clinical cure at EOT, but neither experienced clinical cure at TOC or LFU.

- At TOC, the overall eradication or presumed eradication rate in the sulbactam-durlobactam was 61.9% in the sulbactam-durlobactam arm compared to 40.3% in the colistin arm.

**Table 168. Summary of Outcomes by 28-Day All-Cause Mortality, Clinical Cure and Microbiological Favorable Assessments by *Acinetobacter* Spp. in CRABC m-MITT Population**

| CRABC m-MITT | Sulbactam-Durlobactam N=63 N (%) | Colistin N=62 N (%) | Total N=125 N (%) |
|---|---|---|---|
| 28-day ACM | 12 (19.0) | 20 (32.3) | 32 (25.6) |
| *Acinetobacter baumannii* | 10/50 (20.0) | 17/51 (33.3) | 27/101 (26.7) |
| *Acinetobacter baumannii-calcoaceticus* | 2/9 (22.2) | 2/6 (33.3) | 4/15 (26.7) |
| *Acinetobacter* spp. | 0/3 (0.0) | 1/3 (33.3) | 1/6 (16.7) |
| *A. dijkshoorniae* | 0/1 (0.0) | 0 (0.0) | 0/1 (0.0) |
| *A. nosocomialis* | 0 (0.0) | 0/2 (0.0) | 0/2 (0.0) |
| Clinical cure at TOC | | | |
| *Acinetobacter baumannii* | 30/50 (60.0) | 20/51 (39.2) | 50/101 (49.5) |
| *Acinetobacter baumannii-calcoaceticus* | 6/9 (66.7) | 4/6 (66.7) | 10/15 (66.7) |
| *Acinetobacter* spp. | 2/3 (66.7) | 1/3 (33.3) | 3/6 (50.0) |
| *A. dijkshoorniae* | 1/1 (100.0) | 0 (0.0) | 1/1 (100.0) |
| *A. nosocomialis* | 0 (0.0) | 0/2 (0.0) | 0/2 (0.0) |
| *A. nosocomialis* | 0 (0.0) | 0/2 (0.0) | 0/2 (0.0) |
| Microbiological response at TOC | | | |
| *Acinetobacter baumannii* | 30/50 (60.0) | 20/51 (39.2) | 50/101 (49.5) |
| *Acinetobacter baumannii-calcoaceticus* | 6/9 (66.7) | 4/6 (66.7) | 10/15 (66.7) |
| *Acinetobacter* spp. | 2/3 (66.7) | 1/3 (33.3) | 3/6 (50.0) |
| *A. dijkshoorniae* | 1/1 (100.0) | 0 (0.0) | 1/1 (100.0) |
| *A. nosocomialis* | 0 (0.0) | 0/2 (0.0) | 0/2 (0.0) |

Source: Study Report# PC2514-2022-0003
Abbreviations: ACM, all-cause mortality; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; m-MITT, microbiologically modified intent-to-treat; N, number of subjects; TOC, test of cure

Sulbactam-durlobactam MICs were determined in subjects that had the baseline isolate shipped to the central laboratory; three subjects' baseline isolates were not shipped and therefore no MICs were generated. Of the 60 subjects in the sulbactam-durlobactam arm, the sulbactam-durlobactam MIC values ranged from 0.5 to 4 mg/L with $MIC_{50/90}$ values of 2 and 4 mg/L (Table 169). None of the isolates had MICs >8 mg/L. Table 169 shows the sulbactam-durlobactam MIC distributions of baseline CRABC isolates which showed that:

- There was no trend towards higher sulbactam-durlobactam MIC values among subjects who died or whose death was considered related to the index infection compared to subjects who survived until day 28.
- The overall eradication or presumed eradication rate in the sulbactam-durlobactam arm varied from 50 to 86% when categorized by MIC with 50% at 0.5 mg/L, 64% at 1 mg/L, 74% at 2 mg/L and 86% at 4 mg/L.
- Of the subjects with persistent or recurrent isolates, one subject had an elevated sulbactam-durlobactam MIC value compared to the baseline isolate. The MIC at the TOC visit increase by 2-fold (from 4 mg/L to 8 mg/L). The Applicant stated genomic analysis showed that it was the same infecting isolate. The only genetic difference between baseline and subsequent isolates was a G288S mutation in the AdeJ gene which is

associated with efflux resistance. This mutation was not observed in nonclinical resistance studies, it is not known whether other mutations were present such PBP3 mutations or if MBLs (i.e., NDMs) were present in the isolate, the clinical importance of these mutations is unknown (see Section 20.2).

**Table 169. Day 28 Mortality, Clinical Cure and Favorable Microbiological Response by Baseline Pathogens and Sulbactam-Durlobactam MIC**

| MIC (mg/L) | 28-Day Mortality n/N (%) | Clinical Cure n/N (%) | Eradication/Presumed Eradication n/N (%) |
|---|---|---|---|
| 0.5 | 1/4 (25.0) | 3/4 (75.0) | 2/4 (50.0) |
| 1 | 5/22 (22.7) | 13/22 (59.1) | 14/22 (63.6) |
| 2 | 6/27 (22.2) | 17/27 (63.0) | 20/27 (74.1) |
| 4 | 0/7 (0.0) | 4/7 (57.1) | 6/7 (85.7) |
| No data | 0/3 (0.0) | 2/3 (66.7) | 1/3 (33.3) |

Source: Study Report CS2514-2017-0004
Abbreviations: MIC, minimum inhibitory concentration; n, number of subjects in category; N, number of subjects

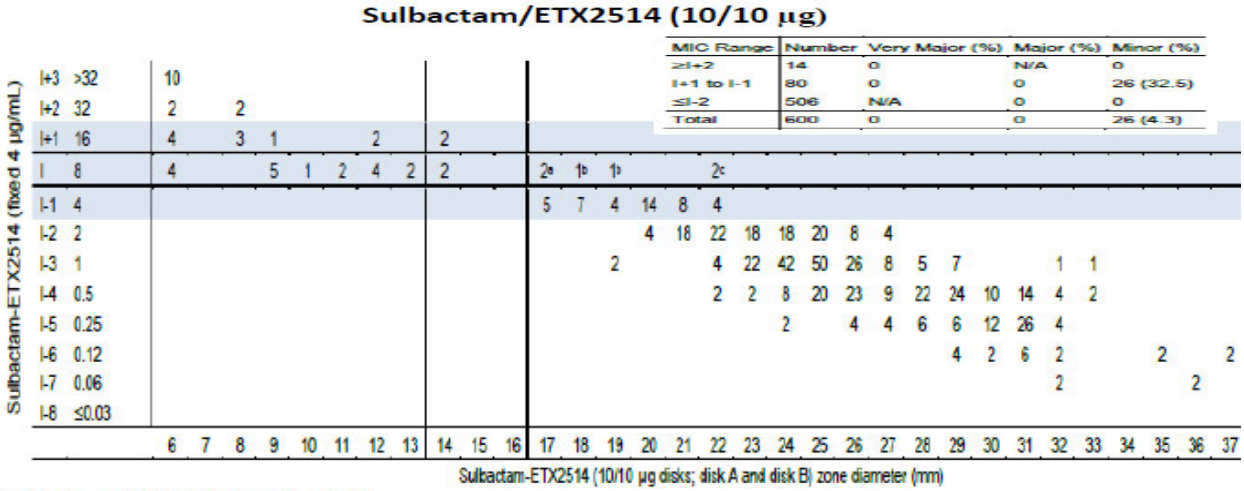
## 19.3. Susceptibility Testing Interpretive Criteria

Based on information from the phase 3 clinical study, the data showed that:

- Surveillance and clinical studies show that the upper bound of the wild-type proportion of the sulbactam-durlobactam MIC is 4 mg/L for sulbactam at a fixed durlobactam concentration of 4 mg/L. US surveillance studies (2016 to 2020) showed that sulbactam-durlobactam $MIC_{50/90}$ values were 1 to 2 mg/L and 2 to 4 mg/L, respectively. In the phase 3 study, there were no isolates that showed sulbactam-durlobactam MICs >8 mg/L. Most of the isolates in the clinical study were predominantly from Asia-South Pacific region which had similar MIC values to those found in the global surveillance studies.
- Animal model studies showed a significant reduction in CFU count against *A. baumannii* isolates with sulbactam-durlobactam MICs ≤4 mg/L. Sulbactam activity was restored in the presence of durlobactam at $ED_{50}$ ranging from 5.93 to 7.54 mg/kg q3h or 35.3 to 100 mg/kg given q6h. Against sulbactam-resistant *A. baumannii* isolates with sulbactam-durlobactam MICs ≤4 mg/L, sulbactam administered at a fixed concentration of 15 mg/kg and varying concentrations of durlobactam showed a dose proportional reduction in bacterial burden. Sulbactam-resistant *A. baumannii* isolates with sulbactam-durlobactam MICs >4 mg/L required higher sulbactam doses (150 mg/kg) as well as an increase in durlobactam concentration to show a dose proportional reduction in bacterial burden.
- PK/PD target attainment analyses showed that plasma free drug exposure will be achieved in more than 98 to 100% of subjects with normal to altered renal impairment with isolates having sulbactam-durlobactam MIC values ≤4 mg/L. This is based on a dosing regimen of 1g sulbactam/1g durlobactam given that greater than 1-$log_{10}$ kill can be achieved when sulbactam exposures exceeded the MIC for 30 to 50% *f*T > MIC and durlobactam *f*AUC/MIC ratio ≥10.

- Clinical evidence shows a high microbiological eradication rate against ABC isolates with sulbactam-durlobactam MIC values ≤4 mg/L. There were no isolates in subjects with sulbactam-durlobactam MICs >8 mg/L. Though there were no trends in favorable outcomes based on increasing sulbactam-durlobactam MIC values; overall at sulbactam-durlobactam MICs ≤4 mg/L the 28-day mortality rate, clinical cure and microbiological eradication/presumed eradication were 19%, 61.9% and 68.3%, respectively against CRABC isolates.
- By the disk diffusion method, the proposed zone diameters are ≥17 mm as susceptible, 14 to 16 mm as intermediate and ≤13mm for resistant resulted in acceptable errors (Figure 35, Table 170). Kirby Bauer disks containing 10 µg/10 µg sulbactam-durlobactam were provided by the Mast Group Ltd for disk diffusion testing. Based on the error rate bounded method, the zone diameters were compared to the susceptibility testing criteria of sulbactam-durlobactam MICs by the broth microdilution method of ≤4 mg/L as susceptible, 8 mg/L as intermediate and ≥16 mg/L as resistant (at a fixed durlobactam concentration of 4 mg/L). There were no very major or major categorical errors with minor categorical errors of 32.5% (an overall minor error rate of 4.3%). No information was provided on the resistance mechanisms for isolates that resulted in minor errors.

**Figure 35. Scattergram and Tabular Presentation Comparing Sulbactam/ETX2514 (Fixed 4 µg/mL) MIC Results to Zone Diameter Values of 10/10 µg Sulbactam ETX2514 Disks in Duplicate Against 300 A. baumannii Complex Isolates**




| MIC Range | Number | Very Major (%) | Major (%) | Minor (%) |
|---|---|---|---|---|
| ≥I+2 | 14 | 0 | N/A | 0 |
| I+1 to I-1 | 80 | 0 | 0 | 26 (32.5) |
| ≤I-2 | 506 | N/A | 0 | 0 |
| Total | 600 | 0 | 0 | 26 (4.3) |

[a] *Acinetobacter baumannii* strain number 909853
[b] *Acinetobacter baumannii* strain number 985120
[c] *Acinetobacter baumannii* strain number 985126
Source: Study Report# PC2514-2017-0004
Abbreviations: ETX2514, durlobactam; MIC, minimum inh bitory concentration; N/A, not applicable

**Table 170. Overall Calculated Error Rates for Sulbactam-Durlobactam (Fixed at 4 µg/mL) MIC Values Versus Sulbactam-Durlobactam Zone Diameters Using 10/10 µg Disk**

| Zone Diameter Criteria (mm) | | | Error Rates (%) | | |
|---|---|---|---|---|---|
| Susceptible | Intermediate | Resistant | Very major | Major | Minor |
| ≥10 | 7 - 9 | ≤6 | 0.7 | 0 | 4.5 |
| ≥11 | 7 -10 | ≤6 | 0.7 | 0 | 4.3 |
| ≥11 | 8 -10 | ≤7 | 0.7 | 0 | 4.3 |
| ≥12 | 8 - 11 | ≤7 | 0.7 | 0 | 4.0 |
| ≥12 | 9 - 11 | ≤8 | 0.7 | 0 | 3.2 |
| ≥13 | 9 - 12 | ≤8 | 0.3 | 0 | 2.8 |
| ≥13 | 10 - 12 | ≤9 | 0.3 | 0 | 3.5 |
| ≥14 | 10 - 13 | ≤9 | 0.3 | 0 | 3.2 |
| ≥14 | 11 - 13 | ≤10 | 0.3 | 0 | 3.3 |
| ≥15 | 11 - 14 | ≤10 | 0 | 0 | 3.3 |
| ≥15 | 12 - 14 | ≤11 | 0 | 0 | 3.7 |
| ≥16 | 12 - 15 | ≤11 | 0 | 0 | 3.7 |
| ≥16 | 13 - 15 | ≤12 | 0 | 0 | 4.0 |
| ≥17 | 13 - 16 | ≤12 | 0 | 0 | 4.0 |
| ≥17 | 14 - 16 | ≤13 | 0 | 0 | 4.3 |
| ≥18 | 14 - 17 | ≤13 | 0 | 0 | 4.8 |
| ≥18 | 15 - 17 | ≤14 | 0 | 0 | 4.8 |
| ≥19 | 15 - 17 | ≤14 | 0 | 0 | 5.8 |
| ≥19 | 16 - 18 | ≤15 | 0 | 0 | 5.8 |
| ≥20 | 16 - 19 | ≤15 | 0 | 0 | 6.7 |
| ≥20 | 17 - 19 | ≤16 | 0 | 0 | 9.7 |
| ≥21 | 17 - 20 | ≤16 | 0 | 0 | 9.7 |

Source: Study Report# PC2514-2017-0004
Abbreviations: MIC, minimum inhibitory concentration

The following susceptibility interpretive criteria are recommended:

**Table 171. Recommended Susceptibility Interpretive Criteria**

| | Minimum Inhibitory Concentrations (mg/L) | | | Disk Diffusion (Zone Diameter in mm) | | |
|---|---|---|---|---|---|---|
| Pathogen | S | I | R | S | I | R |
| *Acinetobacter baumannii* | ≤ 4 | 8 | ≥ 16 | ≥ 17 | 14 - 16 | ≤ 13 |

Abbreviations: I, intermediate; R, resistant; S, susceptible

# 20. Mechanism of Action/Drug Resistance

## 20.1. Mechanism of Action

Sulbactam is a beta-lactam antibacterial and an Ambler Class A serine beta-lactamase inhibitor. Sulbactam inhibits PBP transpeptidase, which is essential for bacterial cell wall synthesis and subsequent crosslinking of peptidoglycan layer. It has antibacterial activity against *Acinetobacter* spp. preferentially binding to PBP1a/b and PBP3 orthologs with MICs ranging from 1 mg/L to 32 mg/L (Penwell et al. 2015; Shapiro et al. 2017). Resistance to sulbactam in *Acinetobacter* spp. is due to the production of β-lactamases. Most *Acinetobacter* spp. possess one or more β-

lactamases that inactivate sulbactam. Sulbactam is readily cleaved by Ambler Class D β-lactamases (OXA-23 and OXA-24/40), and to some extent by Ambler Class A β-lactamases (TEM-1, KPC-2) but generally is less susceptible to cleavage by Ambler Class C β-lactamases (ADC-type AmpC).

Durlobactam is a novel non-β-lactam β-lactamase inhibitor that contains a diazabicyclooctane scaffold rather than a β-lactam core. Durlobactam binds to the catalytic site of serine-β-lactamases by forming a covalent bond in the active site of the serine β-lactamase nucleophile resulting in opening of the cyclic urea ring. Durlobactam displays a time-dependent inactivation, the bond between durlobactam and β-lactamase is reversible, allowing the inhibitor to recyclize and dissociate in its original form (PC2514-2016-0010, PC2514-2016-0011, PC2514-2020-0016) (Durand-Reville et al. 2017; Shapiro et al. 2017; Barnes et al. 2019). Durlobactam showed broad spectrum inhibition of isogenic *A. baumannii* strains overexpressing serine β-lactamases including Ambler Class A (TEM-1, KPC-2), Class C (ADC-30) and Class D (OXA-23, OXA-24/40) by fully restoring sulbactam activity by 2- to 64-fold (PC2514-2021-0012, 2514-2022-0017) (Durand-Reville et al. 2017). The durlobactam half maximal inhibitory concentration values ranged from 0.004 to 0.0008 µM against Class A enzymes (KPC-2, TEM-1, CTX-M-15) and 0.18 to 0.0063 µM against Class D (OXA-23, OXA-24/40, OXA-10, OXA-48), with >200 µM against Class B enzymes (NDM) (PC2514-2016-0010) (Durand-Reville et al. 2017). Durlobactam does not inhibit the Class B metallo-β-lactamases such as New Delhi metallo- β-lactamases [NDM] (PC2514-2016-0035). Durlobactam alone does not have antimicrobial activity against *Acinetobacter* spp. showing MIC values >32 mg/L (PC2514-2016-0002) (McLeod et al. 2020; Yang et al. 2020).

## 20.2. Drug Resistance

Mechanisms of β-lactam resistance in *A. baumannii-calcoaceticus* complex may include either the production of β-lactamases, modification of PBPs or target alteration, up-regulation of efflux pumps or loss of outer membrane porin.

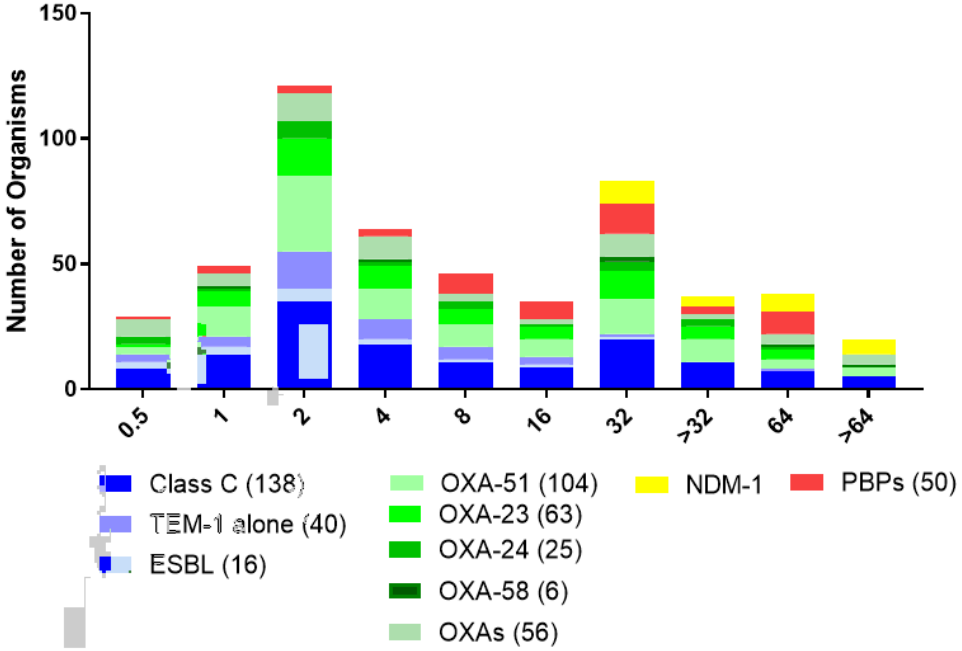
Reduced susceptibility to sulbactam-durlobactam in global surveillance and resistance studies showed that:

- Presence of β-lactamases
  - Sulbactam-durlobactam is not active against organisms that express blaNDM-1 or any other metallo-β-lactamase (Figure 36). In a global study of isolates that had sulbactam-durlobactam MIC values >4 mg/L (n = 75), approximately 47% (n = 29) encoded for a metallo-β-lactamase, mostly NDM variants. Isolates that encoded for metallo- β-lactamases showed sulbactam-durlobactam MIC values that ranged from 32 to >64 mg/L demonstrating no significant shift in MIC for sulbactam when tested alone (PC2514-2020-0012, PC2514-2021-0002).
  - Isolates that either produce multiple β-lactamases or express varying levels of β-lactamases may also contribute to sulbactam-durlobactam resistance; though the combinations of these β-lactamases that contribute to higher sulbactam-durlobactam MICs is unknown. In a study that evaluated non-NDM isolates with sulbactam-durlobactam MICs >8 mg/L (n = 25), the acquired OXA-type

carbapenemases encoded genes identified included *bla*OXA-23 (n = 19), *bla*OXA-72 (n = 5) and *bla*OXA-24 (n = 1). Amongst the intrinsic *bla*OXA-51 like genes, most isolates had *bla*OXA66 (n = 18), *bla*OXA68 (n = 2) and *bla*OXA90 (n = 2) and single isolates each had either *bla*OXA-64, *bla*OxA-69 or *bla*OXA-94. Three isolates harbored ESBLs including *bla*GES-11 (n = 1) or *bla*CTX-M-115 (n = 2); one isolate harbored *bla*CARB-16 and, 7 isolates harbored *bla*TEM-1 which is known to confer resistance to sulbactam (PC2514-2021-0006) (Findlay et al. 2022).

- In addition, carriage or the presence of insertion sequence *ISAba1* upstream to intrinsic cephalosporinase *bla*ADC resulted in overexpression of *bla*ADC-30 or *bla*ADC-73 was reported in 2 of 8 isolates resulting in sulbactam-durlobactam MICs >8 mg/L (PC2514-2021-0006) (Findlay et al. 2022).

**Figure 36. Sulbactam-Durlobactam Showed Varying Susceptibility Against Isolates Carrying Ambler Class A, B, C or D Subtypes**




Source: PC2514-2016-0008 (Reviewer's analyses)
Abbreviations: ESBL, extended-spectrum β-lactamase; NDM-1, New Delhi metallo-beta-lactamase 1; OXA, ambler class D β-lactamase; PBP, penicillin-binding protein; q3h, every 3 hours; q6h, every 6 hours; SUL, su bactam; TEM, ambler class A β-lactamase

- Changes in penicillin-binding proteins

  - Amino acid changes around the active target site of sulbactam (PBP3) correlated with higher sulbactam-durlobactam MIC values. In a global study of isolates that had sulbactam-durlobactam MIC values >4 mg/L (n = 75), approximately 63% (n = 39) encoded for 1 or 2 amino acid changes near the active site of PBP3. The most prevalent changes in PBP3 were T526S (n = 19, including 5 in conjunction with N377Y) and A515V (n = 11). In terms of the lowest to highest inhibition of sulbactam-durlobactam T526S < G523V < A515V < Q488K < N377Y < N392T. Other mutations that were also detected in single isolates included V146I, K235N,

I517N, V565L, F5481 as well as changes in PBP1b and PBP2. Isolates containing these mutations did not appear in any of the sulbactam or sulbactam-durlobactam isolates tested with MICs ≤4 mg/L (PC2514-2020-0012, PC2514-2021-0002). Since these are mutations that likely affect sulbactam binding to its target, changing the relative concentration of the durlobactam would not be expected to fully restore sulbactam susceptibility (PC2514-2017-0008). Similar PBP3 amino acids changes were reported in spontaneous resistance studies and serial passage studies (PC2514-2016-0003, PC2514-2018-0007, PC2514-2021-0006) (Penwell et al. 2015; Findlay et al. 2022).

- Presence of efflux pumps
  - An isogenic panel of *A. baumannii* mutant strains that result in the overexpression of either AdeABC, AdeFGH or AdeIJK efflux systems. These efflux systems had no impact on sulbactam-durlobactam, sulbactam or durlobactam MICs suggesting that sulbactam-durlobactam is not a major substrate for the most common efflux pumps found in *A. baumannii* (PC2514-2021-0006, PC2514-2021-0013) (Findlay et al. 2022). This is consistent with the global study that evaluated isolates with sulbactam-durlobactam MICs greater than 4 mg/L, several different single amino acid changes in efflux components of the AdeABC, AdeFGH and AdeIJK RND efflux systems were detected. In addition, transposon insertions and single amino acid changes were found in adeS or adeR which are part of the AdeRS two component regulatory system for the regulation of AdeABC efflux system. Mutations in AdeRS can lead to an increase in AdeABC expression and an increase in antibiotic efflux. However, for each of the mutations in efflux system, the isolate also encoded for variations in the target of sulbactam (PBP3) or for NDM-1, making it difficult to define the extent to which these changes affected sulbactam-durlobactam activity (PC2514-2020-0012, PC2514-2021-0002).
- Outer membrane proteins
  - There were no relevant marked differences in outer membrane pore expression that correlated with reduced susceptibility to sulbactam-durlobactam. A study that assessed the presence of outer membrane proteins expression (*OmpA* and *CarO*) showed that both sulbactam-durlobactam sensitive and resistant strains (MICs ranging 0.5/4 – 32/4 mg/L) expressed *OmpA* and *CarO* proteins or *OmpA* and *CarO*-like porins in the outer membrane (PC2514-2020-0020). In non-NDM isolates with SUL-DUR MICs >8 mg/L (n=25), no significant mutations or disruptions were detected in major porin encoding genes (*OmpA, carO, OmpW* and *OprD*) (PC2514-2021-0006) (Findlay et al. 2022). Similar observations were reported in other studies (PC2514-2021-0002, PC2514-2020-0012).

Overall, it is likely that co-existence of other resistance mechanisms such as multiple beta-lactamases as well as expressing varying levels of beta-lactamases, mutations of PBPs, overexpression of efflux pump or porin changes can affect sulbactam-durlobactam MIC simultaneously.

The frequency of spontaneous resistance to sulbactam-durlobactam shows a low potential for development of resistance in *A. baumannii*. Against a carbapenemase-hydrolyzing Class D *A. baumannii* isolate, the frequency of spontaneous resistance to sulbactam-durlobactam was low at 2x MIC (range, $2.1 \times 10^{-8}$ to $<7.6 \times 10^{-10}$) and at 4x MIC (range, $7.6 \times 10^{-10}$ to $<9.0 \times 10^{-10}$). Stable mutants could not be isolated at 8x MIC. Mutants showed an increased in the sulbactam-durlobactam MICs by 8 to >32-fold compared to parental strains, most mutations were mapped to the gene encoding PBP3 at or near the sulbactam binding site (PC2514-2016-0003) (Penwell et al. 2015; McLeod et al. 2020). In serial passage studies, resistance to sulbactam-durlobactam arose in each of the 5 MDR *A. baumannii* strains tested, with differing rates and step changes. Sulbactam-durlobactam MICs increased 16x to ≥256x by 8 to 10 days and remained elevated after drug-free passage (PC2514-2018-0007).

# 21. Other Drug Development Considerations

Not applicable.

# 22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Please refer to Section 10 for OSI's assessment. The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of this indication. The Office of Computational Science on November 21, 2022, provided a data quality assessment, adverse event coding report, and overall data fitness assessment for the safety NDA 216974 review. Overall, the data quality for the clinical trials submitted was adequate to perform the review.

# 23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI submitted on September 29, 2022 (see Table 172 below). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

**Table 172. Key Labeling Changes and Considerations**

| Full PI Sections[1] | Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI |
|---|---|
| | |
| 1 INDICATIONS AND USAGE | The Applicant's proposed indication (b) (4) The revised indication is: "For the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex in patients 18 years of age and older."<br><br>Added a Limitation of Use to emphasize that sulbactam-durlobactam spectrum of activity is limited to *Acinetobacter baumannii-calcoaceticus* complex. The Limitations of Use is: "XACDURO is not indicated for the treatment of HABP/VABP caused by pathogens other than susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex *[see Clinical Studies (14)]*."<br><br>Refer to Sections 6.2 and 16 of the Integrated Assessment Review for additional information |
| 2 DOSAGE AND ADMINISTRATION | Revised recommended dosage of XACDURO for adults with altered renal function so that 1 g SUL/1 g DUR is recommended across all renal function categories with the adjustment of dosing frequencies to simplify the process of dosing preparation and drug administration. Refer to Section 8.1.2 of the IA for additional information. |
| 6 ADVERSE REACTIONS | (b) (4) |
| 7 DRUG INTERACTIONS | Revised drug interaction language related to OAT1 inhibitors to include specific instructions for preventing this clinically significant drug interaction as per 21 CFR 201.57 (c)(8). Refer to Section 8.2.1 of the IA for additional information. |
| 8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment) | Revised subsection 8.1 Pregnancy to include a description of the increased incidence of skeletal variations observed in a mouse embryofetal development study. Also added relevant information from reproductive studies conducted in animals with sulbactam from FDA approved labeling for the listed drug UNASYN (Pfizer 1986). Refer to Section 13.2.1.4 of the IA for additional information.<br>Revised Applicant's proposed concentrations of sulbactam in breastmilk in the Lactation subsection 8.2 of the PI based on published data. Refer to the publication. Refer to the Division of Pediatric and Maternal Health Review in DARRTS (dated 5/10/2023) for additional information.<br><br>Revised Renal Impairment subsection 8.6 to reflect the Division's recommendation on the dose adjustments in patients with altered renal function. Refer to Section 8.1.1 of the IA for additional information. |
| 12 CLINICAL PHARMACOLOGY | Revised the statement for Cardiac Electrophysiology under Section 12.2 Pharmacodynamics and revised/reformatted Section 12.3 Pharmacokinetics to reflect our recommendations and to streamline the contents of this subsection in accordance with the FDA's Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products-Content and Format, Guidance for Industry (December 2016) (refer to Sections 5, 8 and 14 of the IA for additional information). |

| Full PI Sections[1] | Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI |
|---|---|
| | Revised mechanism of action, resistance and animal models of infection in section 12.4 Microbiology (refer to Sections 19 and 20 of the IA for additional information). |
| 13 NONCLINICAL TOXICOLOGY | Revised to include all the genotoxicity tests that have been conducted with sulbactam and durlobactam and to provide the results of those tests. Refer to Section 13.2.1 for additional information. |
| 14 CLINICAL STUDIES | (b) (4) |
| 17 PATIENT COUNSELING INFORMATION | Revised the regulatory required verbatim statement in 21 CFR 201.24 (d) to read as: "Patients should be counseled that antibacterial drugs including XACDURO should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). Patients should be told that the medication should be taken exactly as directed."<br>(b) (4)<br>Based on discussions with the OND Labeling Policy Team (email dated 4/11/2023) this rationale provides adequate justification for deviating from the required verbatim text which requires omitting (b) (4) [see 21 CFR 201.56 (d)(4) or (b) (4) 21 CFR 201.56 (a)(2)] aspects of the verbatim statement in this unique labeling circumstance. |
| Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) | Refer to the Integrated Quality Assessment. |

[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviations: CFR, Code of Federal Regulations; CI, confidence interval; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DAARTS, Document Archiving, Reporting, and Regulatory Tracking System; DUR, durlobactam; IA, interdisciplinary assessment; OAT1, organic anion transporter 1; OPQ, Office of Pharmaceutical Quality; m-MITT, microbiologically modified intent-to-treat; PI, Prescr bing Information; SUL, su bactam; TOC, test of cure

## 23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

(1) Prescribing Information

(2) Instructions for Use for Health Care Providers

(3) Carton and Container Labeling

# 24. Postmarketing Requirements and Commitments

The following post marketing requirements/commitments have been requested by FDA and agreed to by the Applicant. Please refer to the approval letter for the final postmarketing requirements and commitments language and timelines.

**Post Marketing Requirements**

REQUIRED PEDIATRIC ASSESSMENTS:

Conduct a multi-dose study to assess the pharmacokinetics, safety and tolerability of sulbactam-durlobactam in children from birth to less than 18 years who are receiving systemic antibiotic therapy for suspected or confirmed infection.

- Final protocol submission: 12/2023
- Study completion: 5/2028
- Final report submission: 11/2028

POSTMARKETING REQUIREMENTS UNDER 505(o):

Conduct a single-arm, open-label, prospective, observational study to assess the safety of sulbactam-durlobactam, including the risk of hypersensitivity reactions (including anaphylaxis) in patients with *Acinetobacter baumannii-calcoaceticus* complex infection.

- Final protocol submission: 02/2024
- Study completion: 02/2029
- Final report submission: 08/2029

Conduct a mouse lymphoma TK assay (MLA) or hypoxanthine phosphorylbosyl transferase (HPRT) forward mutation assay to assess the mutagenic potential of impurity (b) (4)

- Final Protocol Submission: 11/2023
- Study Completion: 2/2024
- Final Report Submission: 05/2024

Conduct a US surveillance study for a five-year period after the introduction of sulbactam-durlobactam to the market to monitor changes in susceptibility of *Acinetobacter baumannii-calcoaceticus* complex organisms to sulbactam-durlobactam.

- Final Protocol Submission: 09/2023
- Interim Report: 11/2024
- Interim Report: 11/2025
- Interim Report: 11/2026
- Interim Report: 11/2027
- Interim Report: 11/2028
- Study Completion: 11/2028

- Final Report Submission: 2/2029

Conduct studies for durlobactam drug substance and drug product, as identified in the final protocol, to further characterize the safety of their impurity profiles and establish drug substance and drug product impurity controls to ensure that each impurity limit is in accordance with ICH Q3A, Q3B, and M7, as applicable.

- Draft Protocol Submission: 12/2023
- Final Protocol Submission: 03/2024
- Interim Report Submission # 1: 06/2024
  (Long term and accelerated stability through 6 months, and in-use stability data using the methods in the NDA)
- Interim Report Submission # 2: 07/2024
  (Completion of impurity isolation and characterization studies)
- Interim Report Submission # 3: 11/2024
  (HPLC impurities method optimization/re-validation study data)
- Interim Report Submission # 4: 12/2024
  (Long term stability through 12 months and in-use stability data using the methods in the NDA)
- Interim Report Submission # 5: 03/2025
  (Identification and qualification study data, if needed)
- Interim Report Submission # 6: 06/2025
  (Comparability long term and additional in-use stability data based on a revised regulatory HPLC method and a revised IV-bag method [if needed])
- Study completion: 09/2025
- Final Report Submission: 12/2025

**Post marketing commitments**:

Complete the repeat dose toxicity study in neonatal 10-day old rats to support the planned clinical trial in children from birth to less than 1 year of age.

- Study Completion: 9/2023
- Final Report Submission: 12/2023

Conduct studies to update the manufacturing process for each of the drug product components (i.e., durlobactam for injection and sulbactam for injection) to demonstrate that the labeled vial content can be withdrawn at the lower end of the fill weight variation range following reconstitution, and as appropriate to establish suitable in-process and finished drug product controls/specifications.

- Draft Protocol Submission: 12/2023
- Final Protocol Submission: 03/2024
- Interim Report Submission: 12/2024
- Final Report Submission: 04/2025

# 25. Financial Disclosure

**Table 173. Covered Clinical Studies: CS2514-2017-0004, Phase 3 Study**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 647 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): None | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here.<br>Significant payments of other sorts: Enter text here.<br>Proprietary interest in the product tested held by investigator: Enter text here.<br>Significant equity interest held by investigator: Enter text here.<br>Sponsor of covered study: Enter text here. | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) NA |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) NA |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): 5 | | |
| Is an attachment provided with the reason: | Yes ☒☐ | No ☐ (Request explanation from Applicant) |

Abbreviations: NA, not applicable

# 26. References

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Guidance for Industry *Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment* (May 2014)

Draft Guidance for Industry *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers (Revision 1)* (May 2022)

Guidance for Industry *M10 Bioanalytical Method Validation and Study Sample Analysis; International Council for Harmonisation* (November 2022)

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# 27. Review Team

**Table 174. Reviewers of Integrated Assessment**

| Role | Names |
|---|---|
| Regulatory project manager | Chris Davi |
| Chief Project Management Staff | Gregory DiBernardo |
| Pharmacology-toxicology reviewer | Owen McMaster |
| Pharmacology-toxicology Deputy Division Director | Terry Miller |
| OCP reviewer | Xiaohui (Tracey) Wei |
| OCP team leader | Dakshina Chilukuri |
| Clinical reviewer | Mayurika Ghosh |
| Clinical team leader | Dmitri Iarikov |
| Biometrics reviewer | Karen Qi |
| Biometrics team leader | Daniel Rubin |
| Cross-disciplinary team leader | Dmitri Iarikov |
| Pharmacology-Toxicology Division Director | Hanan Ghantous |
| Deputy Division Director (OCP) | Zhixia (Grace) Yan Danielsen |
| Director Project Management Staff | Maureen Dillon-Parker |
| Associate Director for Labeling | Abimbola Adebowale |
| Deputy Division Director | Dmitri Iarikov |
| Division Director | Peter Kim |
| Deputy Office Director (designated signatory authority) | Adam Sherwat |

Abbreviations: Division, Division of Anti-Infectives; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; Office, Office of Infectious Diseases

**Table 175. Additional Reviewers of Application**

| Office or Discipline | Name(s) |
|---|---|
| OPQ | Dorota Matecka; George Lunn; Katherine Windsor; Karina Zuck |
| Microbiology | Simone Shurland; Avery Goodwin |
| OPDP | Phillip Williams; Sam Skariah |
| OSI | Cheryl Grandinetti |
| OSE/DMEPA | Deborah Myers; Valerie S. Vaughan |
| DPMH | Christos Mastroyannis; Tamara Johnson; Lynne P. Yao |

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatrics and Maternal Health Review; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology

# 27.1. Reviewer Signatures

**Table 27-176 Signatures of Reviewers**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Biostatistics Discipline<br>Secondary Reviewer | Daniel Rubin<br>OB<br>DBIV | Sections: 6, 15, 16 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Daniel Rubin**

**Digitally signed by Daniel Rubin**

**Date: 5/22/2023 2:46 PM EDT**
**GUID: 2023522184616**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Regulatory Project Manager Discipline<br>Secondary Reviewer | Gregory Dibernardo<br>ORO<br>DROID | Sections: 12 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature:** **Gregory Dibernardo**

**Digitally signed by Gregory Dibernardo**

**Date: 5/22/2023 2:48 PM EDT**
**GUID: 2023522184828**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Microbiology Discipline<br>Primary Reviewer | Simone Shurland<br>OID<br>DAI | Sections: 19, 20, 23, 5.1 | Based on my assessment of the application:<br>☐ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☒ Not applicable. | |

**Signature:** **Simone Shurland**

**Digitally signed by Simone Shurland**

**Date: 5/22/2023 2:54 PM EDT**
**GUID: 2023522185423**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Pharmacology Discipline<br>Primary Reviewer | Xiaohui Wei<br>OCP<br>DIDP | Sections: 5, 6.1, 8, 14.1, 14.2, 14.3, 23 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Xiaohui Wei**

**Digitally signed by Xiaohui Wei**

**Date: 5/22/2023 2:59 PM EDT**
**GUID: 202352218591**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Pharm-tox/Non-clinical Discipline<br>Tertiary Reviewer | Hanan Ghantous<br>OID<br>DPTID | Sections: pharmacology/toxicology | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Hanan Ghantous**

**Digitally signed by Hanan Ghantous**

**Date: 5/22/2023 3:21 PM EDT**
**GUID: 2023522192139**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Pharm-tox/Non-clinical Discipline<br>Secondary Reviewer | Terry Miller<br>OID<br>DPTID | Sections: 7, 8, 13 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Terry Miller**

**Digitally signed by Terry Miller**

**Date: 5/22/2023 3:22 PM EDT**
**GUID: 2023522192248**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Regulatory Project Manager Discipline<br>Tertiary Reviewer | Maureen Dillon Parker<br>ORO<br>DROID | Sections: 12 | Based on my assessment of the application:<br>☐ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☒ Not applicable. | |

**Signature: Maureen Dillon Parker**

**Digitally signed by Maureen Dillon Parker**

**Date: 5/22/2023 3:23 PM EDT**
**GUID: 202352219232**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Discipline<br>Primary Reviewer | Mayurika Ghosh<br>OID<br>DAI | Sections: 2, 3.1.2, 3.2,4,7,8.3,8.4,17,22, 23,24,25 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Mayurika Ghosh**

**Digitally signed by Mayurika Ghosh**

**Date: 5/22/2023 3:30 PM EDT**
**GUID: 2023522193040**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Pharmacology Discipline<br>Secondary Reviewer | Dakshina Chilukuri<br>OCP<br>DIDP | Sections: 5, 6, 8, 12 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Dakshina Chilukuri**

**Digitally signed by Dakshina Chilukuri**

**Date: 5/22/2023 3:34 PM EDT**
**GUID: 2023522193416**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Pharm-tox/Non-clinical Discipline<br>Primary Reviewer | Owen Mcmaster<br>OID<br>DPTID | Sections: 7, 9, 13, 23, 24 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Owen Mcmaster**

**Digitally signed by Owen Mcmaster**

**Date: 5/22/2023 3:36 PM EDT**
**GUID: 2023522193623**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Biostatistics Discipline<br>Primary Reviewer | Xiaojing Qi<br>OB<br>DBIV | Sections: 6.2, 6.3, 15, 16 and 23 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Xiaojing Qi**

**Digitally signed by Xiaojing Qi**

**Date: 5/22/2023 3:42 PM EDT**
**GUID: 2023522194215**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Regulatory Project Manager Discipline<br>Primary Reviewer | Joseph Davi<br>ORO<br>DROID | Sections: 12 | Based on my assessment of the application:<br>☐ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☒ Not applicable. | |

**Signature: Joseph Davi**

**Digitally signed by Joseph Davi**

**Date: 5/22/2023 4:08 PM EDT**
**GUID: 202352220813**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Discipline<br>Secondary Reviewer | Dmitri Iarikov<br>OID<br>DAI | Sections: I, II, III, | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Dmitri Iarikov**

**Digitally signed by Dmitri Iarikov**

**Date: 5/22/2023 4:15 PM EDT**
**GUID: 2023522201511**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Pharmacology Discipline<br>Tertiary Reviewer | Zhixia Danielsen<br>OCP<br>DIDP | Sections: 5, 6, 8, 14 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Zhixia Danielsen**

**Digitally signed by Zhixia Danielsen**

**Date: 5/22/2023 4:27 PM EDT**
**GUID: 2023522202727**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Microbiology Discipline<br>Secondary Reviewer | Avery Goodwin<br>OID<br>DAI | Sections: 19, 20, 23, 5.1 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Avery Goodwin**

**Digitally signed by Avery Goodwin**

**Date: 5/22/2023 4:30 PM EDT**
**GUID: 2023522203055**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| CMC (OPQ/ONDP) Discipline<br>Primary Reviewer | Dorota Matecka<br>ONDP<br>DNDPI | Sections: Section 9 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Dorota Matecka**

**Digitally signed by Dorota Matecka**

**Date: 5/22/2023 4:44 PM EDT**
**GUID: 202352220445**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| CMC (OPQ/ONDP) Discipline<br>Secondary Reviewer | Dorota Matecka<br>ONDP<br>DNDPI | Sections: Sections 9 and 24 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Dorota Matecka**

**Digitally signed by Dorota Matecka**

**Date: 5/22/2023 4:46 PM EDT**
**GUID: 2023522204655**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Pharmacology Discipline<br>Primary Reviewer | Xiaohui Wei<br>OCP<br>DIDP | Sections: 5, 6.1, 8, 14 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Xiaohui Wei**

**Digitally signed by Xiaohui Wei**

**Date: 5/22/2023 4:52 PM EDT**
**GUID: 2023522205213**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Pharmacology Discipline<br>Primary Reviewer | Tajhia Whigham<br>OCP<br>DIDP | Sections: 5, 14 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Tajhia Whigham**

**Digitally signed by Tajhia Whigham**

**Date: 5/22/2023 5:02 PM EDT**
**GUID: 20235222129**

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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DMITRI IARIKOV
05/22/2023 05:01:59 PM

PETER W KIM
05/22/2023 05:03:43 PM

ADAM I SHERWAT
05/22/2023 05:30:13 PM