FDA Briefing Document

NDA 216974

Drug name: Sulbactam-durlobactam for injection

Applicant: Entasis Therapeutics, Inc.

Antimicrobial Drugs Advisory Committee Meeting

04/17/23

Division of Anti-infectives/Office of Infectious Diseases

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this new drug application to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

Table of Contents

Table of Tables

Table of Figures

Glossary

%*f*T>MIC	percentage free-drug concentration greater than the MIC for 24 hours
ABC	*Acinetobacter baumannii-calcoaceticus* complex
AC	Advisory Committee
AE	adverse event
APACHE	Acute Physiology and Chronic Health Evaluation
AUC	area under the concentration-time curve
BPP	Biofire FilmArray 2.0 Pneumonia Panel
CE	clinically evaluable
CI	confidence interval
COVID-19	coronavirus disease 2019
CRABC	carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex
cUTI	complicated urinary tract infection
ELF	epithelium lining fluid
EOT	end-of-treatment
FDA	Food and Drug Administration
HABP	hospital-acquired bacterial pneumonia
IV	intravenous(ly)
ITT	intent-to-treat
LFU	late follow-up
MDR	multidrug resistance
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
MITT	modified intent-to-treat
m-MITT	microbiologically modified intent-to-treat
NI	noninferiority
PBP	penicillin binding protein
PD	pharmacodynamics
PK	pharmacokinetics
PTA	probability of target attainment
qSOFA	quick Sequential Organ Failure Assessment
SAE	serious adverse event
SUL-DUR	sulbactam-durlobactam
TEAE	treatment-emergent adverse event
TOC	test-of-cure
VABP	ventilator-associated bacterial pneumonia
VP	ventilated pneumonia

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee Meeting

The Food and Drug Administration (FDA or *the Agency*) is convening this Advisory Committee (AC) meeting to discuss whether the data contained in the new drug application (NDA) for sulbactam-durlobactam (SUL-DUR; proposed trade name (b) (4)) for injection support its favorable benefit-risk assessment for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) due to susceptible strains of *Acinetobacter* spp., including carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CRABC) organisms.

1.2 Context for Issues to Be Discussed at the AC

CRABC infections represent an urgent threat in the United States due to the emergence and rapid spread of *Acinetobacter* resistance and limited treatment options (CDC 2019). Nosocomial pneumonia is the most common disease caused by *Acinetobacter* spp. with around 50% of *Acinetobacter* healthcare-associated infections in the United States caused by CRABC (Weiner-Lastinger et al. 2020). The SUL-DUR development program is the first example of a streamlined program for a targeted therapy for a high-unmet-need pathogen, namely CRABC. Efficacy data for SUL-DUR are primarily provided for HABP/VABP.

For antibacterial drugs with the potential to treat serious infections in patients who have few or no available treatments, FDA may consider a more flexible program to facilitate development, provided there are adequate data to demonstrate that the drug is safe and effective and the statutory standards for approval are met (FDA 2022).

1.3 Brief Description of Issues for Discussion at the AC

On September 29, 2022, Entasis Therapeutics (Applicant) submitted NDA 216974 for SUL-DUR for injection. The Applicant's proposed indication is treatment of HABP and VABP caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex (ABC) in adults.

The efficacy of SUL-DUR for the proposed indication is supported by a single phase 3 noninferiority (NI), randomized, assessor-blinded, active-controlled 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 trial 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% confidence interval [CI]) of −13.2% (−30.0, 3.5), demonstrating that SUL-DUR was noninferior to colistin.

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 complicated urinary tract infections (cUTI) and a

phase 3 study in subjects with HABP/VABP caused by ABC. 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 drugs in the β-lactam/β-lactamase inhibitor class, but it is important to note the limited size of the current safety database for SUL-DUR.

1.4 Draft Points for Consideration

- Is the overall benefit-risk assessment favorable for the use of SUL-DUR for the treatment of patients with HABP/VABP caused by susceptible strains of ABC organisms?
  - If yes, please provide your rationale.
  - If no, please provide your rationale and explain what additional studies/trials are needed.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Acinetobacter spp. are Gram-negative, non-lactose-fermenting, oxidase-negative coccobacilli. ABC species include *A. baumannii*, which is the predominant and clinically significant pathogen 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 lumped together as *A. baumannii* complex or *A. baumannii-calcoaceticus* or *A. baumannii.*

A. baumannii exhibits several resistance mechanisms—including biofilm formation, reduced cell membrane permeability, upregulation of drug efflux, and production of β-lactamases—which may result in rapid emergence of resistance to many classes of antibacterial drugs, including carbapenems. The major mechanism of carbapenem resistance in *A. baumannii* is production of Class D and less commonly Class A (including *Klebsiella pneumoniae* carbapenemase and Guiana extended spectrum) and Class B (metallo-β-lactamases) carbapenemases (Karakonstantis et al. 2020). 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 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 HABP/VABP caused by CRABC 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. 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. *Acinetobacter* spp. may produce several β-lactamases that inactivate SUL, including Ambler Class A β-lactamases (TEM-1, *K. pneumoniae* carbapenemase-2) and Ambler Class D β-lactamases (OXA-23 and OXA-24/40); in general, SUL is less susceptible to cleavage by Ambler Class C β-lactamases (ADC-type AmpC). Resistance of *Acinetobacter* to SUL may also be mediated by PBP3 mutations and upregulated efflux (Penwell et al. 2015). Because in the United States SUL is approved in combination with ampicillin, the combination needs to be used in the treatment of *Acinetobacter* infections.

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.[1] Cefiderocol was recently approved for the treatment of HABP and VABP, including those caused by *Acinetobacter*,[2] but treatment-emergent resistance of CRABC to cefiderocol has been reported (Falcone et al. 2022).

(b) (4) is a combination of SUL and DUR. The product is formulated as a lyophilized powder for solution to be administered intravenously (IV). DUR is a novel non-β-lactam β-lactamase inhibitor without activity against ABC. It is structurally related to avibactam. 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. SUR in combination with

[1] TYGACIL (tigecycline) for Injection prescribing information; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021821s049lbl.pdf
[2] FETROJA (cefiderocol) for injection prescribing information; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209445s004lbl.pdf

SUL may be an option for the treatment of CRABC resistant to other available therapies. DUR has not been approved in any country.

2.2 Pertinent Drug Development and Regulatory History

Investigational new drug application 131330 for SUL-DUR for injection was submitted by the Applicant on June 22, 2017. SUL-DUR was granted qualified infectious disease product and fast track designations for the treatment of HABP/VABP due to *A. baumannii* and bloodstream infections due to *A. baumannii* on September 1, 2017.

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 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 trial did not inform the efficacy of SUL-DUR.

After discussions with FDA, the Applicant decided to focus the SUL-DUR development program on the treatment of carbapenem-resistant *A. baumannii* infections and to conduct an NI trial comparing SUL-DUR to colistin in patients with HABP, VABP, ventilated pneumonia (VP), or bacteremia caused by CRABC.

In June 2018, the Applicant submitted a protocol for a phase 3 NI trial evaluating the safety and efficacy of SUL-DUR in patients with *A. baumannii* by comparing SUL-DUR to colistin; imipenem-cilastatin was administered in both treatment groups given the narrow spectrum of activity of SUL-DUR and concern for possible coinfection with other Gram-negative pathogens that may not be evident at the time of enrollment.

During an end-of-phase 2 meeting held on November 5, 2018, the Applicant and Agency discussed a streamlined development strategy with a single phase 3 trial in patients with HABP/VABP and bloodstream infections caused by *A. baumannii*. An NI margin of 19% was agreed to be used in the trial. A phase 3 trial 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 was planned to involve patients with carbapenem-resistant infections.

In June 2020, the Applicant requested a meeting to discuss the possibility of performing the final analysis in the ongoing phase 3 trial using an alternative alpha level, citing challenges with enrollment related to the coronavirus disease 2019 (COVID-19) pandemic as well as higher-than-anticipated rates of colistin resistance, which precluded the inclusion some of the enrolled subjects in the primary efficacy analysis. At a meeting in August 2020 the Agency noted that 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 trial was completed in July 2021.

The Pre-NDA meeting to discuss the contents of the planned NDA submission for SUL-DUR was held on March 25, 2022. NDA 216974 was submitted on September 29, 2022.

3 Summary of Issues for the AC

3.1 Efficacy Issues

Evaluation of efficacy data supporting the NI assessment of SUL-DUR versus colistin for the primary endpoint of 28-day all-cause mortality.

3.1.1 Sources of Data for Efficacy

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. Confirmatory evidence is provided by in vitro and animal data demonstrating the activity of SUL-DUR against *Acinetobacter.*

3.1.1.1 Phase 3 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 cUTIs and acute pyelonephritis or surgical or post-traumatic wound infections. Efficacy of SUL-DUR was evaluated based on Part A due to the single-group design of Part B. Therefore, the 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 (refer to Section 6.1.1 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 Sequential Organ Failure Assessment (SOFA) between 7 and 11 at the time of diagnosis of infection or a quick SOFA (qSOFA) score of ≥2 for enrollment if an APACHE II or SOFA score was unavailable. 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 two 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 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.

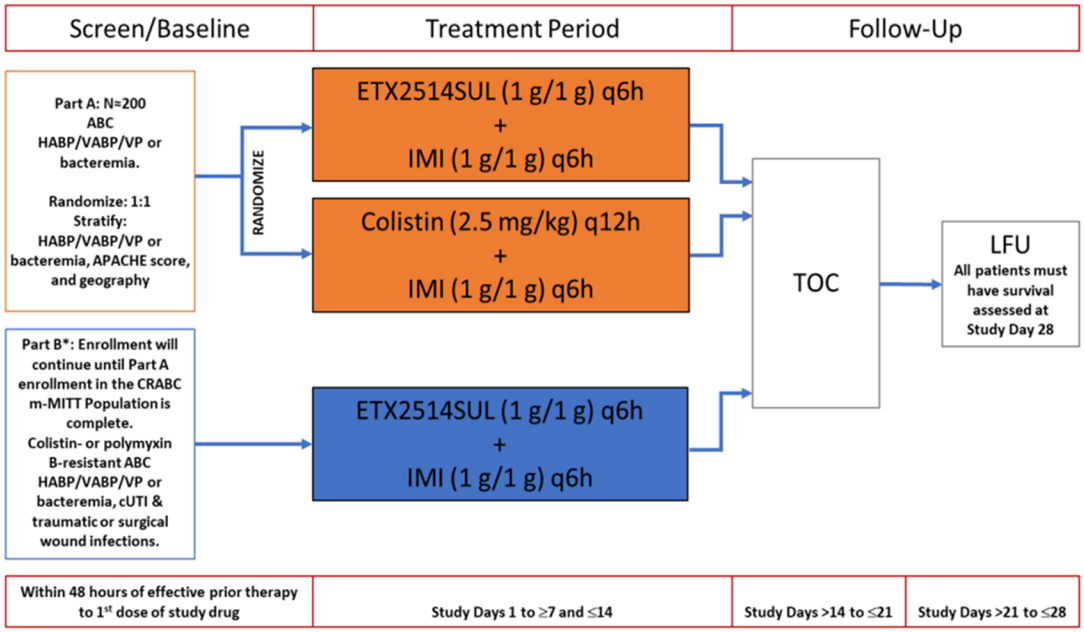
The study duration for a subject was approximately 28 days. If a subject had the late follow-up visit before Day 28, a telephone call on Day 28 or anytime thereafter was made to assess survival status.

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 the 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 6.1.2.

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 6.1.2.

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, durlobactam; HABP, hospital-acquired bacterial pneumonia; IMI, imipenem/cilastatin; LFU, late follow-up; m-MITT, microbiologically modified intent-to-treat; q6h, every 6 hours; q12h, every 12 hours; SUL, sulbactam; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia; VP, ventilated pneumonia

Analysis Populations

The efficacy endpoints were evaluated in several analysis populations. The definitions of the analysis populations are provided in the Appendix.

The primary efficacy analysis population was the CRABC microbiologically modified intent-to-treat (CRABC m-MITT) population, which 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 the 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, microbiologically 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.

Efficacy Analysis

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 patients 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 (FDA 2014)) and patients with serious ABC infections. Further, due to the impact of the 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 3.1.1.2).

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 for 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.

3.1.1.2 Phase 3 Efficacy Results

Subject Disposition

A total of 531 subjects were screened for Parts A and B (Table 1). 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 result, 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 1. Subject Screening and Enrollment, CS2514-2017-0004

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 2). 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 2. Subject Disposition, 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)

Disposition Category	SUL/DUR N (%)	Colistin N (%)	Total N (%)
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[4]	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[3]	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 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# (b) (6) died 3 days after discontinuation of study due to withdrawal by subject.

[3] Other reasons included: 1) local cell culture no ABC; 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.

[4] 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.

[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; PI, principal investigator

Demographics and Baseline Characteristics

The demographics and baseline characteristics were reasonably balanced between the two treatment groups in the primary efficacy analysis population of CRABC m-MITT (Section 6.1.4). The mean age was

63 years. Most subjects were males (74%); the majority of the subjects was 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 trial 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 10% differences in the following groups of age, race, enrollment area and infection type although 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 SUR-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 3). 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 3. 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 Survival Status at Day 28, 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 all-cause mortalities by Day 28; SUL, sulbactam

In the CRABC m-MITT population, three subjects withdrew consent prior to obtaining survival status at Day 28 and were excluded from the primary analysis, comprising 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 (Section 6.1.5).

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 4). 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 (Section 6.1.5). The results for mortality in the CE population were consistent with those in the CRABC m-MITT, m-MITT, and ITT populations.

Table 4. 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, CS2514-2017-0004 Part A

	SUL-DUR	Colistin	Treatment Comparison	
Analysis Population	n/N (%)	n/N (%)	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; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; 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 5). The upper limits of the 95% CIs for the differences in mortality rates were <10%.

Table 5. 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, CS2514-2017-0004 Part A

	SUL/DUR	Colistin	Treatment Comparison	
Analysis Population	n/N (%)	n/N (%)	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 6. 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 6). 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 6. 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, CS2514-2017-0004 Part A

	SUL-DUR	Colistin	Treatment Comparison	
Assessment Time Clinical Response Category	(N=63) n (%)	(N=62) n (%)	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)		
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-treatment; 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 7), 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 7. 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, CS2514-2017-0004 Part A

	SUL/DUR	Colistin	Treatment Comparison	
Assessment Time	**(N=63)**	**(N=62)**		
Microbiological Response Category	**n (%)**	**n (%)**	**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)		
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-treatment; 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 demographics and some baseline characteristics for the primary endpoint are displayed in Table 8. 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 therefore the findings could be due to 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 8. 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, CS2514-2017-0004 Part A

	SUL-DUR	Colistin	Treatment Comparison	
Demographic or Baseline Characteristic	**n/N (%)**	**n/N (%)**	**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)
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)
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)

Demographic or Baseline Characteristic	SUL-DUR n/N (%)	Colistin n/N (%)	Treatment Comparison Difference (%)	95% CI[1]
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)
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 prior 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 prior antibiotics				
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 14.2.8.19 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, sulbactam; TOC, test-of-cure; VABP, ventilator-associated bacterial pneumonia; VP, ventilator pneumonia

Efficacy Summary

Part A of the phase 3 study demonstrated that SUR-DUL was not inferior to colistin in the treatment of HABP/VABP caused by carbapenem-resistant ABC.

3.1.2 Additional Considerations for Efficacy Assessments

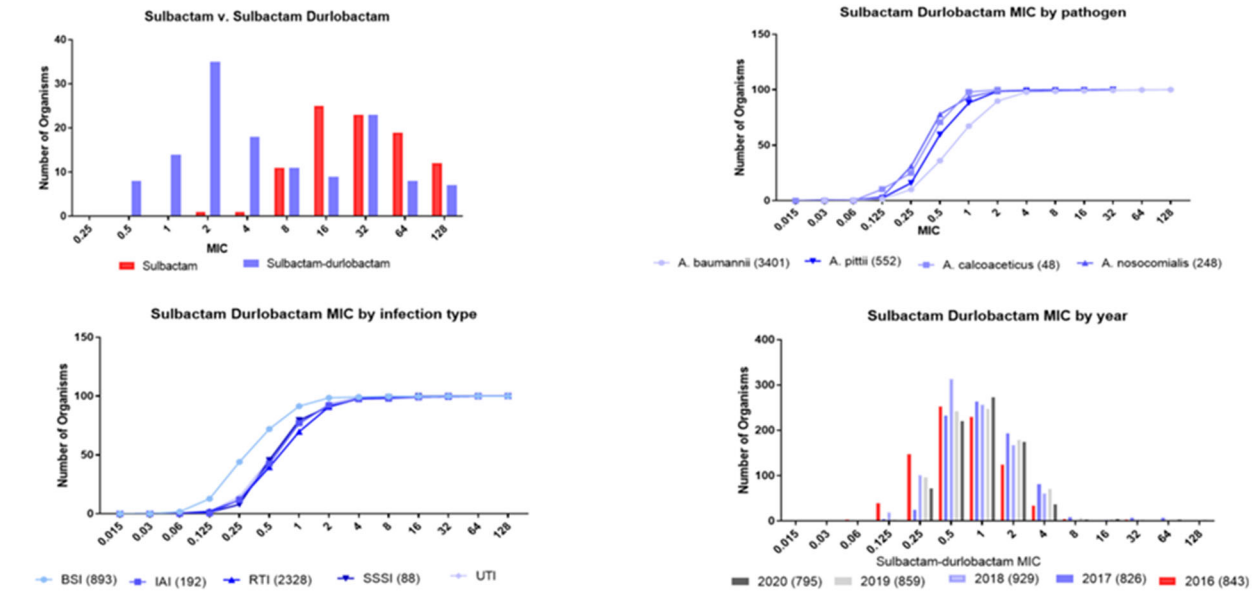
Nonclinical Summary

SUL inhibits PBP1 and PBP3 in *Acinetobacter* spp., which are essential enzymes for bacterial cell wall synthesis. DUR is a novel non-β-lactam β-lactamase inhibitor that contains a diazabicyclooctane scaffold rather than a β-lactam core. DUR 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. DUR showed broad-spectrum inhibition of isogenic *A. baumannii* strains overexpressing serine β-lactamases—including those of Ambler Class A (TEM-1, KPC-2), Class C (ADC-30), and Class D (OXA-23, OXA-24/40)—by restoring SUL activity by 2 to 64-fold (Durand-Reville et al. 2017; Shapiro et al. 2017; Barnes et al. 2019). DUR does not inhibit the Class B metallo-β-lactamases such as New Delhi metallo-β-lactamases (NDM). DUR alone does not have antimicrobial activity against *Acinetobacter* spp. showing minimum inhibitory concentration (MIC) values >32 mg/L (McLeod et al. 2020; Yang et al. 2020).

In vitro studies showed that addition of DUR at a fixed concentration of 4 mg/L lowered the SUL MIC_{90} from >32 mg/L to 2 to 4 mg/L with 98.2% of isolates having SUL-DUR MIC values ≤4 mg/L (Figure 2).

- There was no difference in SUL-DUR activity against ABC subspecies, as indicated by $MIC_{50/90}$ values of 1 and 2 mg/L, respectively, with 98.8% of the isolates having SUL-DUR MICs ≤4 mg/L. The majority 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% were *Acinetobacter* spp.
- SUL-DUR MIC values did not vary by infection source, being ≤4 mg/L in all 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.
- SUL-DUR remained stable globally over time with MIC_{90} values ranging from 2 mg/L to 4 mg/L for the period 2016 to 2020.

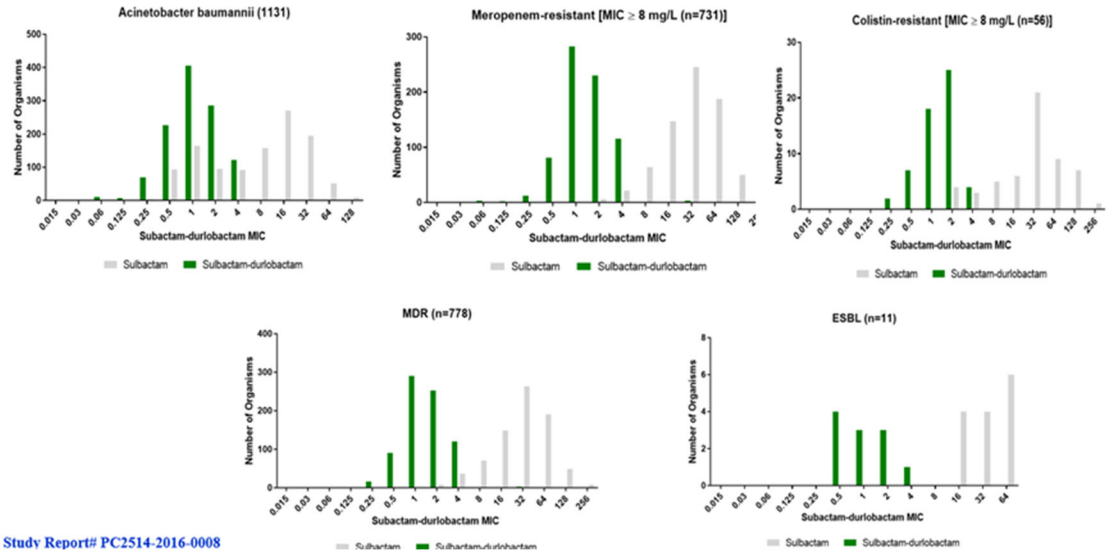
Figure *2*. DUR Restores SUL Activity Against *Acinetobacter* spp.



Source: Study Reports PC2514-2021-0012, PC2514-2022-0017, and PC2514-(2016-2020)-0008.
Abbreviations: BSI, bloodstream infection; DUR, durlobactam; IAI, intra-abdominal infection; MIC, minimum inhibitory concentration; RTI, respiratory tract infection; SSSI, skin and skin structure infection; SUL, sulbactam; UTI, urinary tract infection

SUL-DUR maintained activity against resistant subsets of ABC isolates in comparison to SUL alone (Figure 3). Among SUL-resistant isolates, the SUL-DUR 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 SUL-DUR MICs ≤4 mg/L and 90.2% against extensively drug-resistant ABC isolates (defined as isolates that remain susceptible to one or two antimicrobial categories).

Figure *3*. DUR Restores SUR Activity Against Resistant Subtypes



Source: Study Report# PC2514-2016-0008
Abbreviations: DUR, durlobactam; ESBL, extended spectrum β-lactamases; MDR, multidrug resistant; MIC, minimum inhibitory concentration; SUL, sulbactam

Mechanisms of β-lactam resistance in ABC isolates may include the production of β-lactamases, modification of PBPs or target alteration, upregulation of efflux pumps or loss of outer membrane porin. Reduced susceptibility to SUL-DUR in global surveillance and resistance studies showed that:

- SUL-DUR is not active against organisms that express *bla*NDM-1 or any other metallo-β-lactamase. Isolates that encode for the metallo-β-lactamase, mostly NDM variants, showed SUL-DUR MIC values >32 mg/L, demonstrating no significant shift in MIC when tested by SUL alone. Isolates that produce multiple β-lactamases and express varying levels of β-lactamases may also contribute to SUL-DUR resistance; however, the combinations of these β-lactamases that contribute to higher SUL-DUR MICs are unknown.
- Amino acid changes near the active target site of SUL (PBP3) correlated with SUL-DUR MIC values >4 mg/L. Since these are mutations that likely affect SUL binding to its target, changing the relative concentration of DUR would not be expected to fully restore SUL susceptibility.
- It is likely that there are multiple factors that would lead to higher SUL-DUR MIC values including that isolates may also produce alone or in combination multiple β-lactamases, express varying levels of β-lactamases, and have PBP amino-acid sequence variations or other resistance mechanisms.

PK/PD Target Determination Based on Nonclinical Studies and Probability of Target Attainment Analyses

Based on studies with in vitro (hollow-fiber infection model and chemostat model) and animal models (thigh and pneumonia infections), the Applicant proposed that the pharmacokinetic (PK)/pharmacodynamic (PD) drivers best associated with antibacterial activity are the percentage of dosing interval that the free-drug concentration was above the MIC (%*f*T>MIC) for SUL and the free-drug area under the concentration-time curve from time of dosing to 24 hours postdose (fAUC)$_{0\text{-}24}$/MIC ratio for DUR.

When SUL 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-log$_{10}$ kill and 38.6% (ranged from 28.8% to 52.9%) for 2-log$_{10}$ 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-log$_{10}$ kill and 55.5% (ranged from 43.9% to 70.9%) for 2-log$_{10}$ kill, respectively, against four SUL-resistant *A. baumannii* isolates. When 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-log$_{10}$ kill and 2-log$_{10}$ 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 the above results, the Applicant proposed PK/PD targets of 50% *f*T>MIC for SUL and fAUC$_{0\text{-}24}$/MIC of 10 to achieve 1-log$_{10}$ kill against MDR *A. baumannii* stains. The Applicant performed probability of target attainment analyses (PTA) for both plasma and epithelium lining fluid (ELF) exposures by using these PK/PD targets to support the clinical dose selection. PTA for ELF exposures used the same PK/PD targets for plasma PTA due to 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).

The PTA results showed that the Applicant's proposed dose regimen (Table 16) resulted in achievement of the PK/PD targets of SUL and DUR based on both free plasma concentration and ELF concentration in ≥90% of simulated subjects at MICs ≤4 mg/L (the Applicant's proposed susceptible MIC breakpoint), across renal function categories (Figure 4). Please refer to the Additional Clinical Pharmacology Information section in the Appendix for PTA analyses.

3.2 Safety Issues

There were no unexpected safety signals 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 trial, there were 24 (26.4%) and 30 (34.9%) deaths in the SUL-DUR and colistin groups, respectively. Mortality outcomes were related to the underlying comorbidities, complications in a 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 trial was similar to that observed in other HABP/VABP trials. The overall incidences of treatment-emergent AEs (TEAEs), serious adverse events (SAEs), and drug-related TEAEs were lower in the SUL-DUR group than the colistin group. A greater proportion of subjects in both groups experienced severe TEAEs overall but moderate and severe TEAEs were less frequent in the SUL-DUR group compared to colistin. The most common TEAEs experienced by patients in the SUL-DUR group were diarrhea and hypokalemia. The phase 2 trial did not reveal any concerning safety signals and was consistent with safety findings in the pivotal phase 3 trial.

In a thorough QT study, a supratherapeutic dose of DUR (4 g) did not prolong the QT interval. SUL and DUR are renally eliminated; terminal half-lives are approximately 1 to 3 hours and 2 to 3 hours, respectively. Neither SUL nor DUR undergo significant hepatic metabolism. DUR is a novel non-β-lactam β-lactamase inhibitor, structurally similar to avibactam.

SUL 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 *Clostridioides difficile*-associated diarrhea. The contribution of each component to the development of these adverse reactions is not certain.

3.2.1 Sources of Data for Safety

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 ABC. The subjects in phase 2 and 3 trials also received background imipenem therapy. In addition, 12 subjects received SUL-DUR under an expanded access program. These subjects had *A. baumannii* infections with limited treatment options and did not otherwise qualify for participation in ongoing clinical studies.

The Applicant has also evaluated the safety of DUR 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 every 6 hours for 8 days. Also, the extensive experience with ampicillin-SUL was considered in the evaluation of the safety of SUL-DUR.

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 data from the phase 2 and 3 trials were not pooled for the Agency's safety assessments given differences in randomization, comparators, and treatment duration.

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 trial except for the outcome assessor. The safety population consisted of predominantly white and Asian subjects, mostly males (70%).

Table 9 provides the duration of exposure in the phase 3 trial safety population.

Table 9. Duration of Exposure, Safety Population, Trial 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)
Minimum, maximum	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; Q, quartile; SUL, sulbactam

3.2.2 Safety Summary

Overview of Treatment-Emergent Adverse Events

There were 24 (26.4%) and 30 (34.9%) deaths in the SUL-DUR and colistin groups, respectively. There were four deaths (14%) in the nonrandomized Part B of the trial, with one death due to multiorgan failure beyond 28 days.

The overall incidence of TEAEs was 87.9% in the SUL-DUR group and 94.2% in the colistin group (Table 10). There were lower incidences of SAEs (39.6% versus 48.8%) and drug-related TEAEs (12.1% versus 30.2%) in the SUL-DUR group compared to the colistin group. One subject in the SUL-DUR group had a drug-related SAE (anaphylactic reaction). TEAE resulting in treatment discontinuation were reported in one subject in the SUL-DUR group (anaphylaxis) and four subjects in the colistin group (rash, seizure, acute kidney injury [n=2]). In both groups, subjects experienced a greater proportion of severe TEAEs than mild or moderate TEAEs; moderate and severe TEAEs were less frequent in the SUL-DUR group compared to the colistin group.

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

Table 10. Overview of Adverse Events, Safety Population, Trial cs2514-2017-0004

Safety Population	Part A		Part B
	SUL-DUR N=91	Colistin N=86	SUL-DUR N=28
Event Category	n (%)	n (%)	n (%)
Treatment-emergent adverse events	80 (87.9)	81 (94.2)	24 (85.7)
Treatment-related TEAEs	12(13.2)	26(30.2)	3 (10.7)
Serious adverse events	36 (39.6)	42 (48.8)	9 (32.1)
Serious adverse events with fatal outcomes	24 (26.4)	30 (34.9)	4 (14.3)
Serious treatment related adverse events	1 (1.1)	2 (2.3)	1 (3.6)
TEAE leading to permanent discontinuation of study drug	10 (11.0)	14 (16.3)	4 (14.3)
Severe	39 (42.9)	44 (51.2)	9 (32.1)
Moderate	15 (16.5)	21 (24.4)	5 (17.9)
Mild	26 (28.6)	16 (18.6)	10 (35.7)

Source: FDA Analysis.
Treatment-emergent adverse events defined as AEs that start, or a preexisting condition that worsens, on or after the start (based on date and time) of the first dose of study drug.
Duration is 7 days, with extension up to 14 days where clinically indicated.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; 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

Common Adverse Events

The common relevant AEs occurring in more than 5% of subjects receiving SUL-DUR are shown in Table 11. The TEAEs occurring with a higher frequency in the SUL-DUR group than in the comparator group were diarrhea (16.5% versus 10.5%), hypokalemia (12.1% versus 10.5%), and thrombocytopenia (5.5% versus 3.5%). Acute kidney injury was higher in the colistin group (36%) than SUL-DUR (5.5%).

Table 11. Selected Adverse Events Occurring at >5% Frequency, Safety Population, Trial cs2514-2017-0004

	Part A		Part B
	SUL-DUR (N=91)	Colistin (N=86)	SUL-DUR (N=28)
Preferred Term	n (%)	n (%)	n (%)
Any AE	80 (87.9)	81 (94.2)	24 (85.7)
Liver function test abnormal	17 (18.7)	18 (20.9)	7 (25)
Diarrhea	15 (16.5)	9 (10.5)	2 (7.1)
Anemia	12 (13.2)	12 (14.0)	3 (10.7)
Hypokalemia	11 (12.1)	9 (10.5)	0
Pyrexia	9 (9.9)	8 (9.3)	1 (3.6)
Septic shock	9 (9.9)	8 (9.3)	0
Arrhythmia	8 (8.8)	8 (9.3)	1 (3.6)
Acute kidney injury	5 (5.5)	31 (36)	5 (17.9)
Thrombocytopenia	5 (5.5)	3 (3.5)	0
Constipation	5 (5.5)	5 (5.8)	0

Source: FDA Analysis.
The following terms were combined: Proteinuria and protein in urine. Liver function test abnormal, hepatic function abnormal, increased transaminases, alanine aminotransferase increased and aspartate aminotransferase increased. Renal impairment, blood creatinine increased, toxic nephropathy, renal failure and acute kidney injury. Pneumonia, bacterial pneumonia, and pseudomonal pneumonia.
Abbreviations: AE, adverse event; DUR, durlobactam; N, number of patients in treatment group; n, number of patients with at least one event SUL, sulbactam

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

In the phase 3 study, the incidence of TEAEs related to hepatobiliary disorders was similar (11%) for subjects in both the SUL-DUR and colistin groups (refer to Table 17 in the Appendix). The AEs were mild or moderate in severity and resolved.

The Applicant reported three subjects in the SUL-DUR group (two subjects in Part A and one in Part B), and one subject in the colistin group meeting Hy's Law laboratory criteria in the safety summary; however, all these subjects had alternative plausible explanations for liver test elevation including primary biliary cholangitis, acute ischemic hepatitis and progressing baseline liver insufficiency. The Agency's Hy's law analysis identified one subject in the SUL-DUR group by laboratory criteria; however, this subject had acute ischemic hepatitis.

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

SUL-DUR does not have a specific safety signal in this small safety database. Hepatic dysfunction, including hepatitis and cholestatic jaundice have been associated with the use of ampicillin-SUL, but has not been specifically attributed to SUL. In vitro data do not indicate that durlobactam is metabolized by *CYP450*.

Hypersensitivity

Hypersensitivity reactions were more frequent in the SUL-DUR group compared with the colistin group (16.5% versus 11.5%), which would be expected with penicillin derivatives. The most common reaction related to study drug was rash in both groups (3.4% in the SUL-DUR group and 2.3% in the colistin group). These reactions (rash and contact dermatitis) were mild to moderate in nature and resolved with treatment discontinuation. One subject (Subject# (b) (6)) in the SUL-DUR group discontinued treatment on Day 9, due to a nonserious, moderate event of anaphylactic shock and whole-body rash followed by transient hypotension and oliguria, which resolved after treatment with methylprednisone. One subject in the phase 2 study had urticaria, which led to study drug discontinuation in the SUL-DUR group.

Other Adverse Events of Special Interest

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

The incidence of seizure was higher in the colistin group (six subjects, 7.0%) compared with the SUL-DUR group (one subject, 0.8%). The subject in the SUL-DUR group experienced a tonic clonic convulsion on Day 5 of study treatment. Of note, the subject did not have a history of seizures and was not on

concomitant medications known to lower the seizure threshold. 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. The AE was considered nonserious.

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.

Safety in Subjects on Continuous Renal Replacement Therapy

In the phase 3 trial, 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.

3.2.3 Additional Considerations for Safety Assessments

SUL has been approved in combination with ampicillin since 1986. The labeled dose of SUL in combination with ampicillin is up to 4 g over 24 hours as compared to up to 6 g SUL over 24 hours proposed in combination with DUR. However, in the treatment of *A. baumannii* infections SUL has been used up to 9 g over 24 hours (Tamma et al. 2022).

3.3 Risk Mitigation

Based on the safety review, the review team's current assessment is that no risk mitigation strategies are anticipated at this time in addition to describing the safety findings for SUL-DUR in the labeling.

4 Benefit-Risk Framework

Disclaimer: This predecisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
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 in carbapenem-resistant *A. baumannii* infections was higher than that 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. 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.
Benefits	A phase 3, randomized, controlled, assessor-blinded study in patients with HABP/VABP 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%. The SUL-DUR group had a 28-Day mortality rate of 19% (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). 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 trial with a limited sample size and there are no other clinical trials of SUL-DUR in HABP/VABP due to *Acinetobacter* spp., including CRABC.
Risks 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

5 References

Literature and Websites

Aydemir, H, D Akduman, N Piskin, F Comert, E Horuz, A Terzi, F Kokturk, T Ornek, and G Celebi, 2013, Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia, Epidemiol Infect, 141(6):1214-1222.

Barnes, MD, V Kumar, CR Bethel, SH Moussa, J O'Donnell, JD Rutter, CE Good, KM Hujer, AM Hujer, SH Marshall, BN Kreiswirth, SS Richter, PN Rather, MR Jacobs, KM Papp-Wallace, F van den Akker, and RA Bonomo, 2019, Targeting multidrug-resistant *Acinetobacter* spp.: Sulbactam and the diazabicyclooctenone beta-lactamase inhibitor ETX2514 as a novel therapeutic agent, mBio, 10(2).

Bartal, C, KVI Rolston, and L Nesher, 2022, Carbapenem-resistant *Acinetobacter baumannii*: Colonization, infection and current treatment options, Infect Dis Ther, 11(2):683-694.

CDC, 2019, 2019 AR Threats Report, accessed February 1, 2023, https://www.cdc.gov/drugresistance/biggest-threats.html.

Chopra, T, D Marchaim, RA Awali, A Krishna, P Johnson, R Tansek, K Chaudary, P Lephart, J Slim, J Hothi, H Ahmed, JM Pogue, JJ Zhao, and KS Kaye, 2013, Epidemiology of bloodstream infections caused by *Acinetobacter baumannii* and impact of drug resistance to both carbapenems and ampicillin-sulbactam on clinical outcomes, Antimicrob Agents Chemother, 57(12):6270-6275.

Durand-Reville, TF, S Guler, J Comita-Prevoir, B Chen, N Bifulco, H Huynh, S Lahiri, AB Shapiro, SM McLeod, NM Carter, SH Moussa, C Velez-Vega, NB Olivier, R McLaughlin, N Gao, J Thresher, T Palmer, B Andrews, RA Giacobbe, JV Newman, DE Ehmann, B de Jonge, J O'Donnell, JP Mueller, RA Tommasi, and AA Miller, 2017, ETX2514 is a broad-spectrum beta-lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including *Acinetobacter baumannii*, Nat Microbiol, 2:17104.

Falcone, M, G Tiseo, A Leonildi, L Della Sala, A Vecchione, S Barnini, A Farcomeni, and F Menichetti, 2022, Cefiderocol- compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*, Antimicrob Agents Chemother, 66(5):e0214221.

Karakonstantis, S, EI Kritsotakis, and A Gikas, 2020, Treatment options for *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* co-resistant to carbapenems, aminoglycosides, polymyxins and tigecycline: an approach based on the mechanisms of resistance to carbapenems, Infection, 48(6):835-851.

Lemos, EV, FP de la Hoz, TR Einarson, WF McGhan, E Quevedo, C Castaneda, and K Kawai, 2014, Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis, Clin Microbiol Infect, 20(5):416-423.

McLeod, SM, SH Moussa, MA Hackel, and AA Miller, 2020, *In vitro* activity of sulbactam-durlobactam against *Acinetobacter baumannii-calcoaceticus* complex isolates collected globally in 2016 and 2017, Antimicrob Agents Chemother, 64(4).

Paul, M, GL Daikos, E Durante-Mangoni, D Yahav, Y Carmeli, YD Benattar, A Skiada, R Andini, N Eliakim-Raz, A Nutman, O Zusman, A Antoniadou, PC Pafundi, A Adler, Y Dickstein, I Pavleas, R Zampino, V Daitch, R Bitterman, H Zayyad, F Koppel, I Levi, T Babich, LE Friberg, JW Mouton, U Theuretzbacher, and L Leibovici, 2018, Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial, Lancet Infect Dis, 18(4):391-400.

Penwell, WF, AB Shapiro, RA Giacobbe, RF Gu, N Gao, J Thresher, RE McLaughlin, MD Huband, BL DeJonge, DE Ehmann, and AA Miller, 2015, Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*, Antimicrob Agents Chemother, 59(3):1680-1689.

Rice, LB, 2008, Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE, J Infect Dis, 197(8):1079-1081.

Shapiro, AB, N Gao, H Jahic, NM Carter, A Chen, and AA Miller, 2017, Reversibility of covalent, broad-spectrum serine beta-lactamase inhibition by the diazabicyclooctenone ETX2514, ACS Infect Dis, 3(11):833-844.

Spellberg, B and JH Rex, 2013, The value of single-pathogen antibacterial agents, Nat Rev Drug Discov, 12(12):963.

Tamma, PD, SL Aitken, RA Bonomo, AJ Mathers, D van Duin, and CJ Clancy, 2022, Infectious Diseases Society of America Guidance on the Treatment of AmpC beta-Lactamase-Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections, Clin Infect Dis, 74(12):2089-2114.

Weiner-Lastinger, LM, S Abner, JR Edwards, AJ Kallen, M Karlsson, SS Magill, D Pollock, I See, MM Soe, MS Walters, and MA Dudeck, 2020, Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015-2017, Infect Control Hosp Epidemiol, 41(1):1-18.

Yang, Q, Y Xu, P Jia, Y Zhu, J Zhang, G Zhang, J Deng, M Hackel, PA Bradford, and H Reinhart, 2020, *In vitro* activity of sulbactam/durlobactam against clinical isolates of *Acinetobacter baumannii* collected in China, J Antimicrob Chemother, 75(7):1833-1839.

Zheng, YL, YF Wan, LY Zhou, ML Ye, S Liu, CQ Xu, YQ He, and JH Chen, 2013, Risk factors and mortality of patients with nosocomial carbapenem-resistant *Acinetobacter baumannii* pneumonia, Am J Infect Control, 41(7):e59-63.

Guidances for Industry

FDA, 2014, Guidance for Industry; Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment, accessed December 8, 2020, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hospital-acquired-bacterial-pneumonia-and-ventilator-associated-bacterial-pneumonia-developing-drugs.

FDA, 2022, 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), accessed December 8, 2020, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/antibacterial-therapies-patients-unmet-medical-need-treatment-serious-bacterial-diseases-questions.

6 Appendix

6.1 Additional Details of Efficacy Analyses for the Phase 3 Study

6.1.1 Definitions of HABP, VABP, VP, and/or Bacteremia

Table 12. Definitions of HABP, VABP, VP, and/or Bacteremia, CS2514-2017-0004 Part A

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); OR Admission from LTAC or rehabilitation center, or admission from home <7 days after discharge from an LTAC or rehabilitation center; AND New or evolving infiltrate on chest X-ray, MRI, CT, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound is performed, a confirmatory X-ray or CT should be performed within 24 hours.	• A new onset of cough (or worsening of baseline cough); • Auscultatory findings consistent with pneumonia/pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony); • Dyspnea, tachypnea, or respiratory rate >25 breaths/minute; OR • Hypoxemia (oxygen saturation <90% or pO_2 <60 mmHg while breathing room air, or worsening of the oxygen saturation/FiO_2); OR the following ALONE: • New-onset need for mechanical ventilation.	• 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]); • Elevated total peripheral WBC count (>10,000/mm^3); >15% immature neutrophils (bands) regardless of total peripheral WBC count; OR • Leukopenia (total WBC count <4500/mm^3).
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; Requires ventilator support; AND New or evolving infiltrate on chest X-ray, MRI, CT, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound is performed, a confirmatory X-ray or CT should be performed within 24 hours.	• Auscultatory findings consistent with pneumonia/pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony); • An acute change in the ventilator support system to enhance oxygenation, as determined by a worsening oxygen saturation/FiO2 ratio; • Increased suctioning; OR • 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]) OR • hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; • OR • Leukopenia (total WBC <4500/mm^3).

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; AND New or evolving infiltrate on chest X-ray, MRI, CT, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound is performed, a confirmatory X-ray or CT should be performed within 24 hours.	• Auscultatory findings consistent with pneumonia/pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony); • An acute change in the ventilator support system to enhance oxygenation; • Increased suctioning; OR • 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]); OR • Hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; OR • Leukopenia (total WBC count <4500/mm^3).
Bacteremia With ABC		
All of the Following:	**AND at Least One of the Following:**	
Isolation of ABC from at least one 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]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; • Leukopenia (total WBC count <4500/mm^3); • Tachycardia >100 bpm; • Tachypnea >25 breaths/minute; OR • 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; CT, computed tomography; FiO_2, fraction of inspired oxygen; HABP, hospital-acquired bacterial pneumonia; LTAC, long-term acute care; MRI, magnetic resonance imaging; pO_2, partial pressure of oxygen; VABP, ventilator-associated bacterial pneumonia; WBC, white blood cell

6.1.2 Secondary Efficacy Endpoint Definitions

6.1.2.1 Clinical Response

Based on signs and symptoms, the assessors and investigators chose one of the following three clinical outcomes on Days 5, 7, EOT, TOC, LFU, and early termination visits:

1. 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 was warranted.
2. Clinical failure: symptoms present at study entry had not significantly improved or completely resolved, or new symptoms had developed and required the initiation of a nonstudy Gram-negative antibacterial drug therapy, death, or intolerance to study drug leading to discontinuation from the study treatment.
3. Clinical indeterminate: determination could not be made because of missing data or the patient was lost to follow-up.

If there was a discrepancy between the assessment of the assessor and investigator, then the assessment from the assessor was used. If there was a missing assessment from either assessor or investigator, then the available assessment was used. An adjudication committee might be organized for adjudication if it was deemed necessary by the Data Safety Monitoring Board. In such a case, their activities were described in the Data Safety Monitoring Board charter.

6.1.2.2 Microbiologic Response

The microbiologic outcome was assessed at Days 5, 7, EOT, TOC, and LFU. The following were the criteria to determine the outcome.

For subjects with bacteremia, microbiologic outcome was classified into the following categories:

1. Microbiologic eradication:
    a. For subjects with cUTI or aspiration pneumonia: The baseline strain of ABC was reduced to $<10^3$ CFU/mL on urine culture and negative on repeat blood culture (if positive at baseline); or
    b. For subjects with bacteremia: Absence of the baseline strain of ABC on culture.
    c. Microbiologic presumed eradication: No culture was done, and the subjects met the clinical criteria for clinical cure.
2. Microbiologic persistence:
    a. For subjects with cUTI or aspiration pneumonia: The urine culture grew $\geq 10^3$ CFU/mL of the baseline strain of ABC identified at study entry and/or a blood culture demonstrated the same baseline pathogen(s); or
    b. For subjects with bacteremia: Presence of the baseline strain of ABC on repeat culture.
    c. Subjects who showed persistence at EOT were considered to show persistence at TOC.
3. Microbiologic presumed persistence: No culture was done, and the subject met the clinical criteria for clinical failure.
4. Microbiologic indeterminate: If clinically indicated (for cUTI and bacteremia only), no follow-up culture was available, the culture could not be interpreted for any reason, or the culture was considered contaminated.
5. Microbiologic recurrence:
    a. For subjects with cUTI or aspiration pneumonia: 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
    b. For patients 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.

For subjects with HABP, VABP, and VP, microbiologic outcome was classified as the following categories:

1. Microbiologic presumed eradication: No culture was done, and the patient met the 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.
2. Microbiologic presumed persistence: No culture was done, and the patient met the clinical criteria for clinical failure.

6.1.3 Analysis Populations

Seven analysis populations were defined, as follows:

1. **ITT** population included all subjects randomized in Part A, regardless of whether they actually received study drug.
2. **Modified ITT (MITT)** population included the subjects in the ITT population who received any amount of study drug. Subjects with HABP/VABP/VP who were randomized in Part A on the result of a BPP rapid but were subsequently withdrawn due to lack of a culture growing ABC were included in the MITT population. The MITT population was considered as the safety population.
3. **m-MITT** population included the subjects in the MITT population who had 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 was not available, the local laboratory data were used to confirm the presence of ABC organism, as long as the local laboratory used modern methods of diagnosis.
    a. Subjects with HABP/VABP/VP who were randomized in Part A based on a BPP rapid test result but were subsequently found to have respiratory sample cultures that did not grow ABC (by the local laboratory) were withdrawn from the study treatment were not included in the m-MITT population. Note that these subjects remained in the MITT population.
4. **Carbapenem-resistant ABC m-MITT (CRABC m-MITT)** population included the subjects in the m-MITT population who 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. In addition, the following subgroups of subjects were excluded from the CRABC m-MITT population:
    a. Subjects who had isolates that were deemed by the central laboratory to be resistant to SUL-DUR or colistin.
    b. Subjects whose blood culture or respiratory samples were collected more than 72 hours prior to randomization.
    c. Subjects who were transferred from Part A to Part B.
    d. Subjects who were enrolled with infections other than ABC pneumonia or bloodstream infection (i.e., ABC infections other than HABP, VABP, VP, and bacteremia).
5. **CE** population included subjects in the m-MITT population who met the following evaluability criteria:
    a. Met key inclusion criteria.
    b. Did not meet key exclusion criteria.
    c. Received at least 72 hours of study drug (i.e., 12 doses of SUL-DUR plus 12 doses of imipenem/cilastatin or six doses of colistin plus 12 doses of imipenem/cilastatin in subjects without dose adjustment) to be a clinical cure; OR received at least 48 hours of study drug (i.e., eight doses of SUL-DUR plus 8 doses of imipenem/cilastatin or 4 doses of colistin plus 8 doses of imipenem/cilastatin in subjects without dose adjustment) to be a clinical failure.
    d. Received ≥80% of anticipated doses.
    e. Did not have a clinical response of indeterminate at the TOC visit.

6. **Microbiologically evaluable (ME)** population included the subjects in the CE population who had an appropriately collected culture specimen and interpretable culture result when specimen collection was clinically indicated at the TOC visit.
7. **CRABC ME** population included the subjects in the ME population who had a baseline ABC organism that was confirmed to be carbapenem-resistant (and susceptible to SUL-DUR for Parts A and B and susceptible to colistin for Part A). In other words, the CRABS ME population included subjects in both the CRABC m-MITT and ME populations.

The numbers of subjects in each analysis population and the reasons for their exclusion from the ITT population are displayed in Table 13.

Table 13. 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)

Analysis Populations and Reasons for Exclusion From ITT Population	SUL-DUR N (%)	Colistin N (%)	Total N (%)
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: Table 11 and post-text Table 14.1.3.2 in the CS2514-2017-0004 Clinical Study Report.
Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; APACHE II, Acute Physiology and Chronic Health Evaluation II; BPP, Biofire FilmArray 2.0 Pneumonia Panel; CE, clinically evaluable; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; MITT, modified intent-to-treat; m-MITT; microbiologically modified intent-to-treat; qSOFA, quick Sequential Organ Failure Assessment; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SUL, sulbactam; TOC, test-of-cure; VABP, ventilator-associated bacterial pneumonia; VP, ventilator pneumonia

6.1.4 Demographics and Baseline Characteristics

Table 14. Demographics 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)

Characteristic	SUL-DUR (N=64)	Colistin (N=64)	All (N=128)
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
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

Characteristic	SUL-DUR (N=64)	Colistin (N=64)	All (N=128)
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)
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: APACHE II, Acute Physiology and Chronic Health Evaluation II; BPP, Biofire FilmArray 2.0 Pneumonia Panel; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; m-MITT; microbiologically modified intent-to-treat; qSOFA, quick Sequential Organ Failure Assessment; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; VABP, ventilator-associated bacterial pneumonia; VP, ventilator pneumonia

6.1.5 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 at Day 28 or received the 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 15. The upper limits of 95% CIs for treatment difference in 28-day mortality rate were below 10% in all three populations, meeting both 20% and 10% NI margins.

Table 15. 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.

[1] The 95% CI was calculated using continuity-corrected Z-statistics.

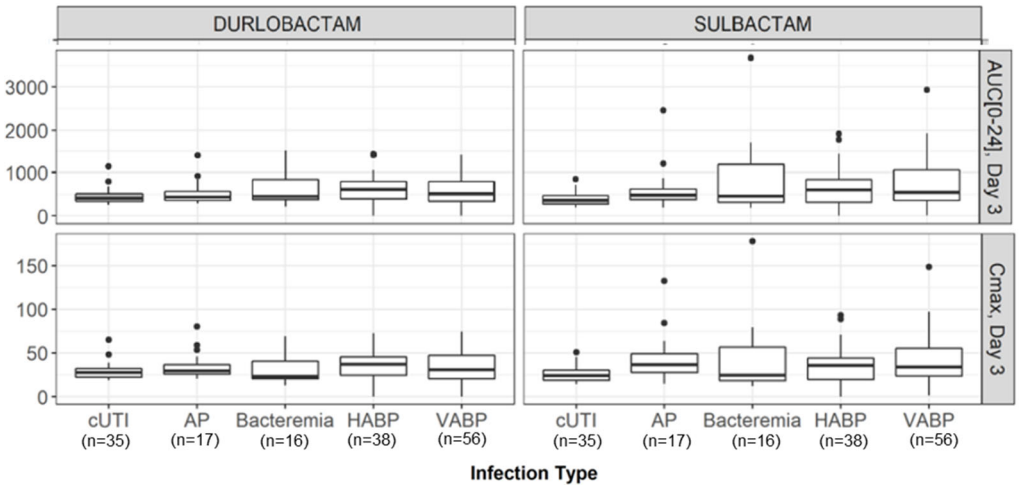
Abbreviations: CI, confidence interval; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; DUR, durlobactam; ITT, intent-to-treat; ME, microbiologically evaluable; m-MITT; microbiologically modified intent-to-treat; n, number of observed or imputed all-cause mortalities by Day 28; N, number of subjects in analysis; SUL, sulbactam

6.2 Additional Clinical Pharmacology Information

6.2.1 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, and 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 clearance and central volume for SUL and central volume for DUR. However, analyses of the distributions of $AUC_{0\text{-}24}$ and maximum plasma concentration on Days 1 to 3 revealed considerable overlap across infection types for subjects enrolled in the Phase 2 and 3 studies (Figure 4 shows data from Day 3). Therefore, drug exposures of SUL and DUR are generally similar across the evaluated infection types.

Figure 4. DUR and SUL Plasma AUC_{0-24} and C_{max} at Steady State (on Day 3) Across Infection Types



Source: Adapted from Figure 13 of Applicant's module 2.7.2 Summary of Clinical Pharmacology for NDA 216974.
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; DUR, durlobactam; HABP, hospital-acquired bacterial pneumonia; SUL, sulbactam; VABP, ventilator-associated bacterial pneumonia

6.2.2 Dose Adjustment Based on Renal Function

SUL and DUR are primarily renally eliminated. Renal function status is identified as the only intrinsic factor warranting dose adjustment. A clinical study 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 (creatinine clearance ≥90 mL/min), mild renal impairment (estimated glomerular filtration rate ≥60 to <90 mL/min/1.73 m^2), and moderate renal impairment (estimated glomerular filtration rate ≥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 (estimated glomerular filtration rate <30 mL/min/1.73 m^2) including subjects with end-stage renal disease on hemodialysis. 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.

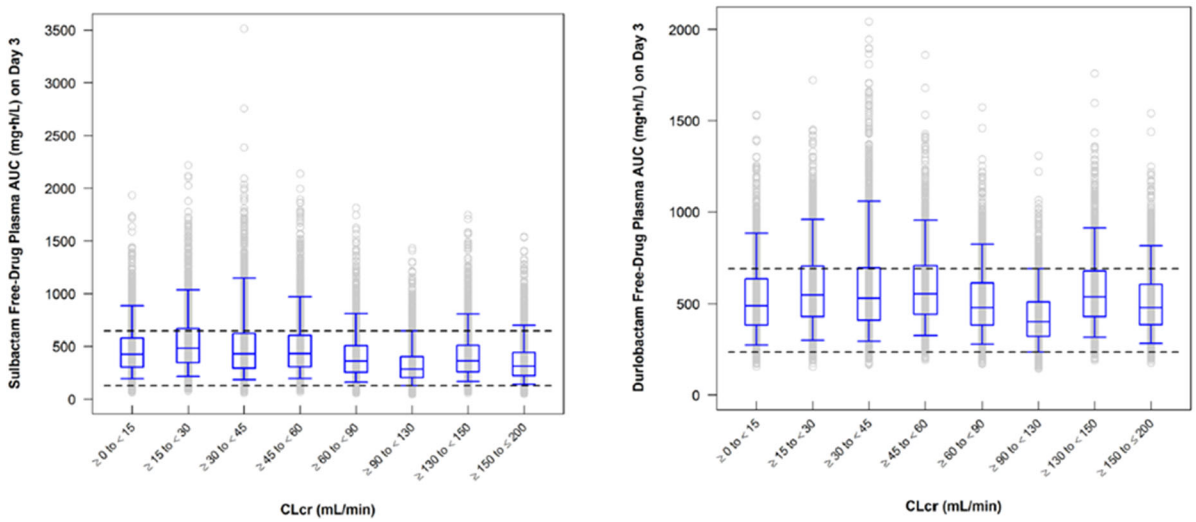
SUL and DUR free-drug plasma AUCs at steady state (Day 3) among simulated patients across renal function categories after administration of the adjusted doses listed in Table 16 were estimated and are presented in Figure 5. The results show that the AUC distribution among simulated patients was generally comparable across renal function categories at the proposed dose regimens.

Table 16. 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: Applicant's draft label 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, sulbactam

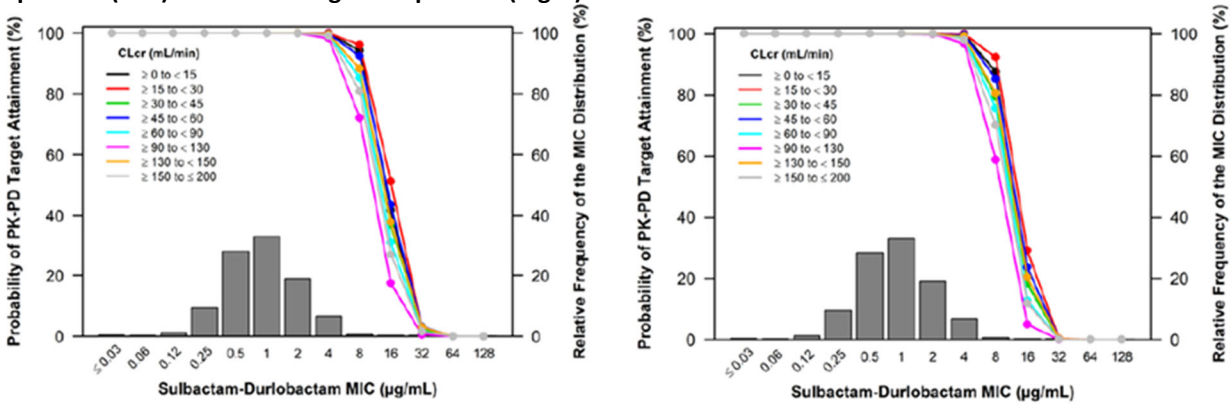
Figure 5. SUL (Left) and DUR (Right) Free-Drug Plasma Distributions of AUC at Steady State (Day 3) in Simulated Patients Across Renal Function Groups



Source: Figure 17 and Figure 18 of Applicant's module 2.7.2 Summary of Clinical Pharmacology for NDA 216974.
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 free-drug plasma AUC.
Abbreviations: AUC, area under the concentration-time curve; CLcr, creatinine clearance; DUR, durlobactam; SUL, sulbactam

Using the PK/PD targets of SUL (%*f*T>MIC of 50%) and DUR (*f*AUC:MIC ratio of 10) which are associated with a 1-$\log_{10}$ CFU reduction, PTA for free-drug plasma and total-drug ELF SUL and DUR exposures was evaluated at the proposed dose regimens (Table 16) in the simulated subjects across various renal function categories and global surveillance MIC distribution. As shown in Figure 6, the proposed dose regimens resulted in >90% PTA for MICs ≤4 mg/L (the Applicant's proposed susceptible MIC breakpoint) across renal function categories.

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)



Source: Figure 60 and Figure 61 of Applicant's module 2.7.2 Summary of Clinical Pharmacology for NDA 216974.
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: CFU, colony-forming units; ELF, epithelium lining fluid; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics

Based on results from a PK study in subjects with renal impairment, intermittent hemodialysis is expected to result in an approximately 30% decrease in daily AUC when hemodialysis is started 1 hour

after the end of the infusion for the morning dose and continued for 4 hours. Hence, in subjects on hemodialysis, SUL-DUR should be administered following the completion of hemodialysis.

In summary, the predicted SUL and DUR exposures and PTA analyses across each renal function group support the proposed dosage adjustments in patients with reduced or augmented renal function.

6.2.3 Effect of Body Weight on the PK of SUL and DUR

In the population PK covariate analysis conducted by the Applicant, body weight was identified as a statistically significant predictor of the variability in clearance and central volume for SUL and DUR. $AUC_{0\text{-}24}$ increased as body weight decreased for both drugs. However, the higher exposures in subjects with low body weight (≤50 kg) at the proposed dose regimens (Table 16) are expected to be within those observed at the highest doses tested for SUL (multiple doses up to 3 g, every 8 hours as in combination with ampicillin (Tamma et al. 2022)) and DUR (single doses up to 8.0 g and multiple doses up to 2.0 g, every 6 hours for 7 days), where SUL and DUR have been shown to be generally safe and well-tolerated.

Lower drug exposures were observed in subjects with high body weight and this trend is more significant at body weight ≥120 kg. The Applicant conducted PTA 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 renal function groups based on the proposed dosing regimens listed in Table 16. 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-$\log_{10}$ CFU reduction are achieved in ≥90% of simulated patients at the MICs up to 4 µg/mL (the Applicant's proposed susceptible MIC breakpoint) 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. Similar %PTA results were observed in simulated patients with a body mass index <30 kg/m^2, 30 to <35 kg/m^2, or ≥35 kg/m^2 at the proposed dose regimens listed in Table 16. Therefore, the Applicant's proposal of no dose adjustment based on body weight appears acceptable.

6.3 Additional Clinical Safety Analyses

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 of the lungs 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 the 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 cefdirocol; cefiderocol and polymyxin B; meropenem, high-dose ampicillin-SUL, and polymyxin B; meropenem; eravacycline and polymyxin B; meropenem and minocycline; cefiderocol, tigecycline, and polymyxin B. Most isolates were MDR and CRABC, notably with cefdirocol resistance and SUL-DUR MICs ranging from 2 to 8 mg/L.

Adverse Events of Special Interest

Hepatobiliary Disorders

The incidence and severity of AEs under the hepatobiliary disorders system organ class in the phase 3 study were comparable between the two treatment groups (Table 17).

Table 17. Hepatobiliary Disorder-Related Adverse Events, Phase 3 Study, Safety Population

	Part A		Part B
Parameter	SUL-DUR N=91 n (%)	Colistin N=86 n (%)	SUL-DUR N=28 n (%)
AE related to hepatobiliary disorders	10 (11.0)	9 (10.5)	1 (3.6)
Alanine aminotransferase increased	3 (3.3)	2 (2.3)	1 (3.6)
Aspartate aminotransferase increased	3 (3.3)	2 (2.3)	1 (3.6)
Bilirubin conjugated increased	2 (2.2)	0	0
Drug-induced liver injury	1 (1.1)	1 (1.2)	0
Hepatic cirrhosis	1 (1.1)	0	0
Hepatitis acute	0	1 (1.2)	0
Liver injury	2 (2.2)	4 (4.7)	0
Maximum severity			
Death	0	0	0
Life-threatening	0	0	0
Severe	0	1 (1.2)	0
Moderate	3 (3.3)	3 (3.5)	1 (3.6)
Mild	7 (7.7)	5 (5.8)	0
Serious	1 (1.1)	0	0
Death	0	0	0

Source: FDA Analysis.
Abbreviations: AE, adverse event; DUR, durlobactam; SUL, sulbactam

Deaths

No deaths were reported in the phase 1 studies or in the phase 2 study. In Part A of the phase 3 study there were 24/91 (26.4%) deaths in the SUL-DUR group and 30/86 (34.9%) deaths in the colistin group. There were four deaths (14%) among the 28 subjects in Part B with one death occurring beyond 28 days. This subject died of multiorgan failure related to the index infection or COVID-19.

The majority of the deaths in both groups occurred by Day 28. The most commonly reported causes were septic shock and sepsis in the SUL-DUR group, and septic shock, sepsis, pneumonia, and *Acinetobacter* sepsis in the colistin group.

A detailed review of the individual cases was conducted with a focus on demographic and baseline factors, potential for lack of efficacy, specific pathogens, TEAE imbalances, and the timing of events. Overall, the mortality outcomes appear to be related to the underlying comorbidities, complications in a critically ill subject or progression of the presenting pneumonia. There was no apparent biologic plausibility or causal assignment to SUL-DUR treatment identified.

Additional Laboratory Analyses

Table 18. Subjects With Last On-Treatment Chemistry Value ≥Level 2 Criteria by Treatment Arm, Safety Population, Trial cs2514-2017-0004

	Part A		Part B
	SUL-DUR N=91	Colistin N=86	SUL-DUR N=28
Parameter	n/N_w (%)	n/N_w (%)	n/N_w (%)
General chemistry			
Sodium, low (mEq/L) <130	1/88 (1.1)	10/76 (13.2)	5/27 (18.5)
Sodium, high (mEq/L) >155	8/88 (9.1)	1/76 (1.3)	0/27 (0)
Potassium, low (mEq/L) <3.4	12/86 (14.0)	8/74 (10.8)	0/15 (0)
Potassium, high (mEq/L) >6	2/86 (2.3)	1/74 (1.4)	0/15 (0)
Chloride, low (mEq/L) <88	0/88 (0)	1/76 (1.3)	0/27 (0)
Chloride, high (mEq/L) >112	17/88 (19.3)	7/76 (9.2)	3/27 (11.1)
Bicarbonate, low (mEq/L) <18	4/89 (4.5)	1/76 (1.3)	0/27 (0)
Bicarbonate, high (mEq/L) >30	18/89 (20.2)	12/76 (15.8)	7/27 (25.9)
Calcium, low (mg/dL) <8	25/89 (28.1)	21/76 (27.6)	8/27 (29.6)
Calcium, high (mg/dL) >11	1/89 (1.1)	0/76 (0)	0/27 (0)
Phosphate, low (mg/dL) <2	3/89 (3.4)	4/76 (5.3)	0/27 (0)
Amylase, high (U/L) >1.5× ULN	2/87 (2.3)	1/75 (1.3)	2/27 (7.4)
Lipase, high (U/L) >1.5× ULN	9/88 (10.2)	9/74 (12.2)	6/27 (22.2)
Blood urea nitrogen, high (mg/dL) >27	27/78 (34.6)	22/67 (32.8)	5/26 (19.2)
Kidney function			
Creatinine, high (mg/dL) ≥2× baseline	2/82 (2.4)	11/70 (15.7)	2/22 (9.1)
eGFR, low (mL/min/1.73 m^2) ≥50% decrease	1/79 (1.3)	9/70 (12.9)	0/22 (0)
CrCl, 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 (6.7)	6/76 (7.9)	3/27 (11.1)
Alanine aminotransferase, high (U/L) >5× ULN	1/89 (1.1)	2/76 (2.6)	0/27 (0)
Aspartate aminotransferase, high (U/L) >5× ULN	2/89 (2.2)	2/76 (2.6)	1/26 (3.8)
Bilirubin, total, high (mg/dL) >2× ULN	2/89 (2.2)	1/76 (1.3)	3/27 (11.1)

Source: FDA Analysis.
Last value on treatment defined as last measured value.
Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.
Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 19. Last On-Treatment Hematology Value ≥Level 2 Criteria by Treatment Group, Safety Population, Trial cs2514-2017-0004

	Part A		Part B
	SUL-DUR N=91	Colistin N=86	SUL-DUR N=28
Parameter	n/N_w (%)	n/N_w (%)	n/N_w (%)
Complete blood count			
WBC, low (cells/µL) <3000	1/88 (1.1)	0/76 (0)	1/27 (3.7)
WBC, high (cells/µL) >13,000	22/88 (25.0)	22/76 (28.9)	5/27 (18.5)
Hemoglobin, low (g/dL) >1.5 g/dL dec. from baseline	13/79 (16.5)	10/66 (15.2)	7/21 (33.3)
Hemoglobin, high (g/dL) >2 g/dL inc. from baseline	5/79 (6.3)	3/66 (4.5)	0/21 (0)
Platelets, low (cells/µL) <125,000	10/87 (11.5)	9/76 (11.8)	4/26 (15.4)

WBC Differential			
Lymphocytes, low (cells/µL) <750	21/88 (23.9)	14/76 (18.4)	6/27 (22.2)
Lymphocytes, high (cells/µL) >10,000	0/88 (0)	0/76 (0)	0/27 (0)
Neutrophils, low (cells/µL) <1000	0/88 (0)	0/76 (0)	1/27 (3.7)
Eosinophils, high (cells/µL) >1500	4/88 (4.5)	1/76 (1.3)	0/27 (0)

Source: FDA Analysis.
Last value on treatment defined as the last measured value.
Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 7 days, with extension up to 14 days where clinically indicated.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; dec, decrement; inc., increment; N, number of patients in treatment group; n, number of patients meeting criteria; Nw, number of patients with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cell