ENTASIS THERAPEUTICS

SULBACTAM-DURLOBACTAM FOR THE TREATMENT OF HOSPITAL-ACQUIRED BACTERIAL PNEUMONIA AND VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA CAUSED BY SUSCEPTIBLE STRAINS OF *ACINETOBACTER BAUMANNII-CALCOACETICUS* COMPLEX

SPONSOR BRIEFING DOCUMENT

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE

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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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Abbreviation	Definition
%*f*T > MIC	Time as percentage of dosing interval the drug concentration exceeds the minimum inhibitory concentration of the infecting organism
ABC	*Acinetobacter baumannii-calcoaceticus* complex
AE(s)	Adverse event(s)
AESI(s)	Adverse event(s) of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Acute pyelonephritis
APACHE	Acute Physiology and Chronic Health Evaluation
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0–24}$	Area under the plasma concentration-time curve from time of dosing to 24 hours post-dose
BMI	Body mass index
BPP	Biofire® FilmArray® 2.0 Pneumonia Panel
CDAD	*Clostridioides difficile*-associated diarrhea
CDC	Centers for Disease Control and Prevention
CFU	Colony-forming units
CL	Total body clearance
CL_{CR}	Creatine clearance
C_{max}	Maximum plasma concentration
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
CRABC	Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex
cUTI	Complicated urinary tract infection
CYP450	Cytochrome P450
DAI	Division of Anti-Infectives
DBO	Diazabicyclooctane
DDI(s)	Drug-drug interaction(s)
EAP	Expanded Access Program
ECG	Electrocardiogram
ELF	Epithelial lining fluid
EOT	End of Treatment
ESKD	End-stage kidney disease
FDA	Food and Drug Administration

FIH	First-in-human
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HABP	Hospital-acquired bacterial pneumonia
ICU	Intensive care unit
IDSA	Infectious Disease Society of America
ITT	Intent-to-Treat
IV	Intravenous(ly)
LDH	Lactate dehydrogenase
LFT	Liver function test
LFU	Late Follow-Up
MBC	Minimum bactericidal concentrations
MDR	Multidrug-resistant
MIC	Minimum inhibitory concentration
MIC_{50}	Minimum inhibitory concentration required to inhibit the growth of 50% of isolates
MIC_{90}	Minimum inhibitory concentration required to inhibit the growth of 90% of isolates
MITT	Modified Intent-to-Treat
m-MITT	Microbiologically Modified Intent-to-Treat
NDA	New Drug Application
NHSN	National Healthcare Safety Network
OAT1	Organic anion transporter 1
PBP1a	Penicillin-binding protein 1a
PBP1b	Penicillin-binding protein 1b
PBP2	Penicillin-binding protein 2
PBP3	Penicillin-binding protein 3
PD	Pharmacodynamic(s)
PDR	Pandrug resistant
PK	Pharmacokinetic(s)
PTA	Probability of target attainment
q6h	Every 6 hours
q12h	Every 12 hours
QIDP	Qualified Infectious Disease Product Designation
RIFLE	Risk-Injury-Failure-Loss-End-Stage Kidney Disease
SAE(s)	Serious treatment-emergent adverse event(s)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query

SOFA	Sequential Organ Failure Assessment
spp	species
$t_{1/2}$	Terminal half-life
TEAE(s)	Treatment-emergent adverse event(s)
T_{max}	Time to maximum (peak) plasma concentration
TOC	Test of Cure
ULN	Upper limit of normal
US	United States
USPI	United States Package Insert
VABP	Ventilator-associated bacterial pneumonia
VP	Ventilated pneumonia
WHO	World Health Organization
XDR	Extensively drug resistant

1 EXECUTIVE SUMMARY

1.1 Introduction

Sulbactam-durlobactam is a combination of sulbactam, a β-lactam antibacterial, and durlobactam, a β-lactamase inhibitor, with the proposed indication in adults (≥ 18 years of age) for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex (ABC).

The recommended dose is 1.0 g sulbactam and 1.0 g durlobactam every 6 hours (q6h) administered as a 3-hour intravenous (IV) infusion in patients with creatinine clearance (CL_{CR}) of 45–129 mL/min. Dose adjustments are required for patients with CL_{CR} < 45 and ≥ 130 mL/min. The proposed duration of treatment is at least 7 days and up to 14 days, depending on clinical response.

Acinetobacter baumannii is a Gram-negative bacterial pathogen that has emerged globally as a major cause of hospital-acquired infections (Ayoub Moubareck and Hammoudi Halat 2020). *A. baumannii* is the predominant member of a closely related group of bacterial species known as ABC (Ayoub Moubareck and Hammoudi Halat 2020; Harding et al 2018). Infections caused by ABC are associated with high morbidity and mortality and have become increasingly difficult to treat as multidrug-resistant (MDR) and carbapenem-resistant strains have emerged (Antimicrobial Resistance 2022). Carbapenem-resistant *A. baumannii* (or CRAB) is considered an urgent public health threat by the United States Centers for Disease Control and Prevention (US CDC) and “priority 1, critical” by the World Health Organization (WHO) (CDC 2019; WHO 2017). This rise in resistant strains leaves physicians with no clear standard-of-care antibiotic regimen for their patients, highlighting a significant unmet need for safe and effective treatments that provide clinically meaningful benefit over existing therapies (Gales et al 2019; Tamma et al 2022).

Entasis Therapeutics (hereafter referred to as Entasis) is seeking approval of sulbactam-durlobactam in adults for the treatment of HABP and VABP caused by susceptible strains of ABC. This indication aligns with the August 2017 FDA guidance on ‘Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases’ and also reflects the population studied in the pivotal Phase 3 trial (FDA 2017).

The totality of evidence with sulbactam-durlobactam supports the positive benefit-risk profile for the proposed indication. This includes:

- A comprehensive nonclinical assessment, including microbiology data, primary and secondary pharmacodynamics (PD), safety pharmacology, drug-drug interactions, pharmacokinetics (PK), and toxicology data, as well as genotoxicity, reproductive, and developmental toxicity.

- Robust PK and PK/PD data with population PK modeling from Phase 1, Phase 2, and Phase 3 trials, probability of target attainment (PTA) analyses, as well as data on clinical and microbiological outcomes from the Phase 3 trial.
- Safety data on sulbactam-durlobactam collected from 8 clinical studies, including six Phase 1 studies, one Phase 2 trial, and one adequate and well-controlled Phase 3 clinical trial.
- Safety and efficacy data from the adequate and well-controlled Phase 3 trial in which sulbactam-durlobactam met all safety and efficacy objectives.
- Over 30 years of well-established safety profile of sulbactam since the approval of Unasyn®.

1.2 Background and Unmet Need

According to the CDC, infections caused by *A. baumannii* typically occur in patients in healthcare settings (CDC 2019). Patients on mechanical ventilators and those with central line-catheters have the highest proportion of infections caused by *A. baumannii*.

Pneumonia and bacteremia are the most common infections caused by ABC, but these organisms can also cause skin, soft tissue, wound, and urinary tract infections as well as osteomyelitis and meningitis (Alsan and Klompas 2010). ABC has become increasingly difficult to treat due to the emergence of multidrug- and carbapenem-resistant strains (Ayoub Moubareck and Hammoudi Halat 2020; Gales et al 2019). ABC has acquired resistance genes for almost all antibiotics used to treat Gram-negative bacteria (Gales et al 2019; Peleg et al 2008; Wong et al 2017). Consequently, CRAB has emerged as a significant public health concern and is classified as an “urgent threat” pathogen (CDC 2019). CRAB is also ranked as “priority 1 critical” on the WHO global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics (WHO 2017). Globally, CRABC is the 5th leading cause of death attributable to antimicrobial resistance, with > 450,000 deaths in 2019 (Antimicrobial Resistance 2022).

Current treatment guidance for infections caused by carbapenem-resistant *Acinetobacter* species underscores the many challenges in selecting appropriate therapy (Tamma et al 2022). As noted in the Infectious Disease Society of America (IDSA) guidance, “there is no clear ‘standard of care,’ antibiotic regimen” and “data supporting a prioritization of specific agents with CRAB activity or the additive benefit of commonly used combination regimens for CRAB remain incomplete,” highlighting the urgent unmet medical need for this patient population (Tamma et al 2022).

Sulbactam-durlobactam, if approved, would be a treatment option for HABP and VABP caused by susceptible strains of ABC.

1.3 Overview of Sulbactam-Durlobactam

Sulbactam-durlobactam is a targeted antibiotic combination of sulbactam, a β-lactam antibacterial with intrinsic activity against ABC, and durlobactam, a β-lactamase inhibitor with broad spectrum activity against Classes A, C, and D serine β-lactamases.

The antibacterial activity of sulbactam is through inhibition of essential cell wall enzymes, penicillin-binding-protein 1 and 3 (PBP1; PBP3) (Penwell et al 2015). Although sulbactam is available as a standalone product in a small number of countries (e.g., Combactam®, Germany), the vast majority of human use is in combination with a β-lactam (e.g., Unasyn®, ampicillin-sulbactam). Unasyn is approved by regulatory authorities in the US, Europe, and the Asia-Pacific region.

Durlobactam is a member of the diazabicyclooctane (DBO) class of β-lactamase inhibitors with a spectrum of activity that encompasses clinically important β-lactamases of Ambler Class A, C, and broad-spectrum Class D β-lactamases. Most importantly, durlobactam effectively restores sulbactam activity in vitro against drug-resistant ABC organisms (Durand-Reville et al 2017; Karlowsky et al 2022).

Evaluation of sulbactam-durlobactam using in vivo efficacy models and in vitro hollow fiber studies indicates that sulbactam-durlobactam is efficacious against *A. baumannii*, including MDR strains. In vivo studies included the use of murine neutropenic thigh and lung infection models, which have been shown to translate well to clinical efficacy (Bulitta et al 2019).

The pharmacology, PK, and safety of durlobactam, both alone and in combination with sulbactam, have been well-characterized in a comprehensive series of in vitro and in vivo nonclinical studies (additional details provided in Sections 4 and 5). These studies have defined the key pharmacological properties including the PK, distribution, metabolism, excretion, and potential to cause drug-drug interactions (DDIs) of sulbactam-durlobactam, as well as the key test article-related safety findings and the reversibility of these changes. Also, addition of imipenem has minimal effect on the activity of sulbactam-durlobactam in ABC pathogens (additional details provided in Section 7.1.2.3.2).

1.4 Clinical Development Program of Sulbactam-Durlobactam

Entasis has received guidance and advice from the Food and Drug Administration Division of Anti-Infectives (FDA DAI) through a series of collaborative interactions throughout the clinical development of sulbactam-durlobactam (additional details provided in Section 6.2). The sulbactam-durlobactam clinical development program consists of 8 clinical studies (Table 1), including five Phase 1 studies in healthy adult participants, one Phase 1 study in adult participants with varying degrees of renal impairment, one Phase 2 trial to evaluate PK and safety in adult patients with complicated urinary tract infections (cUTI) including acute pyelonephritis (AP), and one Phase 3 trial in adult patients with infections caused by ABC, including multidrug- and

carbapenem-resistant strains, from which the primary safety and efficacy data are derived (Sections 7 and 8).

Table 1: Overview of Sulbactam-Durlobactam Clinical Development Program

Phase	Study Number (Type)	Patient Population	Number of Patients Enrolled
Phase 1	CS2514-2016-0001 (First-in-human study)	Healthy participants	124
	CS2514-2017-0001 (Lung penetration study)	Healthy adult participants (non-smoking)	30
	CS2514-2017-0002 (Renal impairment PK study)	Healthy adult, Mild RI, Moderate RI, Severe RI, and ESKD on HD participants	34
	CS2514-2018-0002 (PK, distribution, metabolism, and excretion study)	Healthy adult males	8
	CS2514-2018-0003 (TQT study)	Healthy adult participants (non-tobacco using)	32
	ZL-2402-001 (Healthy Chinese adult PK study)	Healthy adult participants	12
Phase 2	CS2514-2017-0003 (PK and safety in patients)	Hospitalized patients with a cUTI (including AP)	80
Phase 3	CS2514-2017-0004	Patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms	207

ABC=*Acinetobacter baumannii-calcoaceticus* complex; AP=acute pyelonephritis; cUTI=complicated urinary tract infection; ESKD=end-stage kidney disease; HABP=hospital-acquired bacterial pneumonia; HD=hemodialysis; PK=pharmacokinetics; RI=renal impairment; TQT=Thorough QT; VABP=ventilator-associated bacterial pneumonia; VP=ventilated pneumonia.

On 01 September 2017, the FDA DAI granted sulbactam-durlobactam Fast Track Designation and Qualified Infectious Disease Product (QIDP) Designation, acknowledging the potential for sulbactam-durlobactam to address this high unmet need. In 2018, an End of Phase 2 meeting was held with the FDA to align on the design of the global Phase 3 trial. The clinical development program of sulbactam-durlobactam was streamlined to derive the primary data supporting efficacy and safety from a single Phase 3 trial based on FDA guidance for expedited development of treatments for infections caused by resistant pathogens (FDA 2017). The Phase 3 trial began enrollment in 2019 and enrollment was completed in 2021. In March of 2022, a pre-New Drug Application (NDA) meeting was held with the FDA DAI, where the Division agreed that the Phase 3 data along with the microbiology, pharmacology, and toxicology data in the non-clinical package were adequate for the Division's review of the NDA for

sulbactam-durlobactam. Entasis submitted the NDA for sulbactam-durlobactam for the treatment indication on 29 September 2022.

In May 2020, an Expanded Access Program (EAP) was initiated for patients ineligible to participate in the clinical trial and who had a documented serious and immediately life-threatening infection caused by drug-resistant ABC. This program permitted access to investigational sulbactam-durlobactam for treatment outside of the clinical trial when no comparable or satisfactory alternative therapy option was available.

1.5 Efficacy Findings

In the pivotal Phase 3 trial, sulbactam-durlobactam met the primary efficacy endpoint of noninferiority for 28-day all-cause mortality in the primary analysis population (CRABC microbiologically Modified Intent-to-Treat [m-MITT] Population in Part A, as defined in Table 2). In addition, secondary all-cause mortality analyses across various prespecified populations for both Part A and Part B of the Phase 3 trial were consistent with the primary efficacy analysis, supporting the clear benefit of sulbactam-durlobactam in patients with serious infections caused by ABC, including multidrug- and carbapenem-resistant strains.

1.5.1 Two-Part Phase 3 Trial (CS2514-2017-0004)

The Phase 3 trial was a global, two-part (A and B) trial that assessed the efficacy and safety of 1.0 g sulbactam/1.0 g durlobactam for 7–14 days of treatment in patients with serious infections caused by ABC, including multidrug- and carbapenem-resistant strains (Figure 1). The Phase 3 trial employed a non-inferiority design, as discussed and agreed with the FDA DAI. A Test of Cure (TOC) visit was completed 7 ± 2 days after the last dose, and survival was assessed at Day 28.

1.5.1.1 Phase 3 Part A

Part A was the randomized, assessor-blinded, comparative portion of the Phase 3 trial. Patients were randomized (1:1) to 1.0 g sulbactam/1.0 g durlobactam or 2.5 mg/kg colistin. All patients in both treatment groups received 1.0 g imipenem/1.0 g cilastatin as background therapy to treat non-ABC co-infecting pathogens. Imipenem/cilastatin was also considered an effective therapy for patients with infections caused by carbapenem-susceptible ABC, an appropriate therapeutic partner to treat CRABC in the colistin group, and had a dosing regimen (q6h) consistent with sulbactam-durlobactam administration in patients with normal renal function.

Randomization was stratified by infection type (HABP/VABP/ventilated pneumonia [VP] vs bacteremia), severity of illness, and geography. A total of 92 patients were randomized to the sulbactam-durlobactam group and 89 patients to the colistin group.

Eligible patients were ≥ 18 years of age with a diagnosis of a serious infection caused by ABC as either a single pathogen or member of a polymicrobial infection confirmed by culture. In addition, patients must have had ≤ 48 hours of potentially effective antimicrobial therapy before first dose of study drug or clinically failed prior treatment

(i.e., clinical deterioration or failure to improve after ≥ 48 hours of antibiotics) and an Acute Physiology and Chronic Health Evaluation (APACHE) II score 10–30 or Sequential Organ Failure Assessment (SOFA) score 1–11. Patients were excluded from Part A if they had an infection known to be resistant to colistin or polymyxin B. Other key exclusion criteria included hypersensitivity or allergic reaction to a β-lactam, contraindication to use of cilastatin, pulmonary disease that precludes evaluation of therapeutic response, and presence of suspected or confirmed deep-seated infection.

1.5.1.1.1 Selection of Comparator

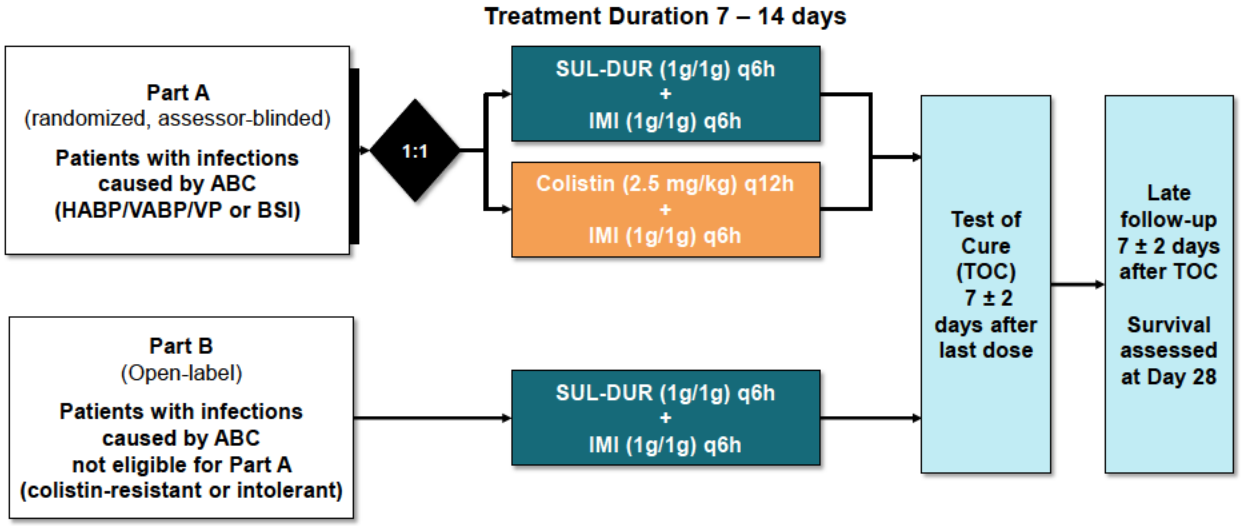
Colistin was selected as the active comparator for this study as it was a treatment option for serious infections caused by resistant *A. baumannii*. At the time of study design, there was no clear standard-of-care for the treatment of CRAB infections and no new treatment options were approved. Colistin has been used worldwide to treat MDR *A. baumannii* either alone or in combination. Overall mortality rates of 25–57% were reported in patients treated with colistin-based therapies (Alvarez-Marin et al 2016; Sirijatuphat and Thamlikikul 2014) which compares to mortality rates of 65–87% in patients who were not treated or had delayed treatment including inappropriate therapy (Erbay et al 2009; Lee et al 2014), indicating that colistin-based therapies were effective for the treatment of serious infections caused by resistant *A. baumannii*. The dosing of colistin was based on the USPI and updated guidance for IV colistin in critically ill patients (Nation et al 2016; Nation et al 2017).

1.5.1.2 Phase 3 Part B

Part B was the open-label portion of the Phase 3 trial that included patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms resistant to colistin or polymyxin B or who failed colistin or polymyxin B regimen prior to trial entry. Eligible patients received 1.0 g sulbactam/1.0 g durlobactam and 1.0 g imipenem/1.0 g cilastatin as background therapy to treat non-ABC co-infecting pathogens in the case of polymicrobial infections. All other general inclusion and exclusion criteria for Part B were similar to those of Part A. A total of 28 patients were enrolled into Part B, with 2 patients transferred from Part A because local microbiology laboratory susceptibility results indicated that the screening ABC isolates were colistin-resistant.

A full list of enrollment criteria for Parts A and B is provided in Appendix 13.1.

Figure 1: Trial CS2514-2017-0004: Design



ABC=*Acinetobacter baumannii-calcoaceticus* complex; BSI=bacteremia; HABP=hospital-acquired bacterial pneumonia; IMI=imipenem/cilastatin; q6h=every 6 hours; q12h=every 12 hours; SUL-DUR=sulbactam-durlobactam; TOC=Test of Cure; VABP=ventilator-associated bacterial pneumonia; VP=ventilated pneumonia.

The primary efficacy endpoint in the Phase 3 trial was 28-day all-cause mortality in the CRABC m-MITT Population in Part A. The primary efficacy patient population consisted of patients in Part A who received any amount of study drug treatment and had a baseline ABC organism that was confirmed to be carbapenem-resistant. Three patients were excluded from the primary efficacy population due to patient withdrawal.

1.5.1.3 Determination of Non-Inferiority Margin

Entasis proposed a 20% non-inferiority margin for the primary efficacy endpoint for Part A. In the first Entasis literature review, as listed in Table 33, the best estimate of the mortality rate for colistin-based therapy was 40% (95% CI: 35%, 45%) from a fixed effects analysis, or 40% (95% CI: 32%, 47%) from a random effects analysis using the method of DerSimonian and Laird (DerSimonian and Laird 1986). However, after updating the meta-analysis with 4 additional studies (Table 34), the estimated mortality rate from the random effects meta-analysis is 41% (95% CI: 36%, 47%). The best estimate of the mortality rate for untreated or delayed treatment is 78% (95% CI: 72%, 83%) from a fixed effect analysis, or 76% (95% CI: 66%, 86%) from a random effects analysis.

Using the most conservative estimates of mortality from the updated meta-analysis, the mortality rate is estimated to be 41% (95% CI: 36%, 47%) for colistin-based therapy, and 76% (95% CI: 66%, 86%) for untreated or delayed therapy. Based upon these data and using the most conservative approach of taking the upper bound of the 95% CI from the colistin-based therapy estimate and the lower bound of the 95% CI from the inappropriate or delayed therapy estimate leads to an estimated treatment benefit of at least 19% (66% minus 47%; M1).

Given the unmet need of this population, the life-threatening condition, and the relevancy of the literature review study populations to this study population, clinically it was determined that it may not be necessary to preserve the entire 50% of the M1. FDA DAI independently determined that a 19% non-inferiority margin should be used; however, later evaluated again and agreed to a 20% margin for this study.

Estimation of the sample size assumed a 41% mortality rate in the colistin arm, a 36% mortality rate in the sulbactam-durlobactam arm, a 1:1 randomization, and an 80% power with a two-sided significance level of 0.05. The non-inferiority was based on the 2-sided 95% CIs computed using a continuity-corrected Z-statistic for the difference ([sulbactam-durlobactam] – [colistin]) in 28-day all-cause mortality rates between the treatment groups. Non-inferiority was concluded if the upper limit of the 2-sided 95% CI was < 20%.

Secondary efficacy endpoints for Parts A and B included:

- 28-day all-cause mortality in the m-MITT and ITT Populations,
- 14-day all-cause mortality in the CRABC m-MITT and m-MITT Populations,
- Clinical cure at TOC, End of Treatment (EOT), and Late Follow-Up (LFU) in the CRABC m-MITT Population, and
- Microbiological favorable assessment at TOC, EOT, and LFU in the CRABC m-MITT Population.

Definitions of the analysis populations are provided in Table 2.

Table 2: Phase 3 Trial: Analysis Populations

Population	Description
Intent-to-Treat (ITT)	All patients randomized to study drug treatment (sulbactam-durlobactam or colistin) in Part A or enrolled in Part B, regardless of whether the patient actually received study drug.
Modified Intent-to-Treat (MITT) and Safety	Patients in Parts A and B who met ITT criteria and received any amount of study drug. The MITT Population was also considered the Safety Population. Patients with HABP/VABP/VP who were randomized to Part A on the basis of a BPP rapid test result but were subsequently withdrawn due to a lack of a culture growing ABC, were counted in the MITT and Safety Populations.
Microbiologically Modified Intent-to-Treat (m-MITT)	Patients who met MITT criteria and 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 identification such as molecular based tests, MALDI-TOF, Vitek, Phoenix, etc. (i.e., not conventional biochemical or manual phenotypic methods). Patients with HABP/VABP/VP who were enrolled based upon a positive BPP rapid test for ABC, but subsequently were found to have respiratory sample cultures that did not grow ABC (by the local laboratory), were withdrawn from the study drug treatment. These patients were not included in the m-MITT Population but remained in the MITT Population.
Carbapenem-resistant ABC m-MITT Population (CRABC m-MITT)*	For Part A, the CRABC m-MITT Population included patients who met m-MITT criteria and had a baseline ABC organism that was confirmed to be carbapenem-resistant (MIC of imipenem or meropenem ≥ 8 µg/mL) by the central laboratory or by the local laboratory if the central laboratory was not able to identify the isolate for any reason. Three patients withdrew consent and were not included in the primary efficacy analysis. Patients were excluded from the CRABC m-MITT Population if they had isolates that were deemed by the central laboratory to be resistant to sulbactam-durlobactam (MIC > 4 µg/mL) or colistin (MIC ≥ 4 µg/mL), if their blood culture or respiratory samples were collected more than 72 hours prior to randomization, if they were transferred from Part A to Part B, or if they were enrolled with infections other than ABC pneumonia or bloodstream infection (i.e., infections other than HABP, VABP, VP, and bacteremia). A sensitivity analysis for the primary efficacy endpoint was performed for patients whose eligible culture was > 48 hours from the first dose of treatment, as well as for all patients with and without evidence of non-susceptibility to colistin and sulbactam-durlobactam at baseline. For Part B, the CRABC m-MITT Population included patients who met m-MITT criteria and had a baseline ABC organism that was confirmed to be carbapenem-resistant (MIC of imipenem or meropenem ≥ 8 µg/mL) by the central laboratory or by the local laboratory if the central laboratory was not able to identify the isolate for any reason. Patients were excluded from the CRABC m-MITT Population if their blood culture or respiratory samples were collected more than 72 hours prior to randomization.
Pharmacokinetic (PK)	Included patients who received any amount of study drug and had evaluable PK data.

*Primary efficacy endpoint analysis population.
BPP=Biofire® FilmArray® 2.0 Pneumonia Panel; CRABC m-MITT=Carbapenem-Resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat; HABP=hospital-acquired bacterial pneumonia; MIC=minimum inhibitory concentration; PK=pharmacokinetic; VABP=ventilator-associated bacterial pneumonia; VP=ventilated pneumonia.

In the ITT Population in Part A, 75% of patients in the sulbactam-durlobactam group and 68.5% of patients in the colistin group completed the trial. In the sulbactam-durlobactam group, the primary reasons patients discontinued were due to death (16.3%), no growth of ABC (2.2%), and patients who withdrew voluntarily (2.2%). In the colistin group, the primary reasons patients discontinued were due to death (23.6%) and patients who withdrew voluntarily (3.4%).

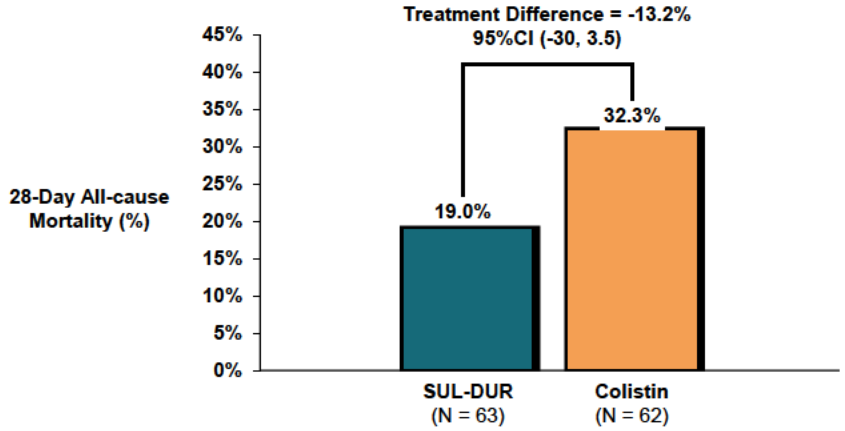
In the ITT Population in Part B, 78.6% of patients completed the trial. Four patients discontinued due to death, 1 patient discontinued due to withdrawal of consent, and 1 patient discontinued due to incorrect enrollment into Part B.

Demographics and baseline characteristics between all treatment groups were generally similar for the CRABC m-MITT Population (Table 10). The median age was approximately 62 years for the sulbactam-durlobactam group in Part A and approximately 59 years in Part B, and approximately 66 years for the colistin group. Across all treatment groups there was a higher proportion of males than females. For Part A, the mean baseline APACHE II score was 16.8 overall: 16.4 in the sulbactam-durlobactam group and 17.2 in the colistin group. For Part B, the mean APACHE II score was 18.0. The majority of patients for both treatment groups in Part A had pneumonia and were in the intensive care unit (ICU) for ≥ 5 days. The majority of patients in Part B had bacteremia (17/28 patients; 60.7%) and were in the ICU > 14 days.

1.5.1.4 Primary Efficacy Endpoint Results – 28-Day All-Cause Mortality in Part A (CRABC m-MITT Population)

The Phase 3 trial met its prespecified primary efficacy endpoint for non-inferiority in Part A. In Part A of the CRABC m-MITT Population, the 28-day all-cause mortality for the sulbactam-durlobactam group was 19.0% (12/63 patients) and was 32.3% (20/62 patients) in the colistin group with a treatment difference of −13.2% (95% CI: −30.0%, 3.5%), which was less than the non-inferiority margin of 20% (Figure 2 and Figure 3). A test for superiority was conducted and the upper limit of the 2-sided CI was not < 0.

Figure 2: Phase 3 Trial: 28-Day All-Cause Mortality in Part A (CRABC m-MITT Population)

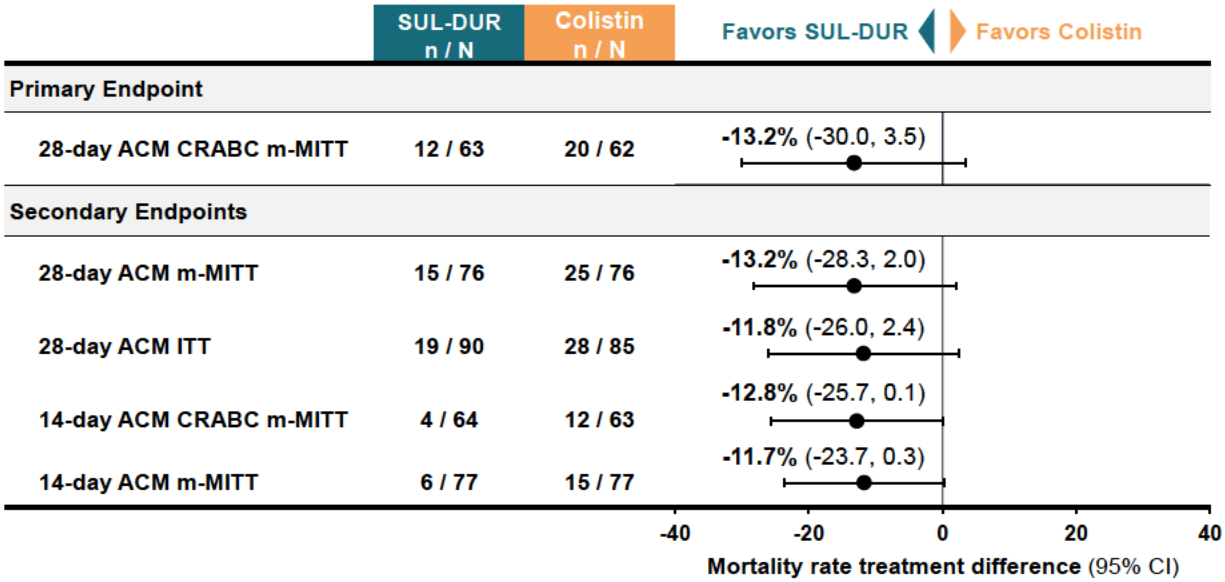


CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat; SUL-DUR=sulbactam-durlobactam.
Note: Participants with missing survival status were treated as deaths.

1.5.1.5 Secondary Efficacy Endpoint Results for Part A

Sulbactam-durlobactam met the secondary efficacy endpoints of all-cause mortality compared to colistin across various prespecified analysis populations at 28 days and 14 days (Figure 3). All endpoints favored sulbactam-durlobactam.

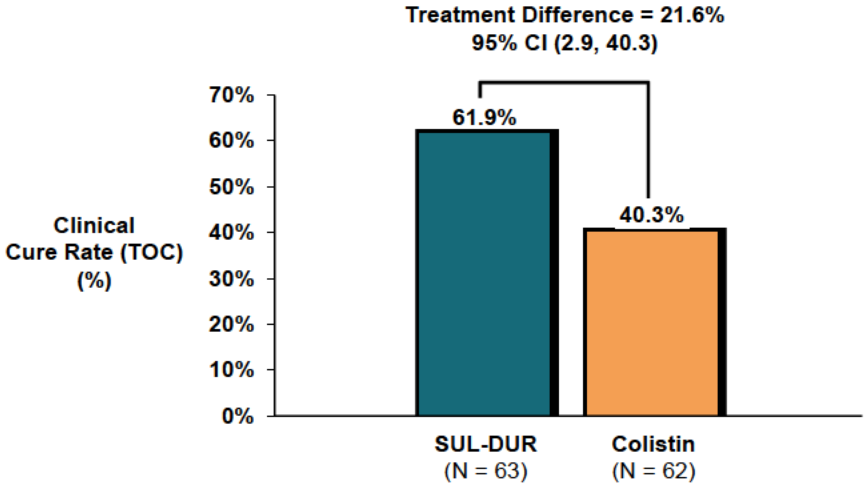
Figure 3: Phase 3 Part A: 28-Day and 14-Day All-Cause Mortality (CRABC m-MITT, m-MITT, and ITT Populations)



ACM=All-cause mortality; CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat; SUL-DUR=sulbactam-durlobactam.

For Part A, a significant treatment difference of 21.6% (95% CI: 2.9%, 40.3%) in clinical cure rate at TOC was observed with 61.9% of patients in the sulbactam-durlobactam group compared to 40.3% of patients in the colistin group for the CRABC m-MITT Population (Figure 4). Clinical cure was defined as complete resolution or significant improvement of baseline signs and symptoms and no new symptoms, such that no additional Gram-negative antimicrobial therapy was warranted.

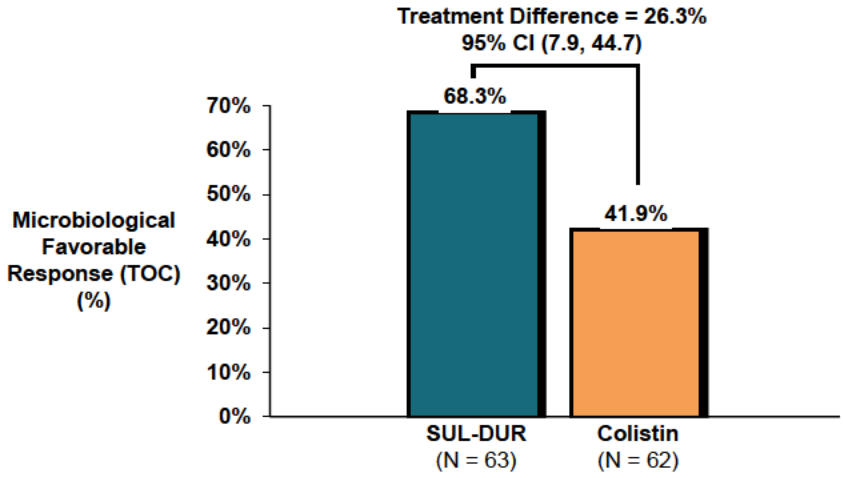
Figure 4: Phase 3 Part A: Clinical Cure Rate at Test of Cure Visit (CRABC m-MITT Population)



CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat; SUL-DUR=sulbactam-durlobactam; TOC=Test of Cure.
Note: Test of cure was 7 ± 2 days after end of treatment.

In addition, a significant treatment difference in microbiological favorable assessment at TOC was observed in the sulbactam-durlobactam group (68.3%) compared to the colistin group (41.9%) in the CRABC m-MITT Population, with a treatment difference of 26.3% (95% CI: 7.9%, 44.7%) (Figure 5). A microbiological favorable assessment included eradication and presumed eradication.

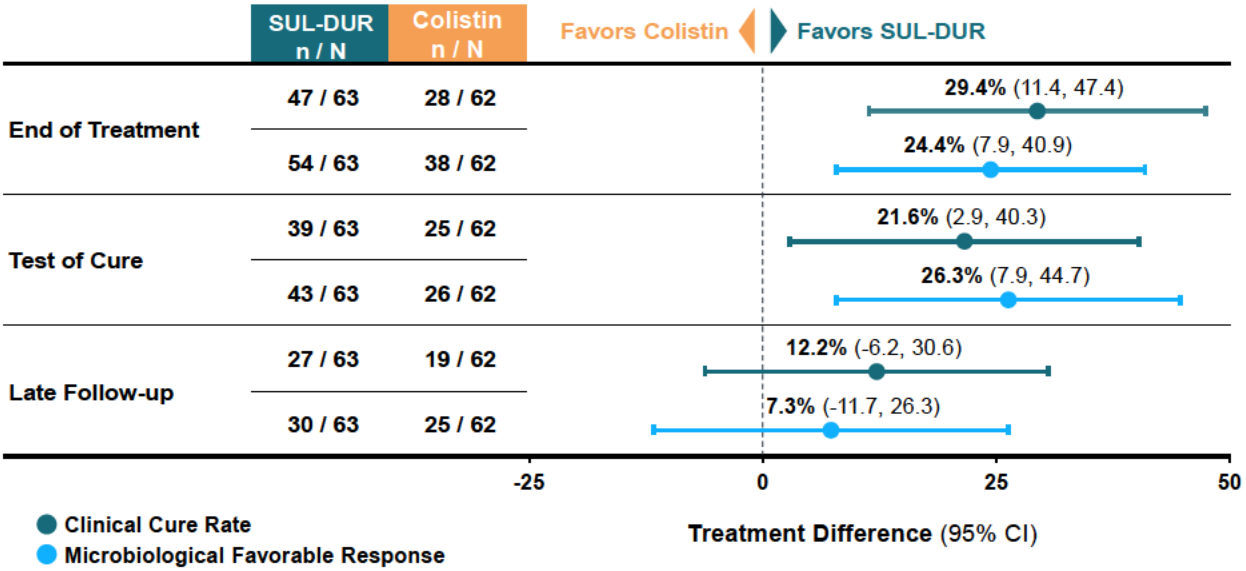
Figure 5: Phase 3 Part A: Microbiological Favorable Response at Test of Cure Visit (CRABC m-MITT Population)



CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat; SUL-DUR=sulbactam-durlobactam; TOC=Test of Cure.
Note: Test of cure was 7 ± 2 days after end of treatment.

Clinical cure rates and microbiological responses were consistent between EOT and TOC for the CRABC m-MITT Population (Figure 6). The difference between sulbactam-durlobactam versus colistin was lower in the late follow-up timepoint; however, sulbactam-durlobactam remained favorable for both clinical cure rate and favorable microbiological response.

Figure 6: Phase 3 Part A: Clinical Cure Rates and Microbiological Favorable Responses at All Measured Timepoints (CRABC m-MITT Population)



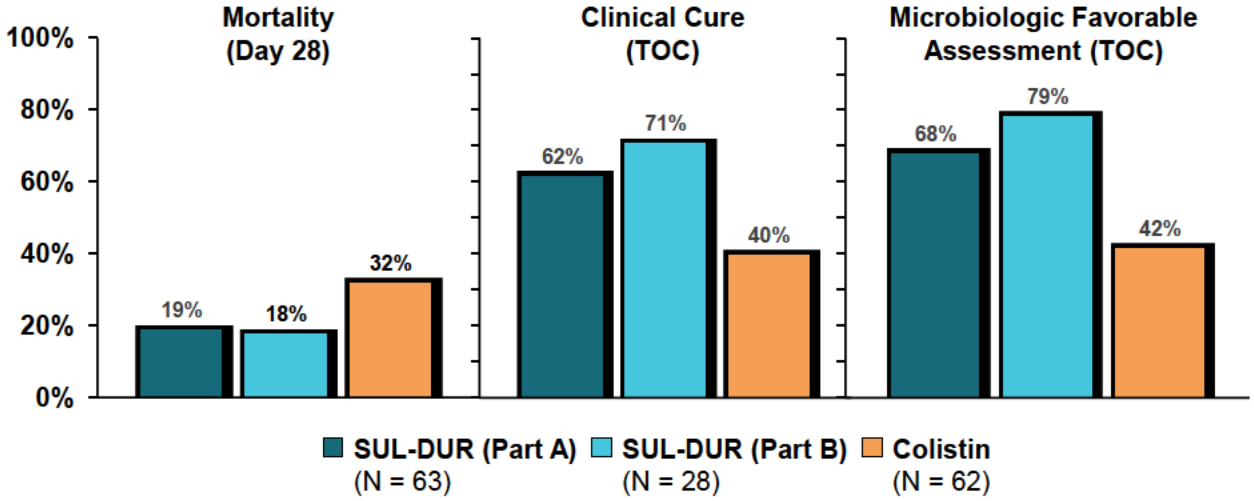
CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat; SUL-DUR=sulbactam-durlobactam.
Note: End of treatment was day of last dose, test of cure was 7 ± 2 days after end of treatment, and late follow-up was 7 ± 2 days after test of cure.

1.5.1.6 Secondary Efficacy Endpoint Results for Part B

Overall, results in Part B for patients who were intolerant to colistin or had infections caused by colistin-resistant ABC (N=28) were similar to patients in Part A treated with sulbactam-durlobactam.

For Part B, 28-day all-cause mortality was 17.9% (5/28; 95% CI: 6.1%, 36.9%) for the ITT Population and was similar to the sulbactam-durlobactam group in Part A for the CRABC m-MITT Population (17.9% and 19.0%, respectively) (Figure 7). In the 17 patients with bacteremia, 2 (11.8%) deaths occurred. Clinical cure at TOC was observed with 71.4% (20/28) of patients for the CRABC m-MITT Population (Figure 7). Microbiological favorable assessment was observed at TOC in 78.6% of patients for the CRABC m-MITT Population (Figure 7).

Figure 7: Phase 3 Trial: 28-Day Mortality, Clinical Cure Rate at Test of Cure, and Microbiological Favorable Assessment at Test of Cure (CRABC m-MITT Population)



CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat; SUL-DUR=sulbactam-durlobactam; TOC=test of cure.
Note: End of treatment was day of last dose, test of cure was 7 ± 2 days after end of treatment, and late follow-up was 7 ± 2 days after test of cure.

1.6 Safety Findings

The cumulative safety data from the Phase 3 trial demonstrate that sulbactam-durlobactam is generally well tolerated in this critically ill patient population. The types and frequency of adverse events (AEs) reported were consistent with expectations for the patient population and were characteristic of the pharmacological class. Moreover, the overall incidence of treatment-emergent AEs (TEAEs), treatment-related AEs, severe TEAEs, serious TEAEs (SAEs), treatment-related SAEs, and TEAEs leading to study drug discontinuation or death were all lower in patients treated with sulbactam-durlobactam compared to those treated with colistin. In addition, the Phase 3 trial met the primary safety objective, with a statistically significant lower incidence of nephrotoxicity compared to colistin based on modified RIFLE criteria.

1.6.1 Treatment Exposure

Overall, 380 individuals have been exposed to durlobactam alone or in combination with sulbactam in the sulbactam-durlobactam clinical development program. The proposed dose of 1.0 g sulbactam/1.0 g durlobactam q6h (adjusted for renal function) was administered to 181 individuals with 158 of those receiving sulbactam-durlobactam for the proposed duration of at least 7 days. Based on the integrated data of patients who received sulbactam-durlobactam at the proposed dose and duration, the mean duration of exposure to sulbactam-durlobactam was 9.1 days.

1.6.2 Two-Part Phase 3 Trial (CS2514-2017-0004)

The safety population in the Phase 3 trial included all patients randomized to sulbactam-durlobactam or colistin in Part A and patients enrolled in Part B who received any amount of study drug. Overall, 119 patients were in the sulbactam-durlobactam group, including 91 patients in Part A and 28 patients in Part B. For Parts A and B combined, the mean duration of exposure to sulbactam-durlobactam was 8.8 days, and 7.6 days for colistin.

The overall incidence of TEAEs without regard to causality was high in all treatment groups as expected in critically ill patients. TEAEs were reported in 104/119 (87.4%) patients in the sulbactam-durlobactam group and in 81/86 (94.2%) patients in the colistin group. The sulbactam-durlobactam group had a lower incidence of treatment-related AEs, severe TEAEs, severe treatment-related AEs, SAEs, treatment-related SAEs, and TEAEs leading to study drug discontinuation or death compared to the colistin group (Table 22).

In Part A, the most common TEAEs reported in > 10% of patients in the sulbactam-durlobactam group included diarrhea (15/91; 16.5%), anemia (12/91; 13.2%), and hypokalemia (11/91; 12.1%). In the sulbactam-durlobactam group, the incidence of treatment-related AEs was similar in Parts A and B (12/91; 13.2% and 3/28; 10.7%). Diarrhea, which was reported in 4/91 (4.4%) patients in Part A of the sulbactam-durlobactam group and 4/86 (4.7%) patients in the colistin group, was the only treatment-related AE reported in > 1 patient treated with sulbactam-durlobactam in the Phase 3 trial.

The incidence of severe TEAEs was lower in the sulbactam-durlobactam group (Part A [39/91; 42.9%]; Part B [9/28; 32.1%]) compared with the colistin group (44/86; 51.2%). In Part A, the most common severe TEAEs, occurring in ≥ 3 patients in the sulbactam-durlobactam group, included septic shock (7/91; 7.7%), acute respiratory distress syndrome (3/91; 3.3%), and tracheoesophageal fistula (3/91; 3.3%).

A lower incidence of SAEs was also observed in the sulbactam-durlobactam group (Part A [36/91; 39.6%]; Part B [9/28; 32.1%]) compared with the colistin group (42/86; 48.8%). In Part A, the most commonly reported SAE occurring in > 3 patients in the sulbactam-durlobactam group was septic shock (7/91; 7.7%).

A lower proportion of patients in the sulbactam-durlobactam group (Part A [10/91; 11.0%]; Part B [4/28; 14.3%]) than in the colistin group (14/86; 16.3%) experienced TEAEs that led to study drug discontinuation. The AE that led to discontinuation of study drug in > 1 patient in the sulbactam-durlobactam group was hepatic function abnormal (2 patients); these events were also reported as SAEs for 2 patients and were assessed as not related to study drug.

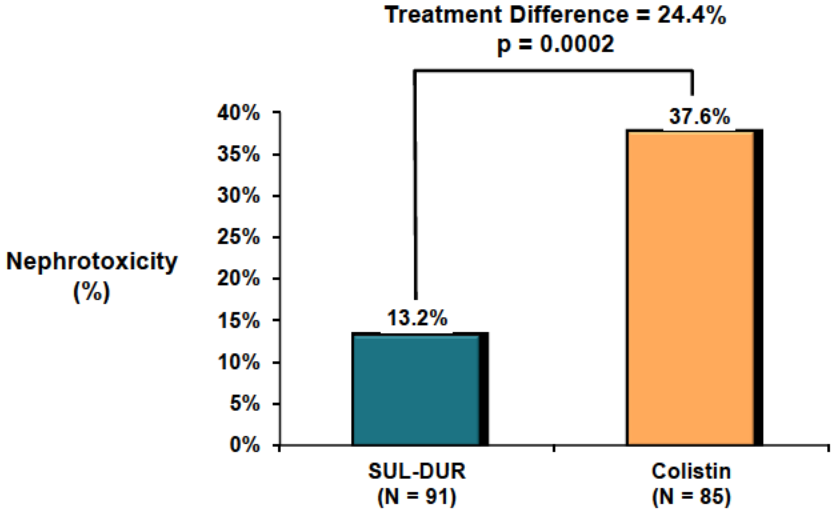
TEAEs leading to death were observed in the sulbactam-durlobactam group (28/119; 23.5%) and the colistin group (30/86; 34.9%). No deaths at any time were assessed as related to study drug in the sulbactam-durlobactam group. One death due to pneumonia

in the colistin group was assessed by the Investigator as treatment-related; this event occurred in a patient who entered the study with severe pneumonia requiring intubation. The Investigator considered the event as treatment-related because the study drug did not control the patient's pneumonia after extubation.

The primary safety objective of the Phase 3 trial was achieved with a significantly lower incidence of nephrotoxicity in the sulbactam-durlobactam group compared with the colistin group in Part A (13.2% vs 37.6%; p=0.0002; Figure 8), based on modified Risk-Injury-Failure-Loss-End-Stage Kidney Disease (RIFLE) criteria as described by Hartzell (2009). The modified RIFLE criteria includes:

- Risk (R): increased creatinine level 1.5x or glomerular filtration rate (GFR) decreased > 25%,
- Injury (I): increased creatinine level 2x or GFR decreased > 50%,
- Failure (F): increased creatinine level 3x, GFR decreased > 75%, or creatinine level ≥ 4 mg/dL,
- Loss (L): persistent acute renal failure or complete loss of function for > 4 weeks, and
- End-Stage Kidney Disease (ESKD; E): ESKD for > 3 months.

Figure 8: Phase 3 Trial: Incidence of Nephrotoxicity as Measured by Modified RIFLE Criteria in Part A (Part A Safety Population Excluding Patients with Chronic Hemodialysis at Baseline)



p-value was obtained based on a Chi-Square test for treatment group differences (Part A).
Note: For the patients who transferred from Part A to Part B, events that occurred before the date of transfer were summarized in Part A. If patients had multiple RIFLE events during post-baseline visits, the patient was counted only once at the highest severity.
RIFLE=Risk-Injury-Failure-Loss-End Stage Kidney Disease; SUL-DUR=sulbactam-durlobactam.

Consistent with the RIFLE assessment, the incidence and severity of AEs of renal and urinary disorders were lower in the sulbactam-durlobactam groups for Parts A and B compared to the colistin group (Table 3).

Table 3: Phase 3 Trial: Incidence of Renal and Urinary Disorders and Severity (Safety Population)

	Part A		Part B
System Organ Class Severity	Sulbactam-Durlobactam (N=91) n (%)	Colistin (N=86) n (%)	Sulbactam-Durlobactam (N=28) n (%)
Renal and urinary disorders	9 (9.9)	27 (31.4)	3 (10.7)
Mild	4 (4.4)	12 (14.0)	1 (3.6)
Moderate	4 (4.4)	8 (9.3)	1 (3.6)
Severe	1 (1.1)	7 (8.1)	1 (3.6)

1.6.3 Adverse Events of Special Interest

Adverse events of special interest (AESIs) were explored for 7 Standardized Medical Dictionary for Regulatory Activities Queries (SMQs): acute renal failure, convulsions, sepsis, infective pneumonia, drug-related hepatic disorders, hypersensitivity, and pseudomembranous colitis.

The overall incidences of infective pneumonia, drug-related hepatic disorders, hypersensitivity, and pseudomembranous colitis SMQs were similar between the sulbactam-durlobactam and colistin groups (25.2%, 20.2%, 15.1%, 16.0% vs 23.3%, 23.3%, 11.6%, 16.3%). The overall incidence of TEAEs in the acute renal failure, convulsions, and sepsis SMQs were lower in the sulbactam-durlobactam group compared with the colistin group (12.6%, 2.5%, 16.8% vs 38.4%, 7.0%, 22.1%). Additional details on AESIs are provided in Section 8.12.

1.6.4 Subgroup Analyses

No clinically relevant differences in TEAEs were found in subgroup analyses based on age, sex, race, ethnicity, body mass index (BMI), geographic region, and renal impairment.

1.6.5 Expanded Access Program

An EAP for patients ineligible to participate in the clinical trial and who had a documented serious and immediately life-threatening infection caused by drug-resistant *A. baumannii* was initiated in May 2020. This program permitted access to investigational sulbactam-durlobactam for treatment outside of a clinical trial when no comparable or satisfactory alternative therapy option was available. Of the 12 patients

treated with sulbactam-durlobactam in combination with other antibiotics, no SAEs related to sulbactam-durlobactam were reported (Table 32).

1.7 Benefit-Risk Summary

1.7.1 Therapeutic Context

ABC is a bacterial pathogen that has emerged as a major cause of severe infections, particularly in vulnerable patients. Despite significant morbidity and mortality associated with infections caused by ABC, there is no clear standard-of-care antibiotic regimen. Current treatments involve many different combinations that lack optimized dosing with a PK/PD understanding, efficacy, and safety data to support ABC treatment. These limitations highlight the urgent unmet medical need for patients with infections caused by ABC.

1.7.2 Benefits

1.7.2.1 Sulbactam-Durlobactam is a Targeted Therapy for Serious Infections Due to ABC

Sulbactam-durlobactam is a targeted therapy for serious infections due to ABC. Sulbactam is well-established, as it has been widely used in the clinical setting for over 30 years as an inhibitor of a subset of Class A β-lactamases (Unasyn USPI). Sulbactam also has intrinsic antibacterial activity against a limited number of species including ABC. However, the efficacy of sulbactam against ABC has diminished due to the acquisition of β-lactamases that degrade sulbactam, resulting in resistant strains. Durlobactam is a potent inhibitor of Classes A, C, and D serine β-lactamases. When dosed in combination, durlobactam restores the efficacy of sulbactam against ABC infections.

1.7.2.2 Sulbactam-Durlobactam Shows Potent In Vitro and In Vivo Activity Against Global Contemporary ABC Isolates.

Sulbactam-durlobactam shows potent in vitro activity against global contemporary ABC isolates, with > 98% testing with MIC values of ≤ 4 µg/mL, the proposed susceptibility breakpoint. This activity is consistent over time and across infection types, geographic regions, and drug-resistant subsets.

Evaluation of sulbactam-durlobactam in in vivo animal efficacy models and in vitro hollow fiber studies indicates that sulbactam-durlobactam was efficacious against *A. baumannii*, including against MDR strains. In vivo studies consisted of murine neutropenic thigh and lung infection models that have been shown to demonstrate good translation to clinical efficacy in multiple sites of infection (Bulitta et al 2019). Dose-response studies with sulbactam (with and without durlobactam) demonstrate agreement with in vitro susceptibility data. The normalization of animal doses to exposure and examination of PK/PD indices related to efficacy served as the basis for human exposure targets and, ultimately, clinical dose selection.

1.7.2.3 Durlobactam Demonstrated No Adverse Findings Within In Vitro and In Vivo Safety Pharmacology Studies

Pivotal toxicology studies completed with durlobactam in rats and dogs up to a limit dose of 2,000 mg/kg were well tolerated with no adverse effects. Durlobactam demonstrated no adverse findings within in vitro and in vivo safety pharmacology studies. The compound was not mutagenic or genotoxic and demonstrated no adverse findings in a full battery of reproductive toxicology studies. In combination with sulbactam following 28 days of administration, minimal but reversible inflammatory changes in liver and lung have been the only adverse toxicities of note, occurring only after the combination was infused daily for approximately 28 days. These findings were consistent with known, monitorable effects of sulbactam. The maximum plasma concentration (C_{max}) values of durlobactam in the combination arms of the 28-day rat study were 3.6- to 6.5-times higher than human exposure, and the C_{max} values of sulbactam ranged from 3.5 to 6.8-fold higher than human exposure. Exposure margins based on area under the plasma concentration-time curve from time of dosing to 24 hours post-dose (AUC_{0-24}), compared to human exposures, ranged from 0.4 to 1.0-fold for durlobactam and 0.8 to 1.8-fold for sulbactam.

1.7.2.4 Clinical Development Program for the Evaluation of Safety and Efficacy of Sulbactam-Durlobactam

The clinical development program for the evaluation of safety and efficacy of sulbactam-durlobactam consisted of 8 clinical trials, including six Phase 1 studies, one Phase 2 trial, and one Phase 3 trial. The Phase 1 and 2 trials demonstrated that sulbactam-durlobactam was generally well tolerated; no deaths or treatment-related SAEs were reported. The most frequently reported TEAEs included infusion site reactions (including bruising, extravasation, inflammation, rash, and phlebitis), infusion site pain, and headaches. Other TEAEs occurring in > 1% of patients included dizziness, nausea, diarrhea, abdominal pain/discomfort, upper respiratory tract infection, nasal congestion, and vulvovaginal candidiasis.

In the randomized Phase 3 clinical trial in patients with serious infections caused by ABC, including multidrug- or carbapenem-resistant isolates, sulbactam-durlobactam met the primary efficacy endpoint of noninferiority for 28-day all-cause mortality in the primary analysis population. The mortality rate was 19.0% in the sulbactam-durlobactam group compared to 32.3% in the colistin group with a treatment difference of −13.2% (95% CI: −30.0, 3.5%). All secondary endpoint analyses, including 28-day and 14-day all-cause mortality rates, clinical cure rates, and microbiological responses demonstrated clinically meaningful and significant improvements with sulbactam-durlobactam compared to colistin in all populations analyzed.

The primary safety objective for the Phase 3 trial was achieved and showed a statistically significant lower incidence (p=0.0002) in nephrotoxicity based on modified RIFLE criteria in patients treated with sulbactam-durlobactam compared with colistin. The overall incidences of TEAEs, treatment-related AEs, SAEs, treatment-related

SAEs, and AEs leading to study drug discontinuation or death were lower with sulbactam-durlobactam compared to colistin. The types and incidences of TEAEs reported in the Phase 3 trial were consistent with expectations for the population of critically ill patients and the β-lactam/β-lactamase inhibitor antibiotic class. In addition, no SAEs related to sulbactam-durlobactam were identified in the EAP.

1.7.3 Risks

Potential risks associated with β-lactams and the use of sulbactam-durlobactam include:

- Diarrhea, including *Clostridioides difficile (C. difficile)*-associated diarrhea (CDAD), and
- Hypersensitivity (including anaphylactic) reactions.

CDAD has been reported with use of nearly all antibacterial agents, including sulbactam-durlobactam, and may range in severity from mild diarrhea to fatal colitis. In the Phase 3 trial, the incidence of at least 1 TEAE (all causality) based on the pseudomembranous colitis SMQ was 16.0% of patients in the sulbactam-durlobactam group compared with 16.3% of patients in the colistin group. Diarrhea was the most commonly reported event within this SMQ in both groups (14.3% in the sulbactam-durlobactam group and 10.5% in the colistin group). *C. difficile* colitis and antibiotic-associated colitis were reported in 1 patient (0.8%) each in the sulbactam-durlobactam group compared with 3 patients (3.5%) and 2 patients (2.3%), respectively, in the colistin group.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving β-lactam antibiotics. These reactions are more likely to occur in individuals with a history of β-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. Hypersensitivity was observed in patients treated with sulbactam-durlobactam in clinical studies. In the Phase 3 trial, the incidence of at least 1 TEAE (all causality) based on the hypersensitivity SMQ was 15.1% in the sulbactam-durlobactam group and 11.6% in the colistin group. Anaphylactic shock was reported in 1 patient in the Phase 3 trial who experienced a diffuse rash and mild drop in blood pressure following sulbactam-durlobactam infusion on Day 9 of treatment.

1.7.4 Benefit-Risk Assessment

Sulbactam-durlobactam provides a clinically meaningful benefit in both safety and efficacy based on:

- A comprehensive microbiology data package,
- Robust PK and PK/PD data, with a population PK model developed from Phase 1, Phase 2, and Phase 3 trials, and PTA analysis,
- A safety profile characterized in 8 clinical studies, and
- Mortality, clinical, and microbiological outcomes from the Phase 3 trial.

These results also demonstrate that sulbactam-durlobactam has clinically meaningful benefit over the existing therapies for the treatment of infections caused by ABC, including multidrug- or carbapenem-resistant strains and has the potential to address this significant unmet need.

2 BACKGROUND ON INFECTIONS CAUSED BY *ACINETOBACTER* SPECIES

Summary

- Carbapenem-resistant *A. baumannii* is a significant public health concern.
  - Classified as an "urgent threat" pathogen by the US Centers for Disease Control and Prevention.
  - Ranked as "critical" on the WHO global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.
- Infections caused by *A. baumannii* are associated with high morbidity and mortality and have become increasingly difficult to treat due to the emergence of multidrug- and carbapenem-resistant strains.
- The incidence and prevalence of multidrug-resistant *A. baumannii* are increasing in patients with prolonged hospitalizations, immunocompromised patients (transplant, burn, cancer), and patients in long-term care facilities (due to previous antibiotic exposures).
- Globally, *A. baumannii* is the fifth leading cause of death attributable to antimicrobial resistance and > 450,000 deaths were associated with carbapenem-resistant *A. baumannii* in 2019.
- *A. baumannii* has acquired resistance genes for almost all antibiotics used to treat Gram-negative bacteria, including fluoroquinolones, aminoglycosides, cephalosporins, and carbapenems.
- Despite significant morbidity and mortality associated with infections caused by *A. baumannii*, there is no clear standard-of-care antibiotic regimen.

2.1 Overview of Infections Caused by *Acinetobacter* Species

2.1.1 Microbiology

A. baumannii is a non-fermenting Gram-negative bacterial pathogen that has emerged as a major cause of severe infections, particularly in critically ill hospital patients. It is the predominant member of a closely related group of bacterial species known as ABC, which also includes *A. calcoaceticus, A. dijkshoorniae, A. seifertii, A. nosocomialis,* and *A. pittii* (Ayoub Moubareck and Hammoudi Halat 2020; Harding et al 2018).

Although pneumonia and bacteremia are the most common infections caused by ABC, these organisms can also cause skin, soft tissue, wound, and urinary tract infections as well as osteomyelitis and meningitis (Alsan and Klompas 2010). Infections caused by ABC are associated with high morbidity and mortality and have become increasingly difficult to treat due to the emergence of multidrug- and carbapenem-resistant strains

with limited treatment options (Ayoub Moubareck and Hammoudi Halat 2020; Gales et al 2019). Mortality associated with bacteremia and pneumonia caused by *A. baumannii* ranges from 30–70% (Cheng 2015; Ibrahim et al 2021; Mohd Sazlly Lim et al 2019). Carbapenem-resistant *A. baumannii* is of particular concern as, globally, it is the fifth leading cause of death associated with antimicrobial resistance, with > 450,000 deaths in 2019 (Antimicrobial Resistance 2022).

2.1.1.1 Drug-Resistant Acinetobacter Species

A. baumannii has acquired resistance genes for almost all antibiotics used to treat Gram-negative bacteria, including fluoroquinolones, aminoglycosides, cephalosporins, and carbapenems (Gales et al 2019; Peleg et al 2008; Wong et al 2017). Data from the National Healthcare Safety Network (NHSN) in the US between 2015–2017 revealed high rates of multidrug resistance in nosocomial infections caused by *A. baumannii*, ranging from 33% of skin and soft tissue infections to up to 75% of bloodstream and ventilator-associated pneumonia, nearly all of which were carbapenem-resistant (Weiner-Lastinger et al 2020). The SENTRY Antimicrobial Surveillance Program, which tracks antimicrobial resistance in North America, Europe, Asia-Pacific, and Latin America, has reported decreasing susceptibility rates among ABC isolates for all observed antimicrobial agents, including carbapenems, in all regions between 1997–2016 (Gales et al 2019). In 2019, the rates of infections caused by carbapenem-resistant *A. baumannii* varied widely around the world, but were notably high in a number of regions, such as 56% in China (CARSS 2019), approximately 70% in both South America (GLASS 2021) and India (ICMR 2021), and over 90% in Greece (eCDC 2020). Therefore, options to treat infections caused by multidrug-resistant *A. baumannii* pathogens are becoming increasingly limited.

2.1.2 Risk Factors

According to the CDC, infections caused by *A. baumannii* typically occur in patients in healthcare settings (CDC 2019). Individuals most at risk include patients in hospitals, especially those who:

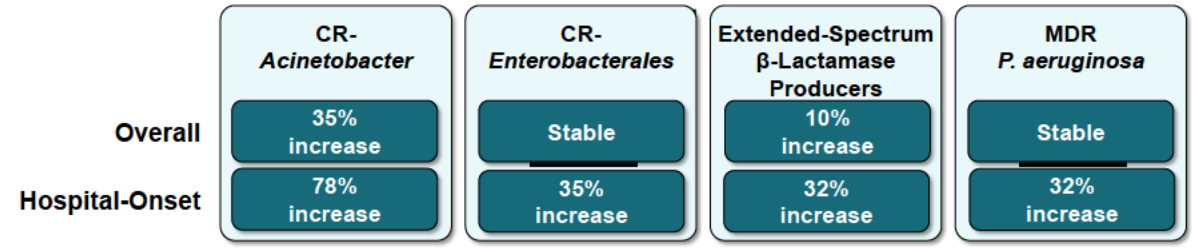
- are on ventilators,
- have devices such as catheters,
- have open wounds from surgery,
- are in ICUs, and
- have prolonged hospital stays.

In the US, infections caused by *A. baumannii* rarely occur outside of healthcare settings. However, individuals who have weakened immune systems, chronic lung disease, or diabetes may be more susceptible.

2.1.3 Epidemiology

Most infections caused by *A. baumannii* occur in critically ill patients in the ICU setting and can account for up to 20% of infections in ICUs worldwide (Lee et al 2017). In the US, approximately 2% of healthcare-associated Gram-negative infections are caused by *A. baumannii* (Wiener-Lastinger et al 2020) and are associated with high morbidity and mortality due, in part, to high rates of multidrug- and carbapenem-resistant strains. Notably, the number of infections caused by carbapenem-resistant *A. baumannii* in the hospital setting increased by 78% in 2020 compared with 2019 due to challenges associated with the COVID pandemic in healthcare settings (Figure 9) (CDC Special Report 2022).

Figure 9: Increases in Infections During COVID Pandemic (2019–2020)



CDC Special Report 2022.
CR=Carbapenem-resistant; MDR=multidrug-resistant.

2.2 Current Treatment Options

As noted in the IDSA guidance, “there is no clear ‘standard of care’ antibiotic regimen” and “data supporting a prioritization of specific agents with carbapenem-resistant *A. baumannii* activity or the additive benefit of commonly used combination regimens for CRAB remain incomplete” (Tamma et al 2022).

2.3 Unmet Medical Need

Infections caused by CRABC are a significant public health concern due to high morbidity and mortality rates with increasing global incidence. Treatment options for patients with CRABC infections are limited and data supporting efficacy of currently available agents are incomplete, highlighting the significant unmet medical need. Patients and their treating physicians need an effective and well tolerated treatment for these highly fatal infections.

3 SULBACTAM-DURLOBACTAM PRODUCT DESCRIPTION

Summary

- Sulbactam-durlobactam is a therapy for HABP and VABP caused by susceptible strains of ABC.
  - Sulbactam is widely used as an inhibitor of a subset of Class A β-lactamases. Sulbactam also has antibacterial activity against a limited number of species including *Acinetobacter* spp.
  - Durlobactam is a diazabicyclooctane β-lactamase inhibitor. It is a potent inhibitor of Classes A, C, and D serine β-lactamases, but it has no activity against Class B metallo-β-lactamases.
  - Durlobactam restores the efficacy of sulbactam against infections caused by ABC due to its potent inhibition of serine β-lactamases.
- Sulbactam-durlobactam is dosed q6h administered as a 3-hour IV infusion, adjusted for renal function, with a proposed duration of at least 7 days and up to 14 days dependent on clinical response.

3.1 Proposed Indication

The proposed indication for sulbactam-durlobactam is in adults (≥ 18 years of age) for the treatment of HABP and VABP caused by susceptible strains of ABC.

3.2 Product Overview

Sulbactam-durlobactam is a targeted antibiotic combination of sulbactam, a β-lactam antibacterial with intrinsic activity against ABC, and durlobactam, a β-lactamase inhibitor, with potent activity against Classes A, C, and D β-lactamases. Durlobactam effectively restores sulbactam activity against ABC organisms (Durand-Reville et al 2017).

The recommended dose is 1.0 g sulbactam and 1.0 g durlobactam q6h administered as a 3-hour IV infusion in patients with CL_{CR} of 45–129 mL/min. Dose adjustments are required for patients with CL_{CR} < 45 and ≥ 130 mL/min. The proposed duration of treatment is at least 7 days and up to 14 days depending on clinical response.

3.3 Mechanism of Action

3.3.1 Sulbactam

Sulbactam is a β-lactam widely used as an inhibitor of a subset of Class A β-lactamases (Noguchi and Gill 1988). The vast majority of human use is in combination with a β-lactam (e.g., ampicillin-sulbactam). In addition to its β-lactamase inhibitor activity, sulbactam also has antibacterial activity against a limited number of species, including

Acinetobacter spp. (Noguchi and Gill 1988). Sulbactam itself is a substrate for many β-lactamases encoded by *Acinetobacter* spp., including Class D carbapenemases and therefore its clinical utility has been eroded in recent decades (Durand-Reville et al 2017; Shapiro 2017).

3.3.2 Durlobactam

Durlobactam is a diazabicyclooctane β-lactamase inhibitor. It is a potent inhibitor of Classes A, C, and D serine β-lactamases (as detailed in Section 4.1.1), but it has no activity against Class B metallo-β-lactamases (Durand-Reville et al 2017). Durlobactam effectively restores sulbactam activity against ABC organisms due to its potent inhibition of serine β-lactamases in vitro and in vivo (Durand-Reville et al 2017).

3.3.3 Sulbactam-Durlobactam

In vitro, the addition of durlobactam to sulbactam restores the activity of sulbactam against *Acinetobacter* spp. The sulbactam minimum inhibitory concentration required to inhibit the growth of 90% of isolates (MIC_{90}) versus a collection of recent ABC clinical isolates is reduced from 64 µg/mL to 2 µg/mL in the presence of durlobactam (held constant at 4 µg/mL; additional details provided in Sections 4.1.1 and 4.1.2).

Evaluation of sulbactam-durlobactam using in vivo efficacy models and in vitro hollow fiber studies indicates that sulbactam-durlobactam is efficacious against *A. baumannii*, including MDR strains.

4 MICROBIOLOGY AND PHARMACOLOGY

Summary

- Sulbactam inhibits essential penicillin-binding proteins of ABC resulting in bactericidal antibacterial activity, but can be hydrolyzed by β-lactamases.
- Durlobactam inhibits Class A, C, and D β-lactamases, thereby protecting sulbactam from hydrolysis and restoring its activity against ABC.
- Sulbactam-durlobactam shows potent in vitro activity against global, contemporary ABC isolates.
- The PK/PD parameter that most correlates with sulbactam efficacy is time, as a percentage of the dosing interval, that unbound concentrations of sulbactam exceed the MIC of the infecting organism (%*f*T > MIC). An AUC_{0-24}/MIC ratio of 10 for durlobactam was found to restore sulbactam activity against MDR isolates when sulbactam %*f*T > MIC was 50% of the dosing interval.
- In laboratory studies, the in vitro frequency of spontaneous resistance to sulbactam-durlobactam is low.

4.1 Microbiology

Studies were conducted to assess the spectrum, potency, mechanism of action, and propensity for resistance development of sulbactam-durlobactam against ABC.

4.1.1 Mechanism of Action

Sulbactam is a semi-synthetic penicillanic acid that was among the first β-lactamase inhibitors developed, in combination with ampicillin, for the treatment of infections caused by β-lactamase-producing bacterial pathogens (Adnan et al 2013). The β-lactamase inhibitory activity of sulbactam is limited to a subset of Class A serine enzymes (Shapiro 2017). A unique feature of sulbactam is its intrinsic antibacterial activity against *Acinetobacter* spp. and a limited number of other bacterial species (Noguchi and Gill 1988), which results from the inhibition of key enzymes required for bacterial peptidoglycan synthesis. Penicillin-binding protein 1a (PBP1a), PBP1b, and PBP3, but not PBP2, are targets of sulbactam in *Acinetobacter* spp. (Penwell et al 2015). The acquisition of a multitude of β-lactamases has rendered sulbactam inactive against most contemporary strains of *Acinetobacter* spp.

Durlobactam is a member of the DBO class of serine β-lactamase inhibitors (Durand-Reville et al 2017). Durlobactam efficiently inhibits Class A, Class C, and Class D enzymes via a covalent, reversible mechanism of inhibition through β-lactamase active-site serine carbamoylation. The potency of durlobactam exceeded that of the prototypical DBO β-lactamase inhibitor, avibactam, by as much as 2,000-fold for some enzymes (Table 4). Durlobactam has intrinsic activity against some genera of

Enterobacterales including *Escherichia coli, Enterobacter cloacae,* and *Klebsiella pneumoniae* through inhibition of PBP2 but has no antibacterial activity against ABC.

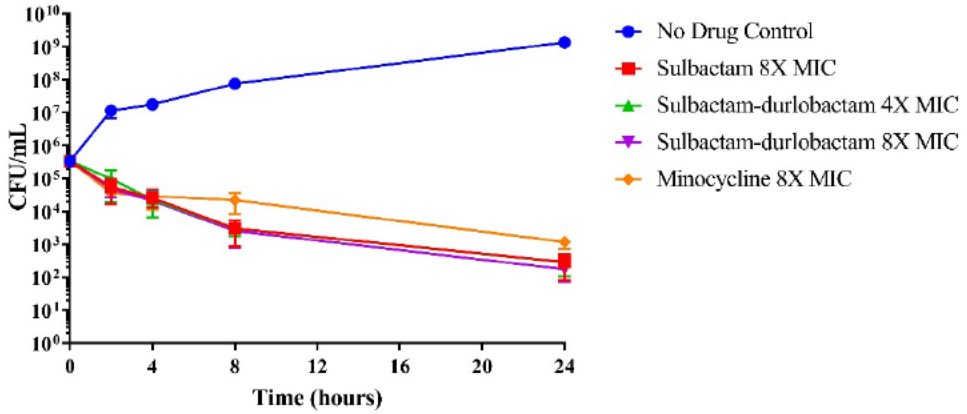
Table 4: Durlobactam Inhibition of Purified Representative Serine β-Lactamases

β-Lactamase	Class	Durlobactam k_{inact}/K_i ($M^{-1}s^{-1}$)	Avibactam k_{inact}/K_i ($M^{-1}s^{-1}$)	Fold Increase in Potency (Durlobactam/Avibactam)
CTX-M-15	A	$7 (\pm 2) \times 10^6$	8×10^5	9
TEM-1	A	$1.4 (\pm 0.6) \times 10^7$	4×10^5	35
KPC-2	A	$9.3 (\pm 0.6) \times 10^5$	6×10^3	155
SHV-5	A	$6.4 (\pm 0.5) \times 10^6$	1×10^5	64
AmpC[a]	C	$9 (\pm 5) \times 10^5$	3×10^3	300
P99[b]	C	$2.3 (\pm 0.4) \times 10^6$	8×10^3	288
OXA-10	D	$9 (\pm 2) \times 10^3$	70	128
OXA-23	D	$5.1 (\pm 0.2) \times 10^3$	100	51
OXA-24/40	D	$9 (\pm 2) \times 10^3$	80	112
OXA-48	D	$8 (\pm 2) \times 10^5$	5×10^3	160
OXA-58	D	$2.5 (\pm 0.3) \times 10^5$	120 ± 40	2083

Orthologs from [a]*P. aeruginosa* and [b]*E. cloacae*.
k_{inact}/K_i = second-order inactivation rate constant.
Barnes et al, 2019; Shapiro et al 2017; Shapiro et al 2021.

Sulbactam-durlobactam demonstrated bactericidal activity against most strains of *A. baumannii* (Carter et al 2022a). Minimum bactericidal concentrations (MBC) were identical or within one two-fold dilution of the sulbactam-durlobactam MIC, which demonstrates that sulbactam-durlobactam is bactericidal. Sulbactam-durlobactam demonstrated time-dependent killing, which is expected for an antibiotic of the β-lactam class (Figure 10).

Figure 10: Representative Kill Curve of Sulbactam Alone or in the Presence of 4 µg/mL Durlobactam Against *A. baumannii*



MIC=minimum inhibitory concentration.

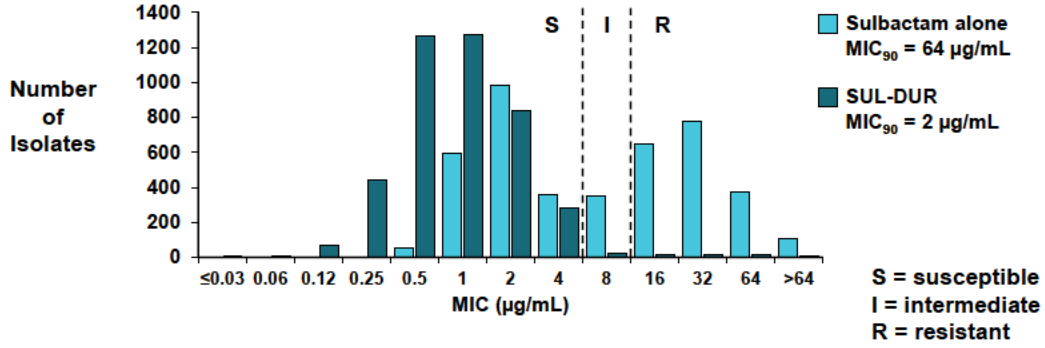
4.1.2 Activity of Sulbactam-Durlobactam Against Acinetobacter Species

The susceptibility testing method that most accurately separated susceptible isolates from resistant isolates was to hold the concentration of durlobactam constant at 4 µg/mL while varying the sulbactam concentration in 2-fold increments in MIC assays. This testing paradigm was used throughout the development of sulbactam-durlobactam.

The activity of sulbactam alone or in the presence of durlobactam was tested against global clinical isolates collected between 2016 and 2020 (McLeod et al 2022) (Figure 11). Sulbactam and sulbactam-durlobactam were tested against 4,252 ABC isolates that were collected from 253 study centers in 31 countries from community- and hospital-associated infection sources. Susceptibility testing of these isolates to other antibiotics in this global surveillance study showed fairly high rates of resistance to many of the drugs tested (Table 5). Of the comparator antibiotics tested, the only agent that was active in vitro against 95% of isolates was colistin. These data further support the choice of colistin as the comparator agent for the Phase 3 trial.

When used in combination, durlobactam restored the antibacterial activity of sulbactam in clinical isolates of *Acinetobacter* spp. that produce serine β-lactamases (Figure 11). The addition of durlobactam restored sulbactam activity to ≤ 4 µg/mL for over 98% of isolates tested. This activity was stable across regions and years of testing. In addition, sulbactam-durlobactam had potent in vitro activity against all species of ABC, including carbapenem-resistant, MDR, extensively drug resistant (XDR), and pandrug resistant (PDR) strains (Table 5).

Figure 11: Distribution of Sulbactam and Sulbactam-Durlobactam MIC Values Against 4,252 Global Clinical Isolates of ABC Collected in 2016–2020



Acinetobacter baumannii-calcoaceticus complex consists of (n): *A. baumannii* (3,401), *A. calcoaceticus* (48), *A. nosocomialis* (248), *A. pittii* (552); *Acinetobacter* spp. (3).
ABC=*Acinetobacter baumannii-calcoaceticus* complex; MIC_{90}=minimum inhibitory concentration required to inhibit the growth of 90% of isolates; SUL-DUR=sulbactam-durlobactam.

Table 5: In Vitro Activity of Sulbactam-Durlobactam Against Subsets of Antibiotic-Resistant ABC Clinical Isolates from a Five Year (2016–2020) Global Surveillance Study

Category (Number of Isolates)	CLSI Resistance Breakpoint (µg/mL)	% Resistance	Sulbactam-Durlobactam Minimum Inhibitory Concentration (µg/mL)			% Sulbactam-Durlobactam Susceptible*
			Range	MIC_{50}	MIC_{90}	
All strains (4,252)	NA	NA	≤ 0.03 - > 64	1	2	98.2
CST-R (187)	≥ 4	4.4	0.25 - 64	2	4	98.9
MIN-R (448)	≥ 16	10.5	0.25 - 64	2	4	97.3
MEM-R (2,180)	≥ 8	51.3	≤ 0.03 - > 64	1	4	96.6
CIP-R (2,352)	≥ 4	55.3	≤ 0.03 - > 64	1	4	97.4
AMK-R (1,613)	≥ 64	37.9	≤ 0.03 - > 64	2	4	96.9
MDR (2,062)	NA	48.5	≤ 0.03 - > 64	1	4	96.7
XDR (469)	NA	11.0	0.25 - > 64	2	4	90.2
PDR (95)	NA	2.2	0.5 - 4	2	4	100.0

*Note: Sulbactam-durlobactam MICs were interpreted using a preliminary susceptibility breakpoint of ≤ 4 µg/mL
ABC=*Acinetobacter baumannii-calcoaceticus* complex; AMK=amikacin; CIP=ciprofloxacin; CLSI=Clinical and Laboratory Standards Institute; CST=colistin; MDR=multidrug-resistant; MEM-meropenem; MIC_{50}=minimum inhibitory concentration required to inhibit the growth of 50% of isolates; MIC_{90}=minimum inhibitory concentration required to inhibit the growth of 90% of isolates; MIN=minocycline; NA=not applicable; PDR=pandrug resistant; R=resistant; XDR=extensively drug resistant.
(O'Donnell et al, 2019; Rodvold et al, 2018).

4.1.3 Frequency and Mechanisms of Resistance to Sulbactam-Durlobactam

Laboratory studies showed that sulbactam-durlobactam has a low frequency of spontaneous resistance in vitro in multiple clinical isolates of *A. baumannii,* with frequencies ranging from $7.6x10^{-10}$ to < $9.0x10^{-10}$ at 4x MIC. Stable mutants could not be isolated at 8x MIC. The sulbactam-durlobactam MIC values of stable mutants were increased by 8 to > 32-fold compared to parental strains, most of which were found to have mutations that mapped to the gene encoding PBP3 at or near the sulbactam binding site.

Characterization of clinical isolates of *A. baumannii* from surveillance studies with sulbactam-durlobactam MIC values > 4 µg/mL showed that the isolates produce the metallo-β-lactamase NDM-1 or had mutations in PBP3.

No cross resistance was observed between sulbactam-durlobactam and non-β-lactam classes of antibiotics (Table 5). Resistance to cefiderocol in *A. baumannii* did not correlate with decreased susceptibility to sulbactam-durlobactam. Furthermore, sulbactam-durlobactam activity is not affected by the over-expression of efflux pumps or changes in outer-membrane porin proteins (Carter et al 2021a).

In the global surveillance studies, < 2% of isolates had MIC values > 4 µg/mL with sulbactam-durlobactam.

In the Phase 3 trial, 8/175 patients or 4.6% of baseline *A. baumannii* isolates had sulbactam-durlobactam MIC values > 4 µg/mL. Of these isolates, 5 had a 2-fold increase in MIC to 8 µg/mL, which is the preliminary breakpoint for intermediate susceptibility, and the other 3 had sulbactam-durlobactam MIC values of 16 µg/mL. Of the 105 patients in the Phase 3 trial who were treated with sulbactam-durlobactam, 73 (69.5%) had favorable microbiological outcomes at TOC (i.e., ABC was eradicated or presumed eradicated). Of the remaining patients with persistent or recurrent infections whose isolates were characterized by the central laboratory, 1/105 (0.95%) had longitudinal isolates with elevated sulbactam-durlobactam MIC values compared to the baseline ABC isolate. The MIC of the TOC ABC isolate from this patient increased by only 2-fold (to 8 µg/mL) and the infection was eradicated at LFU.

4.1.4 Miscellaneous Microbiology Studies

No antagonism has been observed between sulbactam-durlobactam and clinically relevant antibiotics in checkerboard studies, including imipenem, meropenem, cefepime, ciprofloxacin, amikacin, colistin, and minocycline. These studies showed that the predominant interaction between sulbactam-durlobactam and these antibiotics was additive or indifferent (Carter et al 2022a).

- Sulbactam-durlobactam does not have a significant post-antibiotic effect.
- Sulbactam-durlobactam is bactericidal and prevented biofilm formation (Carter et al 2022a).
- The in vitro activity of sulbactam-durlobactam was not affected by testing in human serum, serum albumin, or lung surfactant (Carter et al 2021b).
- Durlobactam was able to potentiate sulbactam activity against sulbactam-resistant intracellular *A. baumannii* at clinically relevant concentrations.
- Varying the starting inoculum concentration, incubation temperature, atmosphere, pH of the growth medium, and concentration of divalent cations in the growth medium did not significantly affect the MIC determination (Carter et al 2021b).
- There was an inoculum effect for some isolates of *A. baumannii* when MICs were determined with a high inoculum ($5x10^7$ colony-forming units [CFU]/mL), with sulbactam-durlobactam MICs increasing 2–4 fold for three of ten strains tested (Carter et al 2021b).

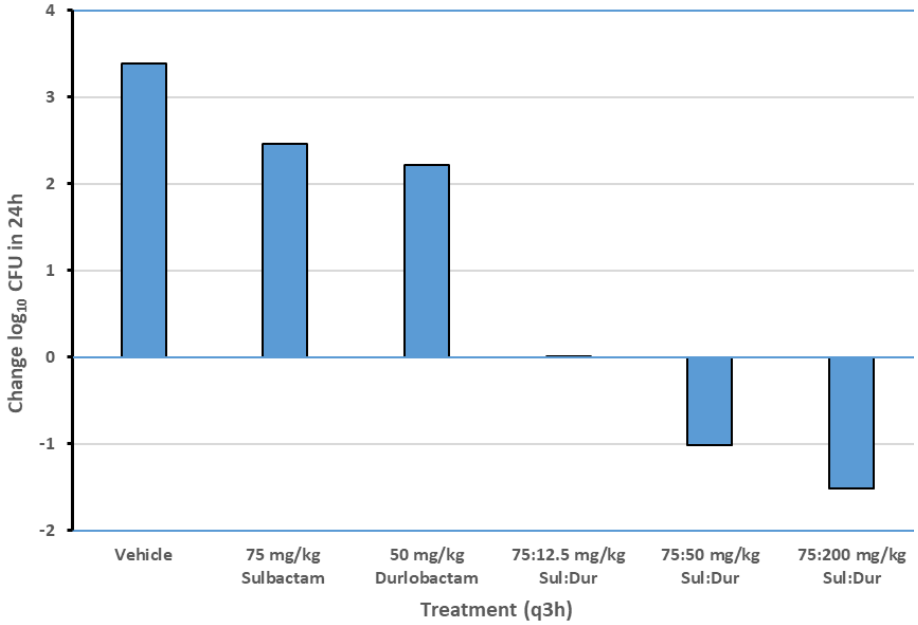
4.2 Nonclinical Pharmacology

Nonclinical pharmacodynamic and efficacy models were completed in vitro and in vivo to establish exposure targets of sulbactam-durlobactam against MDR *A. baumannii* strains. In vitro hollow-fiber and one-compartment models established the PK/PD indices of %*f*T > MIC and AUC_{0-24}/MIC associated with sulbactam and durlobactam activities, respectively.

- Sulbactam and sulbactam-durlobactam were evaluated in neutropenic pneumonia and thigh infection models in mice. Studies utilized clinical comparator controls including meropenem, levofloxacin, and colistin as part of model validation and performance assessments.
- Sulbactam-durlobactam demonstrated robust efficacy across all model systems with bactericidal activity (greater than 1-$\log_{10}$CFU reduction over 24 hours) achieved against bacteria resistant to carbapenems, cephalosporins, and sulbactam alone.
- Exposure magnitudes of sulbactam (%*f*T>MIC) and durlobactam (*f*AUC_{0-24}/MIC) to achieve 1-$\log_{10}$ CFU reduction over 24 hours were determined in both thigh and lung models.
- Exposure-response analyses of comparator controls completed within these studies were consistent with exposures associated with achieving clinical efficacy.

Efficacy studies initially performed in a murine neutropenic thigh model demonstrated a clear sulbactam-durlobactam dose response, with minimal activity observed with treatment with sulbactam or durlobactam alone (Figure 12). The magnitudes of exposures were derived from neutropenic mouse models completed in the thigh and lung. Dose range studies utilizing a 4:1 sulbactam:durlobactam dose ratio and evaluation of the net change in bacterial burden ($\log_{10}$ CFU/g) over 24 hours were used to establish exposure-response analyses supporting 1-$\log_{10}$ CFU and 2-$\log_{10}$ CFU reduction targets. A pooled exposure response analysis utilizing ABC strains spanning a broad range of MICs is summarized in Figure 13 for sulbactam (panel A) and durlobactam (panel B). All in vitro and in vivo work was supported by bioanalytical assays and protein binding to establish unbound exposures associated with the activity of each agent. Clear restoration of sulbactam efficacy was demonstrated against MDR strains when durlobactam was dosed in combination with sulbactam.

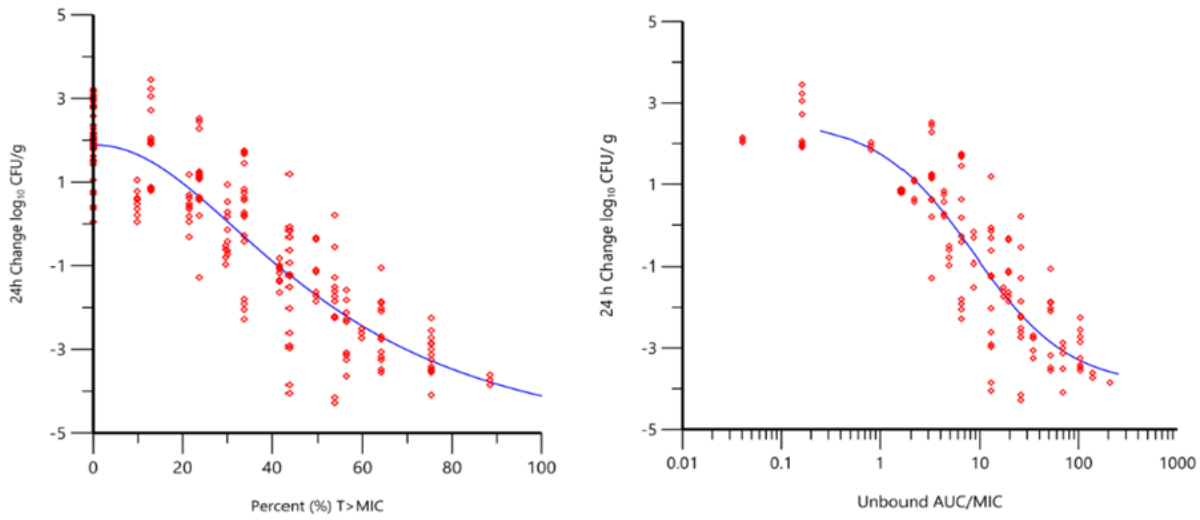
Figure 12: In Vivo Dose-Response Study of Sulbactam-Durlobactam Dose Versus Bacterial Burden Change from Baseline at 24 Hours in a Murine Neutropenic Thigh Model



Note: MDR *A. baumannii* ARC5955 (sulbactam-durlobactam MIC = 8 µg/mL).
CFU=colony-forming units; Dur=durlobactam; MDR=multidrug-resistant; MIC=minimum inhibitory concentration; q3h=every 3 hours; Sul=sulbactam.

Figure 13: Exposure Response Analysis of Sulbactam %*f*T > MIC (A) and durlobactam *f*AUC$_{0-24}$/MIC (B) in Plasma Versus Bacterial Burden Change from Baseline at 24 Hours in a Murine Neutropenic Lung Model

A B



A) n=5 strains.
B) n=4 strains.
%*f*T > MIC=Time as percentage of dosing interval the free drug concentration exceeds the minimum inhibitory concentration of the infecting organism; AUC$_{0-24}$=area under the plasma concentration-time curve from time of dosing to 24 hours post-dose.

4.3 Nonclinical Pharmacokinetics

Nonclinical PK and toxicokinetics were characterized in mice, rats, and dogs and were used in support of exposure-response in efficacy and safety studies. They were also used in allometric projections in support of predicting human PK. In addition to systemic exposures, drug concentrations were determined in epithelial lining fluid (ELF) and urine to establish distribution to relevant sites of infection and to determine the clearance/excretion of the compounds. The PK of sulbactam and durlobactam were similar across non-clinical species with low volume of distribution and moderate clearance, resulting in elimination half-lives of less than an hour. Renal excretion of unchanged drug was the predominant clearance mechanism for sulbactam and durlobactam in all species. The determination of drug exposure within the murine infection models was important for the determination of PK/PD exposure targets (Table 6). These matrices and models have been shown to be relevant in the treatment of clinical infections at different body sites (Bulitta et al 2019).

Table 6: Summary of Matrix Exposure and Murine Models to Support Clinical Infections

Clinical Indication (site)	Relevant Matrix	Non-Clinical Model	PK/PD Targets (Net 1-log_{10} CFU Reduction in 24 Hours)	PK/PD Targets (Net 2-log_{10} CFU Reduction in 24 Hours)
Nosocomial Pneumonia (lung)	Total Epithelial Lining Fluid and Unbound Plasma	Murine Lung	Sulbactam 50% Time > MIC and Durlobactam AUC_{0-24}/MIC =10	Sulbactam 50% Time > MIC and Durlobactam AUC_{0-24}/MIC = 30
Bacteremia (bloodstream)	Unbound Plasma	Murine Thigh		
Intra-Abdominal (tissue)	Unbound Plasma	Murine Thigh		
Pyelonephritis (tissue)	Unbound Plasma	Murine Thigh		
Urinary Tract Infection (urine)	Total Urine	Murine Thigh/In vitro HFIM		

AUC_{0-24}=area under the plasma concentration-time curve from time of dosing to 24 hours post-dose; CFU=colony-forming units; HFIM=hollow-fiber infection model; MIC=minimum inhibitory concentration; PD=pharmacodynamics; PK=pharmacokinetics

4.4 Pharmacokinetic/Pharmacodynamic Modeling Target Summary

Sulbactam-durlobactam was evaluated with PK/PD analyses for efficacy and PK/PD target attainment analyses using population PK models, as well as in vitro and in vivo data.

The PK/PD parameter that most correlated with sulbactam efficacy was time, as a percentage of the dosing interval, in which unbound concentrations of sulbactam exceeded the MIC of the infecting organism (%*f*T > MIC). The %*f*T > MIC value of 50% was associated with a 1-log_{10} kill. The ratio of AUC_{0-24} of durlobactam to the sulbactam-durlobactam MIC was determined to be the PK/PD relationship to target for efficacy, with ratios of approximately 10 and 30 being associated with achieving 1-log_{10} and 2-log_{10} kill, respectively when unbound sulbactam achieves 50% *f*T > MIC.

5 CLINICAL PHARMACOLOGY

Summary

- Eight trials support the clinical pharmacology program of sulbactam-durlobactam.
- The 3-hour IV infusion of 1.0 g sulbactam/1.0 g durlobactam administered q6h, adjusted for renal function, is considered optimal based on PK, probability of target attainment, safety and tolerability, and efficacy results from clinical trials.
- Sulbactam and durlobactam are primarily renally eliminated, and exposures of both drugs are affected by renal function, with increasing exposure correlating with decreasing renal function.
    - Dose adjustments for sulbactam-durlobactam in patients with impaired and augmented renal function are recommended.
- Sulbactam and durlobactam demonstrated good distribution into the ELF, suggesting that sulbactam-durlobactam is well suited for the treatment of pulmonary infections.
- Sulbactam-durlobactam is unlikely to cause DDIs related to cytochrome P450 (CYP450) or transporters.
- Organic anion transporter 1 (OAT1) inhibition can lead to higher and more prolonged serum concentrations of sulbactam; therefore, caution should be used when sulbactam-durlobactam is administered with OAT1 inhibitors such as probenecid.
- Population PK modeling and PTA analyses support the proposed doses.

5.1 Pharmacokinetics

The PK of sulbactam, durlobactam, or sulbactam-durlobactam have been evaluated in 6 Phase 1 studies in adult participants at sulbactam doses of 1.0 g, single durlobactam doses ranging from 0.25–8.0 g, and multiple durlobactam doses of 0.25–2.0 g administered q6h for 8 days. The PK of sulbactam-durlobactam was also studied in patients in the Phase 2 and Phase 3 trials. Population PK modeling and PTA analyses were also conducted to support dose selection.

The PK characteristics of sulbactam are well established and sulbactam has been shown to be dose-proportional (Unasyn USPI; Foulds et al 1983). Durlobactam exhibited linear, dose-proportional PK.

The PK characteristics of sulbactam and durlobactam are shown in Table 7.

Table 7: Pharmacokinetic Properties of Sulbactam and Durlobactam

	Sulbactam (N=37)	Durlobactam (N=37)
Pharmacokinetic Parameter[a]		
C_{max} (µg/mL)	26.7 (59.1%)	27.0 (39.3%)
AUC_{0-24} (h•µg/mL)	391 (76.1%)	418 (53.5%)
CL (L/h)	9.98 (59.7%)	9.40 (36.6%)
V_{ss} (L)	22.0 (60.8%)	28.0 (40.3%)
$T_{1/2}$	1.88 (53.7%)	2.41 (29.9%)
Protein Binding[b]	38%	10%
Intrapulmonary Penetration[c]	50%	37%
Metabolism	Minimally metabolized	
Excretion[d]	Primarily renally eliminated	

a. Presented as geometric mean (%CV) at steady state (Day 3) in patients with normal renal function defined as creatinine clearance ≥ 90 to < 130 mL/min at a dose of 1 g sulbactam/1 g durlobactam.
b. % of drug bound to human plasma protein.
c. ELF to total plasma ratio, expressed as a percentage and based on the area under the plasma concentration-time curve from time 0–6 hours post-dose (AUC_{0-6}).
d. In Phase 1 studies, mean urinary recovery of sulbactam and durlobactam were as high as 94% and 84%, respectively. Hemodialysis was effective in removing sulbactam and durlobactam from plasma.
AUC_{0-24}=Area under the plasma concentration-time curve from time of dosing to 24 hours post-dose; CL=total body clearance; C_{max}=maximum plasma concentration; ELF=epithelial lining fluid; $T_{1/2}$=terminal half-life; V_{ss}= steady-state volume of distribution.

5.1.1 Drug-Drug Interactions

Approximately 75–85% of sulbactam is excreted unchanged in the urine during the first 8 hours after administration to individuals with normal renal function (Unasyn USPI), suggesting minimal metabolism of sulbactam.

In vitro and in vivo studies have shown that hepatic metabolism and/or excretion does not account for a substantial portion of the elimination of durlobactam. Sulbactam-durlobactam is unlikely to cause DDIs related to CYP450 or transporters. Durlobactam is not metabolized by CYP450 and exhibits minimal potential to cause CYP450-mediated DDIs at clinically relevant concentrations. Sulbactam and durlobactam have no DDIs with each other when administered at efficacious doses. Additionally, no DDIs were observed following co-administration of imipenem and cilastatin in the first-in-human (FIH) Phase 1 study. Moreover, no significant inhibition of transporters by durlobactam or sulbactam were observed in vitro at systemic concentrations observed clinically.

Both sulbactam and durlobactam were found to be substrates for the renal transporter OAT1; however, only sulbactam is predicted to have active secretion as a significant portion of total clearance. OAT1 inhibition can lead to higher and more prolonged serum concentrations of sulbactam; therefore, caution should be used when sulbactam-durlobactam is administered with OAT1 inhibitors such as probenecid.

5.1.2 Population Pharmacokinetics Modeling

Population PK models used data from the six Phase 1 studies, the Phase 2 trial, and the Phase 3 trial based on a total of 373 patients with 5,390 plasma concentrations, including 110 patients (595 concentration observations) who received sulbactam-durlobactam and underwent PK sampling in the Phase 3 trial.

The population PK model is a combined model, with four compartments (2 compartments for each drug) with linear kinetics, which accurately described the PK of sulbactam and durlobactam.

A covariate analysis was conducted to evaluate the effect of intrinsic factors on the PK of sulbactam-durlobactam. Body weight, infection type, East Asian region (which grouped patients from mainland China, Taiwan, and South Korea), and renal impairment were statistically significant covariates; however, renal impairment was the most clinically relevant covariate.

- A trend of higher sulbactam and durlobactam exposures as body weight decreased was observed and appeared to be driven predominantly by patients with body weights below approximately 50–60 kg. However, the exposures were within the range observed in the clinical development program and no dose adjustments are recommended for patients with low body weight.
- A trend of lower exposures in patients with high body weights was also observed. However, the %PTA among simulated patients with high body weight (> 90 kg) was > 90% across various CL_{CR} groups indicating that despite being lower, the exposures in patients with body weights > 90 kg are expected to be efficacious based on adequate attainment of plasma PK/PD targets for efficacy for a 1-$\log_{10}$ CFU reduction at an MIC of 4 µg/mL; therefore, no dose adjustment is recommended for patients with weight > 90 kg.
- Sulbactam-durlobactam exposure distributions were generally comparable across patients with different infections (cUTI, AP, bacteremia, VABP, and HABP). Therefore, no dose adjustments are needed based on site of infection.
- Although sulbactam and durlobactam exposures were slightly higher in patients from the East Asian region, the exposure distributions had considerable overlap across regions, suggesting that no dose adjustments are needed based on region of origin.
- Age, country of origin (China vs others), race, and sex were not identified as statistically significant covariates. No dose adjustments are needed based on these covariates.
- Dose adjustments are needed based on renal function (additional details provided in Section 5.2).

5.1.2.1 Probability of Target Attainment

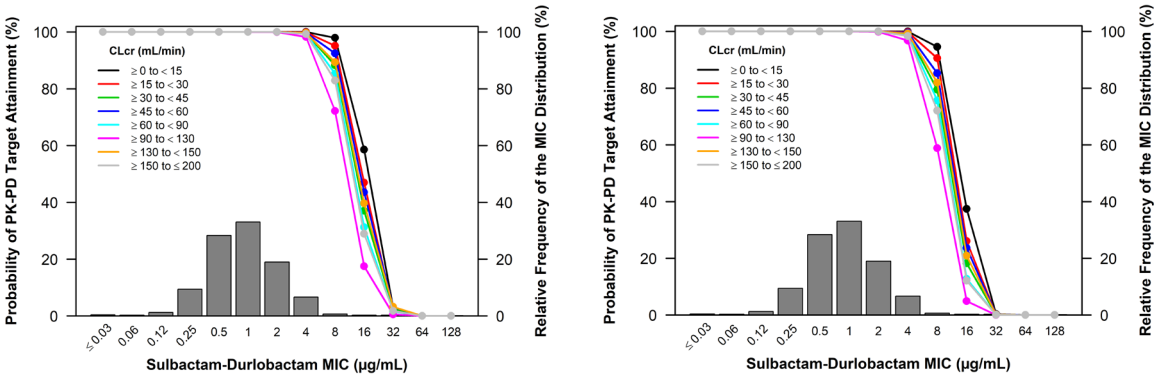
As described in Section 4.4, the PK/PD targets associated with sulbactam-durlobactam efficacy are %*f*T > MIC for sulbactam and *f*AUC/MIC ratio for durlobactam. In vitro and in vivo experiments support PK/PD targets of 50% *f*T > MIC for sulbactam and *f*AUC/MIC ratio of 10 for durlobactam for a 1-$\log_{10}$ CFU reduction.

Using population PK models, simulations were conducted to estimate the PTA of the combined PK/PD targets in a representative patient population using a contemporary collection of 7,026 ABC isolates obtained worldwide from 2013 to 2020.

Percent PTA by MIC on Day 1 based on the assessment of sulbactam and durlobactam free-drug plasma and total-drug ELF PK/PD targets across CL_{CR} group are shown in Figure 14. The PTA was > 90% for a 1-$\log_{10}$ CFU reduction at MIC values ≤ 4 µg/mL across all renal function categories, which span most of the sulbactam-durlobactam MIC distribution for ABC, based on both unbound plasma and total-ELF targets. The high PTA based on both targets further support that the proposed doses are anticipated to be efficacious.

These results provide support for 1.0 g sulbactam/1.0 g durlobactam and dosing regimens adjusted for renal function in patients with infections caused by ABC and for interpretive criteria recommendations for the in vitro susceptibility testing of sulbactam-durlobactam against ABC.

Figure 14: Probability of PK/PD Target Attainment by MIC on Day 1 Based on Free-Drug Plasma and Total-Drug ELF PK/PD Targets for Efficacy and Global Surveillance MIC Data Across Renal Function Categories



CL_{CR}=creatine clearance; ELF=epithelial lining fluid; PD=pharmacodynamic; PK=pharmacokinetic; PTA=probability of target attainment; SUL-DUR=sulbactam-durlobactam; MIC=minimum inhibitory concentration.

5.2 Summary of Dose Justification

The proposed dose regimen for sulbactam-durlobactam is shown in Table 8 and was based on:

- Safety data across the clinical development program,

- Efficacy data from the Phase 3 trial,
- The PK data for sulbactam and durlobactam, which showed distribution into the lung, minimal metabolism, predominant renal elimination, and low DDI potential,
- Pharmacometric approaches, including population PK modeling with data from Phase 1, 2, and 3 trials, and PTA analyses, and
- Robust nonclinical PK, PK/PD, safety, and microbiology assessments.

Table 8: Sulbactam-Durlobactam Dose Recommendations Based on Renal Function

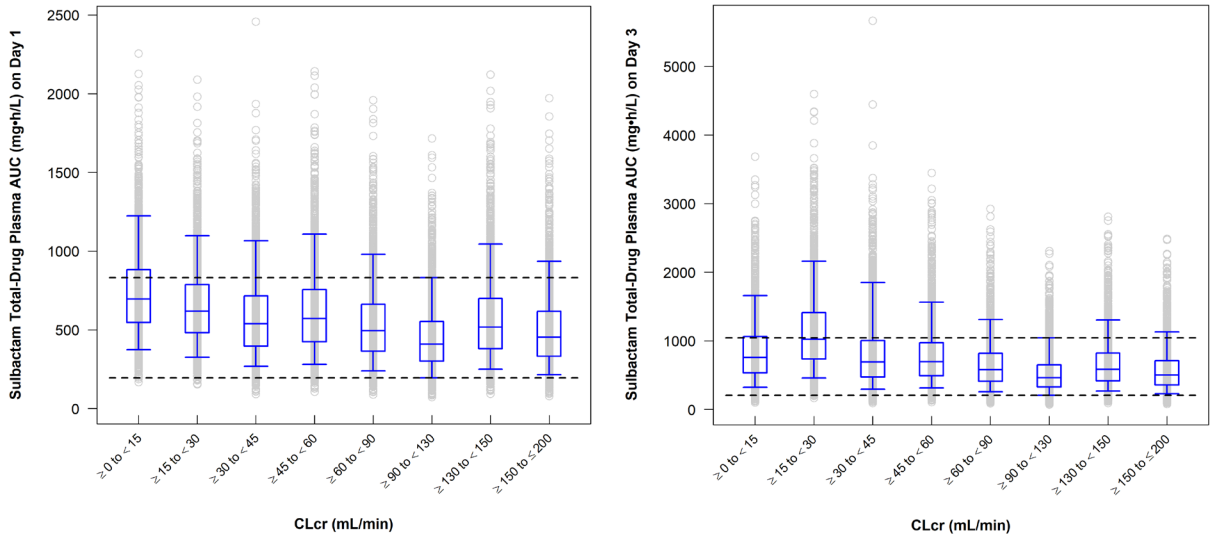
Renal Function Category	Creatinine Clearance (mL/min)[a]	Sulbactam-Durlobactam Dose	Frequency of Dosing
Augmented renal clearance	≥ 130 to ≤ 200	1.0 g/1.0 g	q4h
Normal and mild	≥ 60 to < 130	1.0 g/1.0 g	q6h
Moderate	≥ 45 to < 60	1.0 g/1.0 g	q6h
	≥ 30 to < 45	1.0 g/1.0 g	q8h
Severe	≥ 15 to < 30	1.0 g/1.0 g	q12h
	≥ 0 to < 15[b]	1.0 g/1.0 g	For initiation of treatment: Every 12 hours for the first 3 doses (0, 12, and 24 hours), followed by every 24 hours after the third dose[c] For all other treatment course: Every 24 hours

a. Creatine clearance estimated by Cockcroft-Gault equation.
b. For patients on hemodialysis, the dose should be administered after the dialysis session has ended.
c. This is equivalent to 1.0 g sulbactam/1.0 g durlobactam q12h on Day 1 followed by 1.0 g sulbactam /1.0 g durlobactam every 24 hours.
qXh=every X hours.

The safety and tolerability profile of a broad range of doses of up to 2.0 g durlobactam administered q6h and single doses of up to 8.0 g provided a large safety margin for the recommended dose of 1.0 g sulbactam/1.0 g durlobactam in patients with normal renal function. The 1.0 g dose of sulbactam was selected based on its established safety and efficacy profile when administered in combination with ampicillin (Unasyn USPI), while not exceeding the maximum dose of sulbactam (4.0 g/day based on 2 g:1 g ampicillin:sulbactam q6h [Unasyn USPI]). The duration of infusion of sulbactam-durlobactam was selected based on a population PK model and published data (Soto et al 2014; Yokoyama et al 2015), which show that a 3-hour infusion to achieve a sulbactam PK/PD target 50% *f*T > MIC for an MIC of 4 µg/mL, the target that is associated with sulbactam efficacy.

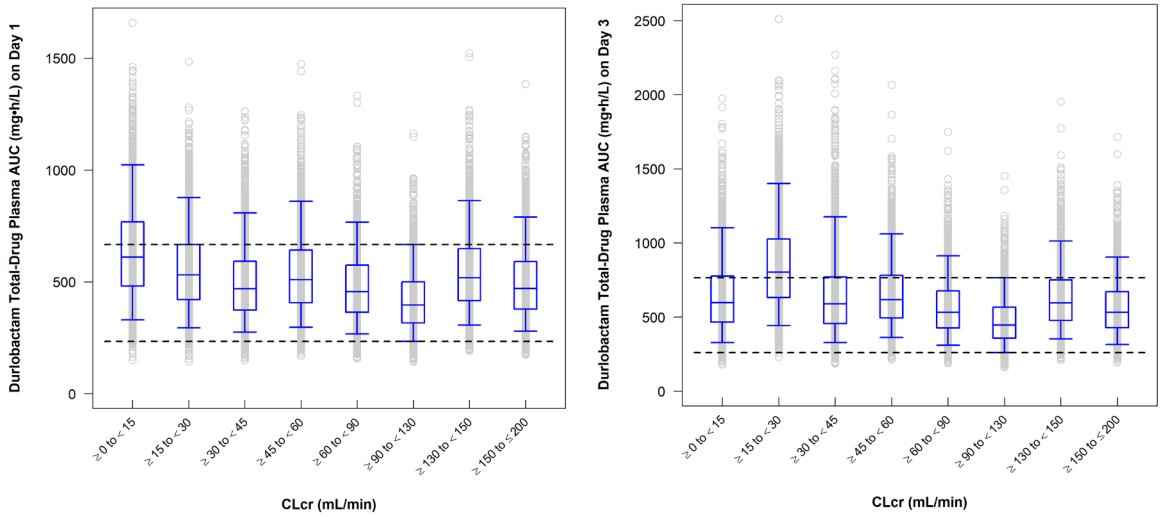
Using the final population PK model, which utilized data from Phase 1, 2, and 3 trials, a covariate analysis was conducted and showed that dose adjustments are needed based on renal function. Additional doses were explored for patients with creatinine clearance < 45 mL/min, with a goal of achieving exposures that were generally similar to those achieved in patients with normal renal function (CL_{CR} 90–130 mL/min). Based on plasma exposures with doses listed in Table 8 and using PK/PD targets, a percent PTA ≥ 90% was achieved across renal function categories for a sulbactam-durlobactam MIC of ≤ 4 µg/mL (Figure 15 and Figure 16). Similar results were observed in ELF. This is consistent with efficacy data observed in the Phase 3 trial in patients with ABC infections and is further supported by the safety data collected throughout the clinical development program of sulbactam-durlobactam.

Figure 15: Sulbactam Total-Drug Plasma AUC on Day 1 and Day 3 Among Simulated Patients by CL_{CR} Group After Administration of Sulbactam-Durlobactam Dosing Regimens



AUC=area under the plasma concentration-time curve; CL_{CR}=creatine clearance.

Figure 16: Durlobactam Total-Drug Plasma AUC on Day 1 and Day 3 Among Simulated Patients by CL_{CR} Group After Administration of Sulbactam-Durlobactam Dosing Regimens



AUC=area under the plasma concentration-time curve; CL_{CR}=creatine clearance.

6 REGULATORY AND DEVELOPMENT HISTORY

Summary

- The clinical development program for sulbactam-durlobactam was designed to provide substantial evidence of safety and efficacy to address the unmet medical need in patients with HABP and VABP caused by susceptible strains of ABC consistent with 2017 FDA guidance on Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases (FDA 2017).
- Sulbactam-durlobactam was granted Fast Track designation and QIDP status in 2017.
- The primary evidence supporting approval of sulbactam-durlobactam in patients with HABP and VABP caused by susceptible strains of ABC, comes from the pivotal, randomized, active-controlled Phase 3 trial.

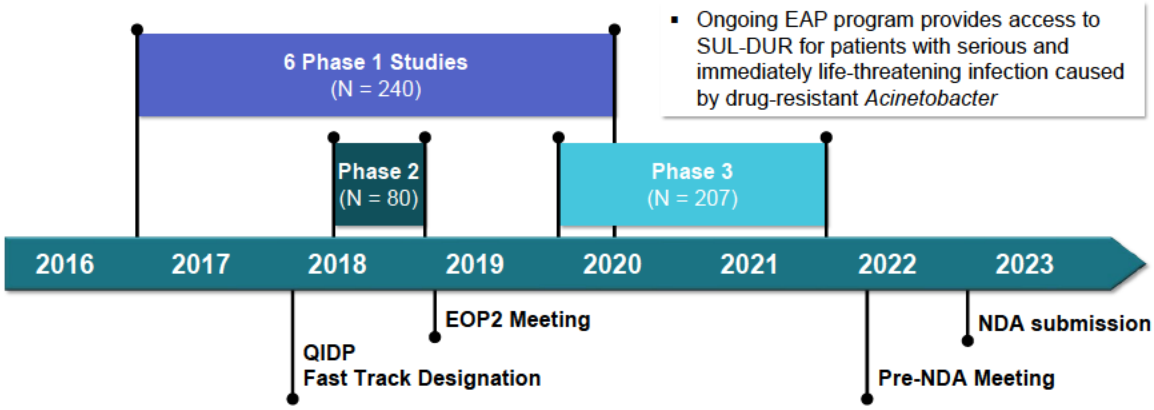
6.1 Key Regulatory Milestone

The potential for sulbactam-durlobactam to address the unmet medical need in patients with infections due to ABC, including multidrug- or carbapenem-resistant strains, was recognized with Fast Track and QIDP status granted by the FDA DAI on 01 September 2017.

6.2 Key Regulatory Interactions

Key regulatory interactions between FDA DAI and Entasis in the clinical development of sulbactam-durlobactam are presented in Figure 17.

Figure 17: Sulbactam-Durlobactam Pathogen-Focused Clinical Development Program Designed in Collaboration with the FDA DAI



EAP=Expanded Access Program; EOP2=End of Phase 2; FDA DAI=Food and Drug Administration Division of Anti-Infectives; NDA=New Drug Application; QIDP=Qualified Infectious Disease Product; SUL-DUR=sulbactam-durlobactam.

On 01 September 2017, the FDA DAI granted sulbactam-durlobactam Fast Track Designation and QIDP Designation, acknowledging the potential for sulbactam-durlobactam to address this high unmet need. In 2018, an End of Phase 2 meeting was held with the FDA to align on the global development plan for the Phase 3 trial. The clinical development program of sulbactam-durlobactam was streamlined to derive the primary data supporting efficacy and safety from a single Phase 3 trial based on FDA guidance for expedited development of treatments for infections caused by resistant pathogens (FDA 2017). The Phase 3 trial began enrollment in 2019 and was completed in 2021. In March of 2022, a pre-NDA meeting was held with the FDA DAI, where the Division agreed that the Phase 3 data along with the microbiology, pharmacology, and toxicology data in the non-clinical package were adequate for the Division's review of the NDA for sulbactam-durlobactam. Entasis submitted the NDA for sulbactam-durlobactam for the treatment indication on 29 September 2022.

6.3 Clinical Development Program

Entasis designed the clinical program through discussions with the FDA and consistent with the August 2017 FDA guidance on 'Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases' (FDA 2017).

Eight clinical trials, including 1 Phase 3 trial (Study CS2514-2017-0004), 1 Phase 2 trial (Study CS2514 2017-0003), and 6 Phase 1 studies (Studies CS2514-2016-0001, CS2514-2017-0001, CS2514-2017-0002, CS2514-2018-0002, ZL-2402-001, and CS2514-2018-0003) support the use of sulbactam-durlobactam for the treatment of infections caused by *A. baumannii* spp. that are multidrug- or carbapenem-resistant, with data from 380 patients and healthy participants (Table 9) as summarized in Sections 7 and 8.

The available data from clinical studies and relevant nonclinical studies were used in population PK and PK/PD target attainment analyses to support dose recommendations initially for the Phase 2 and 3 trials, and subsequently for the proposed dosing recommendations for the treatment of infections due to ABC, including multidrug- or carbapenem-resistant ABC (Sections 4 and 5).

The primary data supporting efficacy comes from the pivotal Phase 3 trial. As recommended by FDA DAI, the primary safety data for the proposed indication in adults for the treatment of HABP and VABP caused by susceptible strains of ABC, are derived from unpooled data from the Phase 3 trial, with subgroup analyses performed separately for the Phase 3 trial and combined with Phase 2. Supportive safety data are derived from the completed Phase 2 trial and 6 completed Phase 1 studies.

In addition, an EAP for patients ineligible to participate in a clinical trial and who have a documented serious and immediately life-threatening infection caused by drug resistant *Acinetobacter* spp. was initiated in May 2020. This program permitted access to investigational sulbactam-durlobactam for treatment outside of a clinical trial when no comparable or satisfactory alternative therapy option was available.

Table 9: Clinical Development Program Overview of Sulbactam-Durlobactam

Study Number (Type) NCT Number Status	Study Design	Sulbactam-Durlobactam Dose	Study Population	Number of Patients Enrolled
CS2514-2016-0001 (first-in-human, single and multiple ascending dose study, with drug-drug interaction cohorts) Completed	Phase 1, single-center, randomized, double-blind, placebo-controlled	Part A (SAD): 8 cohorts with 6 participants each, given single durlobactam doses of 0.25 g, 0.5 g, 1.0 g, 2.0 g, 4.0 g, and 8.0 g IV over 3 h, (except 1 cohort receiving 1.0 g over 2 h). Part B (MAD): 4 cohorts with 6 participants each, given durlobactam at doses of 0.25 g, 0.5 g, 1.0 g, and 2.0 g over 3 h q6h for 8 days. Part C (single-dose DDI): Cohort 13: 6 participants received single 1.0 g of durlobactam on Day 1, single 1.0 g of durlobactam on Day 3, and 1.0 g sulbactam/1.0 g durlobactam on Day 5. Cohort 14: 6 participants received single doses of 1.0 g durlobactam on Day 1, 0.5 g imipenem/cilastatin on Day 3, 1.0 g durlobactam plus 0.5 g imipenem/cilastatin on Day 5, and 1.0 g sulbactam/1.0 g durlobactam plus 0.5 g imipenem/cilastatin on Day 8. Two participants received placebo on Day 1, placebo plus 0.5 g imipenem/cilastatin on Day 5, and placebo and 1.0 g sulbactam plus 0.5 g imipenem/cilastatin on Day 8. Part D (multiple-dose DDI): 1 cohort with 10 participants given 1.0 g of durlobactam plus 1.0 g of sulbactam over 3 h for 10 days with 1 dose administered on Day 11.	Healthy participants	124

Study Number (Type) NCT Number Status	Study Design	Sulbactam-Durlobactam Dose	Study Population	Number of Patients Enrolled
CS2514-2017-0001 (Lung penetration study) NCT03303924 Completed	Phase 1, multiple dose, open-label PK	3 doses of 1.0 g of sulbactam and 1.0 g of durlobactam infused over 3 h q6h	Healthy adult participants (non-smoking)	30
CS2514-2017-0002 (Renal impairment PK study) NCT03310463 Completed	Phase 1, up to 3-center, open-label, non-randomized	<u>Cohorts 1–3:</u> Single dose of 1.0 g sulbactam and 1.0 g durlobactam infused over 3 h <u>Cohort 4:</u> Single dose of 0.5 g sulbactam and 0.5 g durlobactam infused over 3 h <u>Cohort 5:</u> Two doses of 0.5 g sulbactam and 0.5 g durlobactam infused over 3 h with a week between doses	<u>Cohort 1:</u> Healthy adult participants <u>Cohort 2:</u> Mild RI <u>Cohort 3:</u> Moderate RI <u>Cohort 4:</u> Severe RI <u>Cohort 5:</u> ESKD on HD	34
CS2514-2018-0002 (PK, distribution, metabolism, and excretion study) NCT04018950 Completed	Phase 1, open-label, single-dose, PK	Single IV dose of 1 g of non-labeled durlobactam and 1 µCi of ^{14}C-labeled durlobactam infused over 3 h	Healthy adult males	8
CS2514-2018-0003 (TQT study) NCT03985410 Completed	Phase 1, partially double-blind conducted as placebo and active-controlled, single-infusion, TQT, 3-way crossover	Single IV dose of 4 g durlobactam infused over 3 h	Healthy adult participants (non-tobacco using)	32
ZL-2402-001 (Healthy Chinese adult PK study) Completed	Phase 1 single-dose, open-label	Single doses of 1.0 g sulbactam/1.0 g durlobactam	Healthy adult participants	12
CS2514-2017-0003 (PK and safety in patients) Completed	Phase 2, double-blind, randomized, placebo-controlled	1.0 g of sulbactam and 1.0 g of durlobactam infused over 3 h q6h for 7 days	Hospitalized patients with cUTI (including AP)	80

Study Number (Type) NCT Number Status	Study Design	Sulbactam-Durlobactam Dose	Study Population	Number of Patients Enrolled
CS2514-2017-0004 NCT03894046 Completed	Phase 3, randomized, active-controlled	Part A, Group 1: 1.0 g of sulbactam and 1.0 g of durlobactam infused over 3 h q6h (adjusted for renal function) Part B 1.0 g of sulbactam and 1.0 g of durlobactam infused over 3 h q6h (adjusted for renal function)	Patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms	207

ABC=*Acinetobacter baumannii-calcoaceticus* complex; AP=acute pyelonephritis; cUTI=complicated urinary tract infection; DDI=drug-drug interaction; ESKD=end-stage kidney disease; HABP=hospital-acquired bacterial pneumonia; HD=hemodialysis; IV=intravenous; MAD=multiple ascending dose; PK=pharmacokinetics; q6h=every 6 hours; RI=renal impairment; SAD=single ascending dose; TQT=Thorough QT; VABP=ventilator-associated bacterial pneumonia; VP=ventilated pneumonia.

7 CLINICAL EFFICACY

Summary

- The pivotal Phase 3 trial was a well-designed, randomized, active-controlled, trial that evaluated the safety and efficacy of 1.0 g sulbactam/1.0 g durlobactam q6h (adjusted for renal function) administered as a 3-hour IV infusion in patients with serious infections due to ABC.
    - Sulbactam-durlobactam met the primary efficacy endpoint of noninferiority for 28-day all-cause mortality in the primary analysis population.
    - The mortality rate in the sulbactam-durlobactam group was 19.0% (12/63 patients) compared to 32.3% (20/62 patients) in the colistin group with a treatment difference of −13.2% (95% CI: −30.0%, 3.5%).
- Mortality rates in Part B patients who were intolerant of colistin or had infections due to colistin-resistant ABC were similar to Part A patients treated with sulbactam-durlobactam.
- Prespecified secondary endpoints of clinical cure and microbiologically favorable response in the sulbactam-durlobactam group were consistently higher than in the comparator group at all timepoints and in all assessed populations.

7.1 Two-Part Phase 3 Trial

7.1.1 Trial Design

The Phase 3 trial (CS2514-2017-0004) was a randomized, active-controlled trial that evaluated the safety and efficacy of IV sulbactam-durlobactam in patients with ABC infections, including multidrug- and carbapenem-resistant ABC (Figure 1). The Phase 3 trial employed a non-inferiority design as discussed and agreed with the FDA DAI. The trial was enrolled in 2 parallel parts, Part A and Part B, with the PK data from the first approximately 30 patients in Part A reviewed prior to initiating enrollment in Part B.

7.1.1.1 Randomized Part A

Part A was the randomized, assessor-blinded, comparative portion of the trial in patients with documented ABC HABP, VABP, VP, or bacteremia. Eligible patients were randomized (1:1) to:

- 1.0 g sulbactam/1.0 g durlobactam IV infused over 3 hours q6h, or
- 2.5 mg/kg colistin IV infused over 30 minutes every 12 hours (q12h; after an initial loading dose of colistin 2.5–5 mg/kg).

All eligible patients received 1.0 g imipenem/1.0 g cilastatin IV infused over 1-hour q6h as background therapy to treat non-ABC co-infecting pathogens. Imipenem/cilastatin was also considered an effective therapy for patients with carbapenem-susceptible ABC infections, an appropriate therapeutic partner to treat CRABC in the colistin group, and had a dosing regimen (q6h) consistent with sulbactam-durlobactam administration in patients with normal renal function. All study treatments were adjusted for renal function.

Randomization was stratified by:

- Indication (HABP/VABP/VP vs bacteremia),
- Severity of illness, based on:
  - APACHE II score (10–19 vs 20–30),
  - SOFA score (7–9 vs ≥ 10), or
  - qSOFA score (2 vs 3 at screening), and
- Geography (China Mainland vs Rest of World).

Enrollment of HABP, VP, and bacteremia patients was limited to a total of no more than 40% of patients in Part A, regardless of resistance.

7.1.1.1.1 Selection of Colistin as Comparator

Colistin was selected as the active comparator for this study as it was a treatment option for serious infections caused by resistant *A. baumannii*. At the time of study design, there was no clear standard-of-care for the treatment of CRAB infections and no new treatment options were approved. Colistin has been used worldwide to treat MDR *A. baumannii* either alone or in combination. Overall mortality rates of 25–57% were reported in patients treated with colistin-based therapies (Alvarez-Marin et al 2016; Sirijatuphat and Thamlikikul 2014) which compares to mortality rates of 65–87% in patients who were not treated or had delayed treatment including inappropriate therapy (Erbay et al 2009; Lee et al 2014), indicating that colistin-based therapies were effective for the treatment of serious infections caused by resistant *A. baumannii*. The dosing of colistin was based on the USPI and updated guidance for IV colistin in critically ill patients (Nation et al 2016; Nation et al 2017).

7.1.1.2 Open-Label Part B

Part B was an open-label, supportive portion of the trial that included patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms resistant to colistin or polymyxin B, who failed a colistin or polymyxin B regimen prior to trial entry, who were intolerant to colistin, or were on acute renal replacement therapy, and patients with infections due to colistin- or polymyxin B-resistant ABC with sources of infection other than HABP, VABP, VP, and/or bacteremia. Eligible patients received 1.0 g sulbactam/1.0 g durlobactam IV infused over 3 hours q6h and 1.0 g imipenem/1.0 g cilastatin as background therapy to treat non-ABC co-infecting pathogens.

7.1.1.3 Key Enrollment Criteria

Participants in the Phase 3 trial were enrolled in 59 clinical sites in 16 countries. Part A and B included patients who met the enrollment criteria, including the following:

- ≥ 18 years of age,
- A confirmed diagnosis of a serious infection and the expectation, in the judgment of the Investigator, that the patient's infection would require treatment with IV antibiotics,
- A known infection caused by ABC as either a single pathogen or member of a polymicrobial infection based on evidence from culture or, if available, rapid diagnostic test from a sample collected within 72 hours prior to randomization (HABP/VABP/VP patients), and 1 of the following:
    a) Had received no more than 48 hours of potentially effective (i.e., Gram-negative coverage) antimicrobial therapy prior to the first dose of trial drug, or
    b) Was clinically failing prior treatment regimens (i.e., clinical deterioration or failure to improve after at least 48 hours of antibiotic treatment).

A full list of enrollment criteria is provided in Appendix 13.1.

7.1.1.4 Analysis Populations

The analysis populations are defined in Table 2.

7.1.1.5 Endpoint Definitions

The primary efficacy endpoint was 28-day all-cause mortality in the CRABC m-MITT Population in Part A.

The secondary efficacy endpoints for Parts A and B included the following:

- 28-day all-cause mortality in the m-MITT and ITT Populations,
- 14-day all-cause mortality in the CRABC m-MITT and m-MITT Populations,
- Clinical cure at TOC, EOT, and LFU in the CRABC m-MITT and m-MITT Populations, and
- Microbiological favorable assessment at TOC, EOT, and LFU in the CRABC m-MITT Population.

7.1.1.6 Statistical Analyses

7.1.1.6.1 Determination of Non-Inferiority Margin

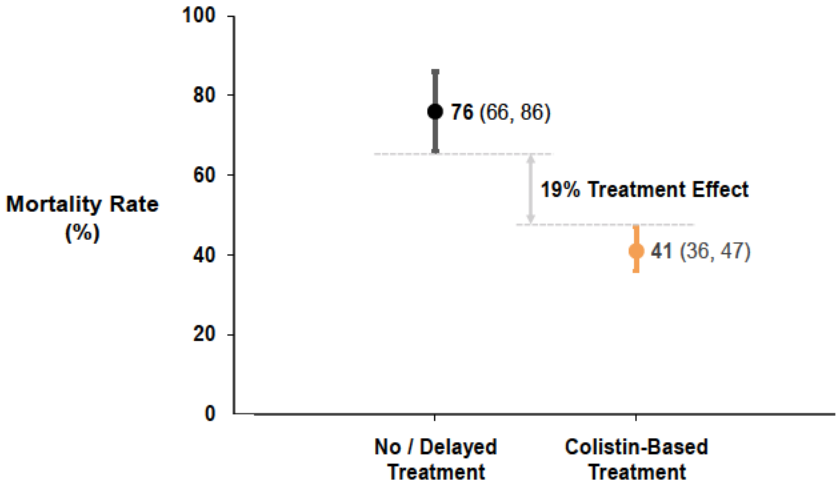
Entasis proposed a 20% non-inferiority margin for the primary efficacy endpoint for Part A. In the first Entasis literature review, as listed in Table 33, the best estimate of the mortality rate for colistin-based therapy was 40% (95% CI: 35%, 45%) from a fixed effects analysis, or 40% (95% CI: 32%, 47%) from a random effects analysis using the

method of DerSimonian and Laird (DerSimonian and Laird 1986). However, after updating the meta-analysis with 4 additional studies (Table 34), the estimated mortality rate from the random effects meta-analysis is 41% (95% CI: 36%, 47%). The best estimate of the mortality rate for untreated or delayed treatment is 78% (95% CI: 72%, 83%) from a fixed effect analysis, or 76% (95% CI: 66%, 86%) from a random effects analysis.

Using the most conservative estimates of mortality from the updated meta-analysis, the mortality rate is estimated to be 41% (95% CI: 36%, 47%) for colistin-based therapy, and 76% (95% CI: 66%, 86%) for untreated or delayed therapy (Figure 18). Based upon these data and using the most conservative approach of taking the upper bound of the 95% CI from the colistin-based therapy estimate and the lower bound of the 95% CI from the inappropriate or delayed therapy estimate leads to an estimated treatment benefit of at least 19% (66% minus 47%; M1).

Given the unmet need of this population, the life-threatening condition, and the relevancy of the literature review study populations to this study population, clinically it was determined that it may not be necessary to preserve the entire 50% of the M1. FDA DAI independently determined that a 19% non-inferiority margin should be used; however, later evaluated again and agreed to a 20% margin for this study.

Figure 18: Random Effects Meta-Analysis: Mortality Rates of Untreated/Delayed and Colistin-Based Treatment



The non-inferiority assessment for the primary efficacy analysis was based on the 2-sided 95% CIs computed using a continuity-corrected Z-statistic for the difference ([sulbactam-durlobactam] – [colistin]) in 28-day all-cause mortality rates between the treatment groups. Non-inferiority was concluded if the upper limit of the 2-sided 95% CI was < +20%. If non-inferiority was achieved, superiority was investigated. Superiority was concluded if the upper limit of the 2-sided 95% CI was < 0.

Patients in the CRABC m-MITT Population who discontinued study drug prematurely in Part A for any reason were included in the assessment of 28-day mortality, provided

consent had not been withdrawn. Patients who withdrew consent from the survival status were excluded from the analysis. Patients who had missing survival status were assigned outcome of death. Patients who were randomized into Part A but then transferred into Part B were not included in Part A efficacy analysis. For patients with a missing secondary efficacy value, the efficacy variable was considered as non-responder.

7.1.2 Patient Disposition and Baseline Characteristics

7.1.2.1 Disposition

A total of 207 patients were either randomized into Part A or enrolled into Part B. Two patients were transferred from Part A to Part B because local microbiology laboratory susceptibility results indicated that their screening ABC isolates were colistin-resistant.

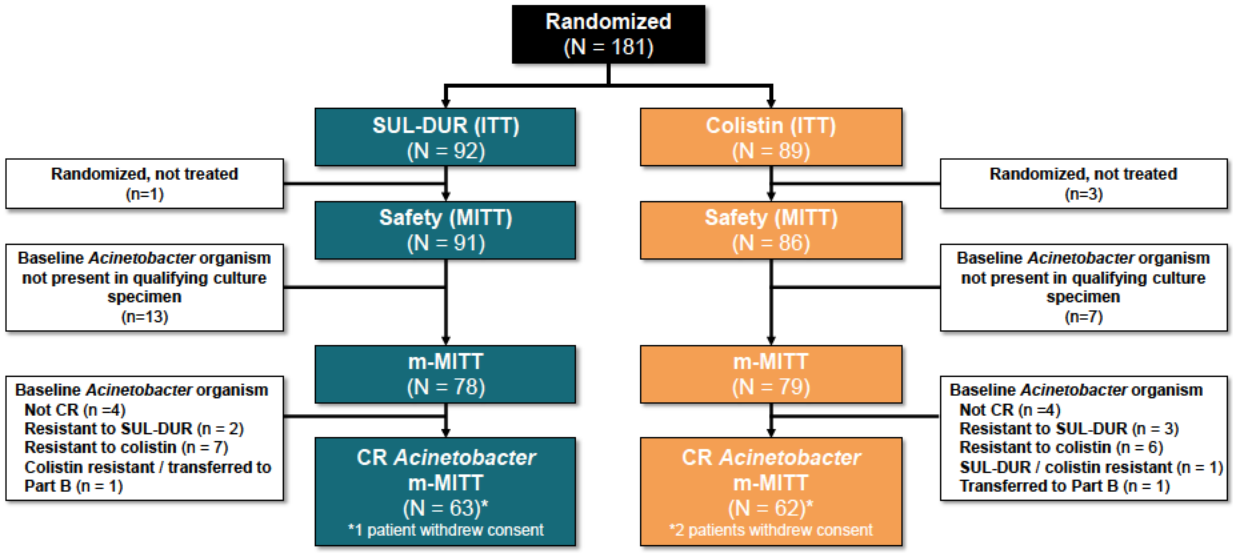
7.1.2.1.1 Randomized Part A

A total of 181 patients were randomized: 92 patients to the sulbactam-durlobactam group and 89 patients to the colistin group (Figure 19). Approximately 98% of these patients received any amount of study drug making up the MITT Population, which was also the Safety Population. Most patients in the ITT Population had a laboratory confirmed ABC infection at baseline and were included in the m-MITT population for efficacy analyses: 78 patients in the sulbactam-durlobactam group, and 79 patients in the colistin group. More than 80% of this population was confirmed to be carbapenem-resistant, the primary endpoint analysis population.

Of the randomized patients, 122 (67.4%) completed treatment: 67 (72.8%) patients in the sulbactam-durlobactam group and 55 (61.8%) patients in the colistin group. The top 3 reasons for not completing treatment were AE (18 [9.9%] patients overall: 8 [8.7%] patients in the sulbactam-durlobactam group and 10 [11.2%] patients in the colistin group), other reasons (13 [7.2%] patients overall: 6 [6.5%] patients in the sulbactam-durlobactam group and 7 [7.9%] patients in the colistin group), and no growth of ABC (12 [6.6%] patients overall: 7 [7.6%] patients in the sulbactam-durlobactam group and 5 [5.6%] patients in the colistin group). Approximately half of the patients who discontinued treatment for other reasons discontinued due to treatment failure as determined by the Investigator.

A total of 130 (71.8%) patients in Part A completed the trial: 69 (75.0%) patients in the sulbactam-durlobactam group and 61 (68.5%) patients in the colistin group. The primary reason patients did not complete the trial was due to death (36 [19.9%] patients overall: 15 [16.3%] patients in the sulbactam-durlobactam group and 21 [23.6%] patients in the colistin group).

Figure 19: Phase 3 Part A: Patient Disposition and Analysis Populations



CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat; SUL-DUR=sulbactam-durlobactam.
Populations are defined in Table 2.

7.1.2.1.2 Open-Label Part B

A total of 28 patients were enrolled to the open-label Part B portion of the Phase 3 trial. Of the 28 patients who were enrolled, 22 (78.6%) patients completed treatment. Three (10.7%) patients did not complete treatment due to an AE, and 1 (3.6%) patient each did not complete treatment due to death, withdrawal by the patient, or were ineligible for Part B enrollment.

A total of 22 (78.6%) patients completed the trial. The reasons patients did not complete the trial were death (4 [14.3%] patients), withdrawal of consent (1 [3.6%] patient), and incorrect enrollment in Part B (1 [3.6%] patient).

7.1.2.2 Baseline Demographics

Demographics were generally comparable between all treatment groups for the CRABC m-MITT Population (Table 10). In all 3 treatment groups, the majority of patients were male, < 65 years of age, white, and not Hispanic or Latino. The median age was approximately 62 years for the sulbactam-durlobactam group in Part A and approximately 59 years in Part B, and approximately 66 years for the colistin group.

Table 10: Baseline Demographics (CRABC m-MITT Population)

	Part A		Part B
	Sulbactam-Durlobactam (N=64)	Colistin (N=64)	Sulbactam-Durlobactam (N=28)
Age (years), median (min, max)	62 (25, 91)	66 (19, 98)	59 (18, 80)
Age group, n (%)			
< 65 years	36 (56.3)	31 (48.4)	19 (67.9)
65–75 years	16 (25.0)	12 (18.8)	5 (17.9)
> 75 years	12 (18.8)	21 (32.8)	4 (14.3)
Male, n (%)	46 (71.9)	49 (76.6)	21 (75.0)
Race, n (%)			
White	36 (56.3)	27 (42.2)	24 (85.7)
Asian	23 (35.9)	34 (53.1)	4 (14.3)
American Indian or Alaska Native[1]	4 (6.3)	2 (3.1)	0
Black or African American	0	1 (1.6)	0
Other	1 (1.6)	0	0
Ethnicity, n (%)			
Hispanic or Latino	9 (14.1)	9 (14.1)	1 (3.6)
Not Hispanic or Latino	54 (84.4)	55 (85.9)	27 (96.4)
Not reported	1 (1.6)	0	0

1. A total of 6 patients were identified as American Indian or Alaska Native race, but none of these patients were in the United States. These patients were in Peru. American Indian or Alaska Native refers to a person having origins in any of the original peoples of North, South, or Central America and who maintains tribal affiliation or community attachment.
CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat.

7.1.2.3 Baseline Disease Characteristics

Overall, baseline disease characteristics were comparable between treatment groups across Parts A and B and were representative of the patient population (Table 11).

For Part A, the mean (SD) APACHE II score was 16.8 (± 5.2) overall: 16.4 (± 5.1) in the sulbactam-durlobactam group and 17.2 (± 5.2) in the colistin group. Apache scores were slightly higher in the colistin arm whereas more patients with ventilator associated pneumonias were randomized to the sulbactam-durlobactam arm. The majority of patients for both treatment groups had pneumonia and were in the ICU for ≥ 5 days. The top underlying comorbidities were cerebrovascular disease, diabetes without end-organ damage, congestive heart failure, and chronic pulmonary disease which were comparable between the two treatment groups (Table 11). There were 51 (39.8%)

patients with renal impairment (creatinine clearance < 90 mL/min). Infection type, duration of ICU stay, and renal clearance were comparable between the 2 treatment groups. All 128 patients had a carbapenem-resistant ABC pathogen at baseline: 64 patients in each treatment group. A majority of patients had a monomicrobial ABC baseline infection with 57.8% of patients in the sulbactam-durlobactam group and 70.3% of patients in the colistin group.

For Part B, the mean (SD) APACHE II score was 18.0 (± 5.0). A majority of patients had bacteremia and had a baseline ICU stay > 14 days. There were 6 (21.4%) patients with renal impairment which was also a top underlying comorbidity in patients. Other underlying comorbidities were diabetes without end-organ damage and chronic pulmonary disease. All 28 patients had a carbapenem-resistant ABC pathogen at baseline. The majority of patients had a monomicrobial ABC baseline infection (82.1% of patients).

Table 11: Baseline Disease Characteristics (CRABC m-MITT Population)

	Part A		Part B
	Sulbactam-Durlobactam (N=64)	Colistin (N=64)	Sulbactam-Durlobactam (N=28)
APACHE II Score, mean (SD)	16.4 (5.11)	17.2 (5.21)	18.0 (5.03)
10–19	43 (67.2)	37 (57.8)	18 (64.3)
20–30	15 (23.4)	19 (29.7)	9 (32.1)
SOFA score, n (%)			
7–9	1 (1.6)	6 (9.4)	4 (14.3)
≥ 10	2 (3.1)	2 (3.1)	2 (7.1)
qSOFA score, n (%)			
2	7 (10.9)	10 (15.6)	3 (10.7)
3	1 (1.6)	1 (1.6)	0
Creatine clearance (mL/min), n (%)			
< 90	25 (39.1)	26 (40.1)	7 (25.0)
≥ 90	39 (60.9)	38 (59.4)	21 (75.0)
Infection type, n (%)			
Bacteremia	2 (3.1)	1 (1.6)	17 (60.7)
HABP	24 (37.5)	31 (48.4)	4 (14.3)
VABP	38 (59.4)	30 (46.9)	7 (25.0)
VP	0	2 (3.1)	0
Duration of ICU stay at baseline (days), n (%)			
No ICU stay	21 (32.8)	19 (29.7)	5 (17.9)
< 5	2 (3.1)	3 (4.7)	1 (3.6)
5–14	23 (35.9)	24 (37.5)	4 (14.3)
> 14	18 (28.1)	18 (28.1)	18 (64.3)
Monomicrobial infection, n (%)	37 (57.8)	45 (70.3)	23 (82.1)
Polymicrobial infection, n (%)	27 (42.2)	19 (29.7)	5 (17.9)
Mechanical ventilation at baseline, n (%)	47 (73.4%)	50 (78.1%)	8 (28.6%)
Charlson Comorbidity Index, mean (SD)	4.6 (3.20)	4.8 (3.35)	2.7 (2.59)
Comorbidities, n (%)			
Cerebrovascular disease	21 (32.8)	18 (28.1)	1 (3.6)
Diabetes without end-organ damage	13 (20.3)	15 (23.4)	5 (17.9)
Congestive heart failure	15 (23.4)	11 (17.2)	2 (7.1)
Chronic pulmonary disease	9 (14.1)	15 (23.4)	3 (10.7)
Hemiplegia	12 (18.8)	7 (10.9)	1 (3.6)
Moderate or severe renal disease	7 (10.9)	12 (18.8)	6 (21.4)
Mild liver disease	7 (10.9)	7 (10.9)	0

APACHE=Acute Physiology and Chronic Health Evaluation; CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat; HABP=hospital-acquired bacterial pneumonia; ICU=intensive care unit; qSOFA=Quick Sequential Organ Failure Assessment; VABP=ventilator-associated bacterial pneumonia; VP=ventilated pneumonia.

7.1.2.3.1 Antibiotic Susceptibility of Baseline ABC Pathogens

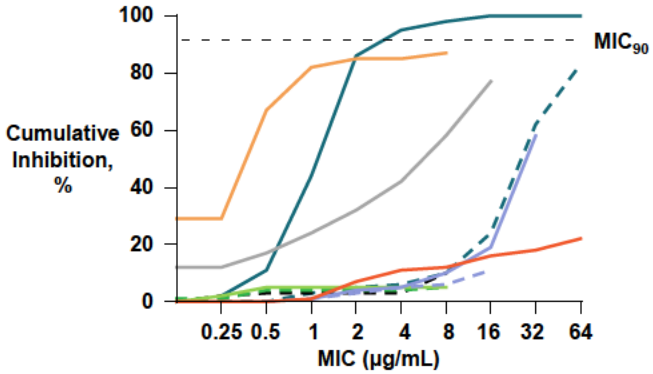
Of the baseline ABC pathogens in the m-MITT Population, 175 were available for testing by the central laboratory and were found to be highly antibiotic-resistant (Table 12 and Figure 20). Most isolates were multidrug- and carbapenem-resistant. In addition, 85% of isolates were XDR, in that they were non-susceptible to all but 2 antibiotic classes used to treat *A. baumannii*, and 15% were PDR or non-susceptible to all tested antibiotic classes approved for the treatment infections caused by *A. baumannii*. Approximately 17% were non-susceptible to colistin. In contrast, over 90% of *A. baumannii* isolates were susceptible to sulbactam-durlobactam (MIC ≤ 4 µg/mL), even in the colistin-resistant, XDR, and PDR subsets.

Table 12: Antibiotic Susceptibility of Baseline ABC Isolates (m-MITT Population, Parts A and B)

	Acinetobacter Baseline Isolates, n (%)	Sulbactam-Durlobactam MIC (µg/mL)		
		Range	MIC_{50}	MIC_{90}
All	175 (100)	0.25–16	2	4
Carbapenem-resistant	168 (96)	0.5–16	2	4
Colistin-resistant	30 (17)	1–8	2	4
Multidrug resistant*	168 (96)	0.5–16	2	4
Extensively drug resistant*	148 (85)	0.5–16	2	4
Pandrug resistant	26 (15)	1–8	2	4

*As defined by Magiorakos et al, 2012.
Carbapenem resistant=imipenem or meropenem MIC ≥ 8 µg/mL; colistin resistant=colistin MIC ≥4 µg/mL.
ABC=*Acinetobacter baumannii-calcoaceticus* complex; MIC_{50}=minimum inhibitory concentration required to inhibit the growth of 50% of isolates; MIC_{90}=minimum inhibitory concentration required to inhibit the growth of 90% of isolates; m-MITT=microbiologically Modified Intent-to-Treat.

Figure 20: Antibiotic Susceptibility of 175 Baseline ABC Isolates



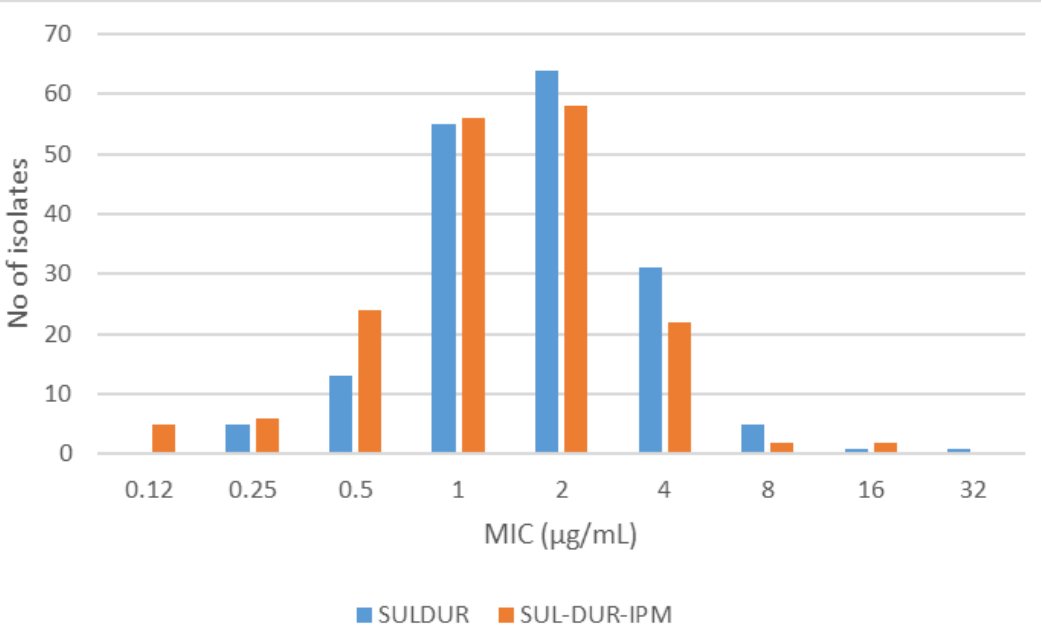
Antibiotic	$MIC_{50/90}$	%NS (CLSI)
AMK	> 64 / > 64	85
FEP	> 16 / > 16	95
CPZ-SUL	32 / > 32	NA
COL	0.5 / > 8	17
IPM	> 8 / > 8	96
MEM	> 8 / > 8	96
LVX	> 4 / > 4	96
MIN	4 / 16	43
SUL	32 / > 64	95*
SUL-DUR	2 / 4	4.6*

* Preliminary susceptibility breakpoint for sulbactam-durlobactam is 4 µg/mL. ABC=*Acinetobacter baumannii-calcoaceticus* complex; AMK=amikacin; CLSI=Clinical Laboratory Standards Institute; COL=colistin; CPZ-SUL=cefoperazone-sulbactam (2:1); DUR=durlobactam; FEP=cefepime; IPM=imipenem; LVX= levofloxacin; MEM=meropenem; MIC_{50}=minimum inhibitory concentration required to inhibit the growth of 50% of isolates; MIC_{90}=minimum inhibitory concentration required to inhibit the growth of 90% of isolates; MIN=minocycline; NA=not applicable; NS=non-susceptible; SUL=sulbactam.

7.1.2.3.2 Addition of Imipenem Had Minimal Effect on Sulbactam-Durlobactam Activity Against ABC Baseline Pathogens

All patients received 1.0 g imipenem/1.0 g cilastatin as background therapy to treat non-ABC co-infecting pathogens. To determine whether imipenem would affect the activity of sulbactam-durlobactam against ABC baseline isolates, 175 ABC baseline isolates from m-MITT patients were tested for sulbactam-durlobactam susceptibility alone or in the presence of imipenem. As shown in Figure 21, the addition of imipenem had a minimal effect on the activity of sulbactam-durlobactam against these isolates.

Figure 21: MIC Distribution for Sulbactam-Durlobactam Versus Sulbactam-Durlobactam-Imipenem of 175 Baseline ABC Isolates (m-MITT Population)



Note: Susceptibility testing was performed by titrating sulbactam either alone or in a 1:1 ratio with imipenem in two-fold dilutions in the presence of durlobactam fixed at 4 µg/mL. ABC=*Acinetobacter baumannii-calcoaceticus* complex; MIC=minimum inhibitory concentration; SUL-DUR-IPM=sulbactam-durlobactam-imipenem; m-MITT=microbiologically Modified Intent-to-Treat.

7.1.3 Part A: Primary Efficacy Endpoint Results – 28-Day All-Cause Mortality in the CRABC m-MITT Population

Sulbactam-durlobactam met the primary efficacy endpoint of 28-day all-cause mortality for non-inferiority in Part A compared to colistin in the CRABC m-MITT Population (N=125; Table 13). The mortality rate in the sulbactam-durlobactam group was 19.0% compared to 32.3% in the colistin group. The treatment difference was −13.2% and the upper limit of the 95% CI was within the prespecified 20% non-inferiority margin.

Table 13: Phase 3 Trial Part A: 28-Day All-Cause Mortality (CRABC m-MITT Population)

	Sulbactam-Durlobactam (N=63)	Colistin (N=62)	Treatment Comparison[1]	
			Difference (%)	95% CI
28-day all-cause mortality, n (%)	12 (19.0)	20 (32.3)	-13.2	(-30.0, 3.5)

Note: Excludes patients who withdrew consent. No patients missed survival status due to reason other than withdrawal of consent. Patients who transferred from Part A to Part B were not included in the Part A analysis.
1. Treatment difference was the difference in the 28-day all-cause mortality rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic.
CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat.

7.1.4 Part A: Secondary Efficacy Endpoint Results

7.1.4.1 All-Cause Mortality

Sulbactam-durlobactam met the secondary efficacy endpoint of 28-day all-cause mortality compared to colistin in the ITT Population for Part A. The mortality rate in the sulbactam-durlobactam group was 21.1% (19/90 patients) compared to 32.9% (28/85 patients) in the colistin group with a treatment difference of −11.8% (95% CI: −26.0%, 2.4%) for the ITT Population in Part A (Table 14).

Additional secondary analyses were performed for 28-day all-cause mortality in the m-MITT Population and for 14-day all-cause mortality in the m-MITT and CRABC m-MITT Populations; all analyses provided similar results (Table 14) and are consistent with the primary efficacy analysis.

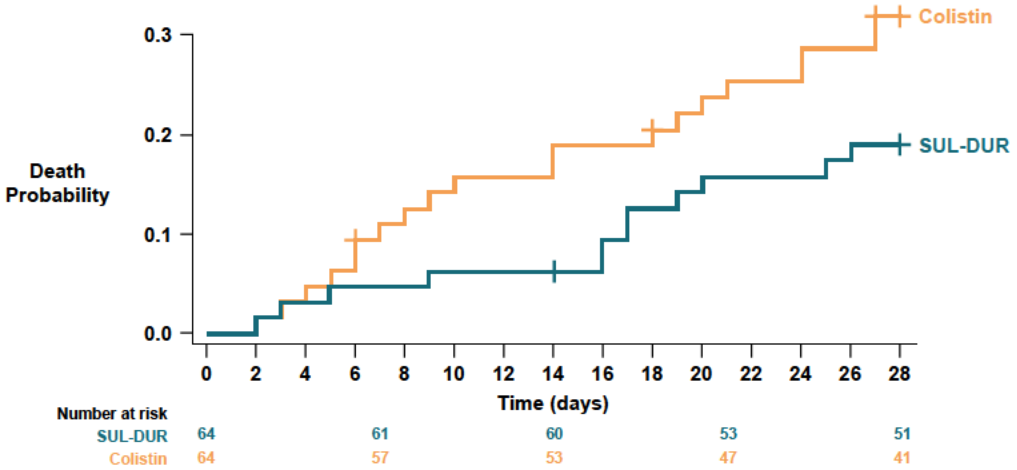
Table 14: Phase 3 Trial Part A: 14-Day and 28-Day All-Cause Mortality

	Sulbactam-Durlobactam n/N (%)	Colistin n/N (%)	Treatment Comparison[1]	
			Difference (%)	95% CI
28-Day				
m-MITT Population	15/76 (19.7)	25/76 (32.9)	-13.2	(-28.3, 2.0)
ITT Population	19/90 (21.1)	28/85 (32.9)	-11.8	(-26.0, 2.4)
14-Day				
CRABC m-MITT Population	4/64 (6.3)	12/63 (19.0)	-12.8	(-25.7, 0.1)
m-MITT Population	6/77 (7.8)	15/77 (19.5)	-11.7	(-23.7, 0.3)

Note: Excludes patients who withdrew consent. Patients with missing survival status were treated as a death. Patients who transferred from Part A to Part B were not included in the Part A analysis.
1. Treatment difference was the difference in the all-cause mortality rate between the 2 treatment arms ([sulbactam-durlobactam + imipenem/cilastatin] – [colistin + imipenem/cilastatin]). The 95% CI was computed using a continuity-corrected Z-statistic.
CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat.

A Kaplan-Meier analysis indicated a higher rate of survival for patients receiving sulbactam-durlobactam compared to colistin beginning after Day 6 of therapy (Figure 22). The hazard ratio for time to death was 0.32 (95% CI: 0.10, 0.98; p=0.035) at Day 14 and 0.55 (95% CI: 0.27, 1.12; p=0.094) at Day 28 in the CRABC m-MITT population. The causes of death by treatment days are listed in Table 15. As determined by the Investigator, 4 deaths were due to the Index infection in the sulbactam-durlobactam group compared with 8 deaths in the colistin group, 5 of which occurred between Days 6–14.

Figure 22: Phase 3 Trial Part A: Time to Death (CRABC m-MITT Population)



CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex Microbiologically Modified Intent-to-Treat; SUL-DUR=sulbactam-durlobactam.

Table 15: Phase 3 Trial Part A: Deaths That Occurred in the Efficacy Population (CRABC m-MITT Population)

	Cause of Death Events by Preferred Term		
	Days 0–5	**Days 6–14**	**Days 15–28**
Sulbactam-Durlobactam	- Shock (Index Infection*) - Hemorrhagic shock - GI hemorrhage	- Septic shock (Index infection)	- Septic shock (Index infection) - Sepsis (Index infection) - Coronary arteriosclerosis - Intra-abdominal hemorrhage - ARDS - Malignant neoplasm progression -Sepsis -Mesenteric vessel and peripheral artery thrombosis
Colistin	- Septic shock (Index infection) - Septic shock - ARDS - Cardiac arrest	- Septic shock (Index infection) - Pneumonia (Index infection) - Pneumonia (Index infection) - Pneumonia (Index infection) - ARDS (Index infection) - Multiple organ dysfunction syndrome/Sepsis - Cerebral hemorrhage	- Sepsis (Index infection) - Cardiac arrest (Index infection) - Weaning failure - Pneumonia - Pneumonia - Stroke - Concomitant disease progression (ALS) - Multiple organ dysfunction syndrome

*Death due to Index Infection as determined by Investigator.
Note: One patient died on Day 7 in the colistin group but an AE was not reported.
ALS=amyotrophic sclerosis; ARDS=acute respiratory distress syndrome; CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex Microbiologically Modified Intent-to-Treat; GI=gastrointestinal.

7.1.4.2 Clinical Cure Rate at Test of Cure, End of Treatment, and Late Follow-Up in the CRABC m-MITT Population

Clinical response was based on the assessment of signs and symptoms and classified into one of the following categories: clinical cure, clinical failure, or clinical indeterminate. Clinical cure was defined as complete resolution or significant improvement of baseline signs and symptoms and no new symptoms, such that no additional Gram-negative antimicrobial therapy was warranted. A significant treatment difference of 21.6% (95% CI: 2.9%, 40.3%) in clinical cure rate at TOC was observed with 61.9% of patients in the sulbactam-durlobactam group compared to 40.3% of patients in the colistin group (Table 16). Clinical cure rate at EOT was similar to the response at TOC and lower at LFU.

Table 16: Phase 3 Trial Part A: Clinical Cure Rate at Test of Cure, End of Treatment, and Late Follow-Up (CRABC m-MITT Population)

Visit Clinical Response	Sulbactam-Durlobactam (N=63)	Colistin (N=62)	Treatment Comparison[1]	
			Difference (%)	95% CI
End of Treatment (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)		
Test of Cure (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)		
Late Follow-Up (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)		

Note: Excludes patients who withdrew consent.
1. Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam] – [colistin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic.
CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex Microbiologically Modified Intent-to-Treat.

7.1.4.3 Clinical Cure Rate at Test of Cure, End of Treatment, and Late Follow-Up in the m-MITT Population

Clinical cure rates at TOC were comparable in the sulbactam-durlobactam group for the m-MITT analysis population (Table 17). As seen in the CRABC m-MITT Population, clinical response in the m-MITT analysis population was comparable to TOC at EOT and lower than TOC at LFU.

Table 17: Phase 3 Trial Part A: Clinical Cure Rate at Test of Cure, End of Treatment, and Late Follow-Up (m-MITT Population)

Visit Clinical Response	Sulbactam-Durlobactam (N=77)	Colistin (N=78)	Treatment Comparison[1]	
			Difference (%)	95% CI
End of Treatment (EOT)				
Cure	58 (75.3)	36 (46.2)	29.2	(13.2, 45.1)
Failure	17 (22.1)	37 (47.4)		
Indeterminate	2 (2.6)	5 (6.4)		
Test of Cure (TOC)				
Cure	48 (62.3)	29 (37.2)	25.2	(8.6, 41.7)
Failure	25 (32.5)	46 (59.0)		
Indeterminate	4 (5.2)	3 (3.8)		
Late Follow-Up (LFU)				
Cure	32 (41.6)	22 (28.2)	13.4	(-2.8, 29.5)
Failure	33 (42.9)	50 (64.1)		
Indeterminate	12 (15.6)	6 (7.7)		

1. Treatment difference was the difference in the clinical cure rate between the 2 treatment arms ([sulbactam-durlobactam] – [colistin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic.
m-MITT=Microbiologically Modified Intent-to-Treat.

7.1.4.4 Microbiological Favorable Response at Test of Cure, End of Treatment, and Late Follow-Up in the CRABC m-MITT and m-MITT Populations

For the CRABC m-MITT Population, a significant treatment difference of 26.3% (95% CI: 7.9%, 44.7%) in microbiological favorable assessment at TOC was observed with 68.3% of patients in the sulbactam-durlobactam group compared to 41.9% of patients in the colistin group (Table 18). Microbiological responses were consistent between EOT and TOC and lower in the late follow-up timepoint for the CRABC m-MITT Population.

As seen in the CRABC m-MITT Population, microbiological response in the m-MITT analysis population was comparable to TOC at EOT and lower than TOC at LFU.

Table 18: Phase 3 Part A: Microbiological Favorable Response at Test of Cure, End of Treatment, and Late Follow-Up (CRABC m-MITT and m-MITT Populations)

			Treatment Comparison[1]	
	Sulbactam-Durlobactam	Colistin	Difference (%)	95% CI
CRABC m-MITT Population, N	63	62		
End of Treatment (EOT)	54 (85.7)	38 (61.3)	24.4	(7.9, 40.9)
Test of Cure (TOC)	43 (68.3)	26 (41.9)	26.3	(7.9, 44.7)
Late Follow-Up (LFU)	30 (47.6)	25 (40.3)	7.3	(-11.7, 26.3)
m-MITT Population, N	77	78		
End of Treatment (EOT)	64 (83.1)	48 (61.5)	21.6	(6.6, 36.5)
Test of Cure (TOC)	51 (66.2)	32 (41.0)	25.2	(8.7, 41.7)
Late Follow-Up (LFU)	37 (48.1)	30 (38.5)	9.6	(-7.2, 26.4)

Note: Excludes patients who withdrew consent.
1. Treatment difference was the difference in the microbiological favorable assessment between the 2 treatment arms ([sulbactam-durlobactam] – [colistin]). The 95% CI (2-sided) was computed using a continuity-corrected Z-statistic.
CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex Microbiologically Modified Intent-to-Treat.

7.1.4.4.1 Resistance to Sulbactam-Durlobactam

Of the 105 patients in the Phase 3 trial who were treated with sulbactam-durlobactam, 73 (69.5%) had favorable microbiological outcomes at TOC (ABC was eradicated or presumed eradicated). Of the isolates from patients treated with sulbactam-durlobactam with persistent or recurrent infections which were characterized by the central laboratory, 1/105 (0.95%) had longitudinal isolates with elevated sulbactam-durlobactam MIC values compared to the baseline ABC isolate. This patient was not included in the CRABC m-MITT Population because the baseline *A. baumannii* isolate was colistin-resistant. The patient's baseline isolate was XDR but categorized as susceptible to sulbactam-durlobactam based on the preliminary breakpoint, with an MIC value of 4 µg/mL. The sulbactam-durlobactam MIC value increased to 8 µg/mL at TOC, which is the proposed intermediate susceptibility breakpoint. This patient survived to 28 days and was considered a clinical cure at TOC but a microbiological failure at TOC. However, the infection caused by *A. baumannii* was successfully eradicated at LFU.

7.1.5 Sensitivity Analyses

Results of sensitivity analyses were consistent with the primary efficacy results for the CRABC m-MITT Population. In each analysis, treatment with sulbactam-durlobactam had a lower 28-day all-cause mortality rate when compared to treatment with colistin, including in a subset of patients who had negative cultures prior to dosing, missing survival status, and prior antibiotic use less than 24 hours prior to sulbactam-durlobactam treatment.

7.1.6 Part B: Secondary Efficacy Endpoint Results

7.1.6.1 All-Cause Mortality

As for Part A, all-cause mortality in Part B was assessed at 28-day all-cause mortality in the ITT, m-MITT, CRABC m-MITT Populations, and for 14-day all-cause mortality in the m-MITT and CRABC m-MITT Populations. No differences in 28-day and 14-day all-cause mortality results in the ITT, m-MITT, and CRABC m-MITT Populations were observed as the analysis populations were identical (Table 19). In the 17 patients with bacteremia, 2 (11.8%) deaths occurred.

Table 19: Phase 3 Trial Part B: 14-Day and 28-Day All-Cause Mortality

	Sulbactam-Durlobactam n/N (%)	95% CI
28-Day		
CRABC m-MITT Population	5/28 (17.9)	(6.1, 36.9)
14-Day		
CRABC m-MITT Population	3/28 (10.7)	(2.3, 28.2)

Note: Patients with missing survival status were treated as a death. Patients who transferred from Part A to Part B were included in the Part B analysis.
CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat.

7.1.6.2 Clinical Cure Rate at Test of Cure, End of Treatment, and Late-Follow-Up in the CRABC m-MITT Population

For Part B, the clinical cure rate at the TOC visit was 71.4% in the CRABC m-MITT Population. Clinical response at EOT was slightly higher (82.1%) when compared to the response at TOC and lower at LFU (Table 20).

Table 20: Phase 3 Trial Part B: Clinical Cure at Test of Cure, End of Treatment, and Late-Follow Up (CRABC m-MITT Population)

Visit Clinical Response	Sulbactam-Durlobactam (N=28) n (%)
End of Treatment (EOT)	
Cure	23 (82.1)
Failure	4 (14.3)
Indeterminate	1 (3.6)
Test of Cure (TOC)	
Cure	20 (71.4)
Failure	5 (17.9)
Indeterminate	3 (10.7)
Late Follow-Up (LFU)	
Cure	13 (46.4)
Failure	7 (25.0)
Indeterminate	8 (28.6)

Note: Patients transferred from Part A to Part B were included in the Part B analysis.
CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat.

7.1.6.3 Clinical Cure Rate at Test of Cure in the m-MITT Population

For Part B, clinical cure rate at TOC was observed with 71.4% (20/28) of patients for the m-MITT Population.

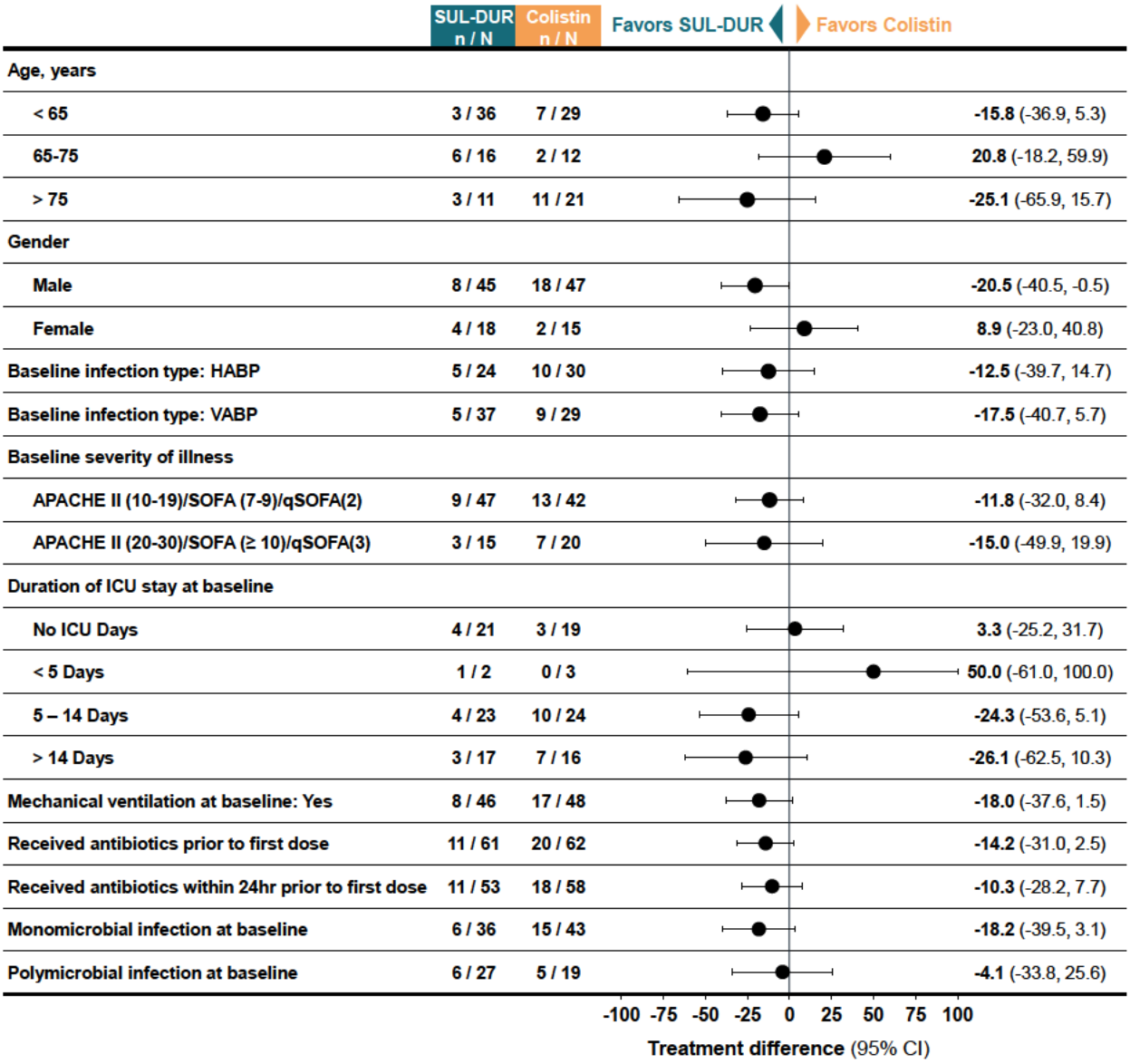
7.1.6.4 Microbiological Favorable Response at Test of Cure, End of Treatment, and Late Follow-Up (CRABC m-MITT Population)

For Part B, microbiological favorable assessment at EOT was observed with 89.3% (25/28) of patients for the CRABC m-MITT Population and at TOC in 78.6% (22/28) of patients. Overall, microbiological favorable assessment at LFU was observed in 53.6% (15/28) of patients.

7.1.7 Subgroup Analyses of Primary Efficacy Endpoint

Subgroup analyses were examined for 28-day all-cause mortality for the CRABC m-MITT Population in Part A (Figure 23).

Figure 23: Subgroup Analyses: 28-Day All-Cause Mortality by Subgroup (CRABC m-MITT Population)



APACHE=Acute Physiology and Chronic Health Evaluation; CRABC m-MITT=Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex microbiologically Modified Intent-to-Treat; HABP=hospital-acquired bacterial pneumonia; ICU=intensive care unit; qSOFA=Quick Sequential Organ Failure Assessment; SUL-DUR=sulbactam-durlobactam; VABP=ventilator-associated bacterial pneumonia.

7.1.8 Exposure-Efficacy Analysis

An exposure-efficacy analysis was conducted to explore relationships between PK/PD indices and efficacy outcome in patients with an ABC infection in the Phase 3 trial. Only a small number of analyses yielded statistically significant PK/PD relationships for sulbactam or durlobactam PK/PD indices. However, these relationships were not supported by assessments of time to all-cause mortality, and no relationships were

identified for 28-day all-cause mortality. Therefore, the exposure-efficacy analysis data did not suggest relationships between PK/PD indices and efficacy endpoints. This result would be expected as nearly all patients received a dose associated with exposures greater than PK/PD targets.

7.2 Efficacy Conclusions

In the Phase 3, randomized, active-controlled, pivotal trial, treatment with IV sulbactam-durlobactam demonstrated statistical non-inferiority versus colistin. The Part B 28-day all-cause mortality was consistent with Part A. In addition, consistent treatment differences between the sulbactam-durlobactam group and the colistin group were observed across the various trial populations, and also at both 14-day and 28-day timepoints. Clinical cure rates and favorable microbiological responses were significant at both EOT and TOC for the CRABC m-MITT Population for Part A in the sulbactam-durlobactam group compared to the colistin group.

Overall, the clinical efficacy data from the pivotal Phase 3 trial support the clinical use of sulbactam-durlobactam for the treatment of HABP and VABP caused by susceptible strains of ABC.

8 CLINICAL SAFETY

Summary

- 158 individuals have received sulbactam-durlobactam at the proposed dose and duration across 8 clinical studies.
  - 6 Phase 1 studies contributed clinical PK data of durlobactam key to the selection of doses for Phase 2 and 3 trials.
    - Durlobactam doses of up to 8.0 g as single doses, or 2.0 g as multiple doses were generally well tolerated, with no dose-limiting AEs in these studies.
    - The thorough QT study demonstrated that a supratherapeutic dose of 4.0 g durlobactam had no clinically relevant effects on studied electrocardiogram (ECG) parameters.
  - The Phase 2 safety and tolerability trial further characterized the safety profile in patients with cUTI.
  - The Phase 3 trial provided safety data in patients with the proposed indication.
  - In the Phase 3 trial, sulbactam-durlobactam met the primary safety objective with a statistically significant lower incidence (p=0.0002) in nephrotoxicity as compared to colistin (13.2% vs 37.6%) based on modified RIFLE criteria.
  - The AEs related to renal disorders in patients treated with sulbactam-durlobactam were less severe and less frequent as compared to colistin.
- No unexpected safety signals were observed in the Phase 3 trial based on the analyses of AEs. The types and incidences of AEs were consistent with expectations for the population of critically ill patients and were characteristic of the pharmacological class.
- The overall incidence of treatment-related AEs was lower in patients treated with sulbactam-durlobactam compared to those treated with colistin (12.6% vs 30.2%).
- There were fewer severe TEAEs, severe treatment-related AEs, SAEs, treatment-related SAEs, and TEAEs leading to study drug discontinuation or death with sulbactam-durlobactam treatment compared to colistin.
- The AESIs of acute renal failure, convulsions, sepsis, infective pneumonia, drug-related hepatic disorders, hypersensitivity, and pseudomembranous colitis were similar or lower with sulbactam-durlobactam vs colistin.

8.1 Safety Overview for Sulbactam-Durlobactam Program

8.1.1 Overall Treatment Exposure

Overall, 380 individuals have been exposed to durlobactam alone or in combination with sulbactam in 8 clinical studies (Table 21). The proposed dose of 1.0 g sulbactam/1.0 g durlobactam q6h (adjusted for renal function) has been administered to 181 individuals and 158 individuals have received the proposed dose at the proposed duration of at least 7 days.

The 8 clinical studies included 6 Phase 1 studies contributing to the clinical PK understanding of durlobactam and key data for the selection of doses in the Phase 2 and 3 trials. Durlobactam doses of up to 8.0 g as single doses, or 2.0 g as multiple doses were generally well tolerated, with no dose-limiting AEs in these studies. The thorough QT study demonstrated that a supratherapeutic dose of 4.0 g durlobactam had no clinically relevant effects on studied ECG parameters.

The Phase 2 safety and tolerability trial further characterized the safety profile in patients with cUTI leading to the pivotal Phase 3 trial. The primary safety analysis of the Phase 3 trial included patients with infections caused by ABC, including multidrug- and carbapenem-resistant strains.

A total of 12 patients with serious infections caused by ABC have received sulbactam-durlobactam through an EAP since May 2020, (additional details provided in Section 9).

Table 21: Overall Exposure to Sulbactam-Durlobactam

Clinical Study Phase	Study Number	Number of Patients	Number of Patients at Proposed Dose of Sulbactam-Durlobactam	Number of Patients at Proposed Duration of Sulbactam-Durlobactam
Phase 1	CS2514-2016-0001	94	10	10
	CS2514-2017-0001	30	0	0
	CS2514-2017-0002	34	0	0
	CS2514-2018-0002	8	0	0
	CS2514-2018-0003	31	0	0
	ZL-2402-001	12	0	0
Phase 2	CS2514-2017-0003	53	53	51
Phase 3	CS2514-2017-0004	118	118	97
Total		380	181	158

8.1.1.1 Treatment Exposure in Phase 3 Trial

In the Phase 3 trial, 119 patients received sulbactam-durlobactam, including 91 patients in Part A and 28 patients in Part B. One patient was determined to have a colistin resistant isolate and was transferred to Part B and received sulbactam-durlobactam in

both Part A and Part B. Therefore, 118 unique patients were exposed to sulbactam-durlobactam in the trial. The majority of patients (77.3% in the sulbactam-durlobactam group and 72.1% in the colistin group) completed the trial.

8.2 Overall Safety for Phase 3 Trial

Table 22 presents an overall summary of AEs in the Safety Population of the Phase 3 trial. Most patients were reported to have experienced an AE in this critically ill patient population. Overall, patients treated with sulbactam-durlobactam experienced fewer AEs compared to the colistin group. The sulbactam-durlobactam group had a lower incidence of TEAEs, treatment-related AEs, severe TEAEs, severe treatment-related AEs, SAEs, treatment-related SAEs, and TEAEs leading to death or study drug discontinuation compared to the colistin group (Table 22). No deaths were assessed as related to sulbactam-durlobactam treatment. One death due to pneumonia was assessed as treatment-related in the colistin group.

Table 22: Phase 3 Trial: Overall Summary of Adverse Events (Safety Population)

	Part A		Part B	Parts A/B Combined
	Sulbactam-Durlobactam (N=91) n (%)	Colistin (N=86) n (%)	Sulbactam-Durlobactam (N=28) n (%)	Sulbactam-Durlobactam (N=119) n (%)
TEAE	80 (87.9)	81 (94.2)	24 (85.7)	104 (87.4)
Treatment-related AE[a]	12 (13.2)	26 (30.2)	3 (10.7)	15 (12.6)
Severe TEAE[b]	39 (42.9)	44 (51.2)	9 (32.1)	48 (40.3)
Severe treatment-related AE[a,b]	2 (2.2)	4 (4.7)	1 (3.6)	3 (2.5)
SAE	36 (39.6)	42 (48.8)	9 (32.1)	45 (37.8)
Treatment-related SAE[b]	1 (1.1)	2 (2.3)	1 (3.6)	2 (1.7)
TEAE leading to study drug discontinuation	10 (11.0)	14 (16.3)	4 (14.3)	14 (11.8)
TEAE leading to death	24 (26.4)	30 (34.9)	4 (14.3)	28 (23.5)
Treatment-related deaths	0	1 (1.2)	0	0

a. Related included events reported as related, probably related, and possibly related, as well as events with a missing relationship.
b. Severe was defined as severe, life-threatening, or fatal. Adverse events with missing severity were included as severe.
Note: All Phase 3 patients received background therapy of 1.0 g/1.0 g imipenem/cilastatin IV infused over 1 hour every 6 hours adjusted for renal function. One patient received colistin in Part A and sulbactam-durlobactam in Part B and is included in summaries for both treatments. One patient received sulbactam-durlobactam in both Parts A and B and is counted once in Part A and Part B and twice in Part A/B combined. If a patent experienced > 1 event in a given category, that patient is counted once.
IV=intravenously; SAE=serious treatment-emergent adverse event; TEAE=treatment-emergent adverse event.

8.3 Treatment-Emergent Adverse Events

Table 23 presents a summary of TEAEs that occurred in > 5 patients in any treatment group in the Phase 3 trial.

Most patients in the trial experienced at least one TEAE. Overall, the most common TEAEs reported in > 10% of patients in the sulbactam-durlobactam group were diarrhea, anemia, and hypokalemia (Table 23). These events were also the most frequently reported TEAEs in the colistin group with the addition of acute kidney injury, which was reported in 12.8% (n=11) of the patients receiving colistin compared to 4.4% (n=4) in the sulbactam-durlobactam group.

Table 23: Phase 3 Trial: Common Treatment-Emergent Adverse Events (> 5 Patients in Any Treatment Group; Safety Population)

	Part A		Part B
Preferred Term	Sulbactam-Durlobactam (N=91) n (%)	Colistin (N=86) n (%)	Sulbactam-Durlobactam (N=28) n (%)
Any TEAE	80 (87.9)	81 (94.2)	24 (85.7)
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
Urinary tract infection	7 (7.7)	7 (8.1)	1 (3.6)
Acute kidney injury	4 (4.4)	11 (12.8)	0
Cardiac arrest	2 (2.2)	5 (5.8)	1 (3.6)
Blood creatinine increased	2 (2.2)	7 (8.1)	3 (10.7)
Seizure	1 (1.1)	6 (7.0)	0
Renal impairment	0	6 (7.0)	1 (3.6)

Note: All Phase 3 patients received background therapy of 1.0 g/1.0 g imipenem/cilastatin IV infused over 1 hour every 6 hours adjusted for renal function. One patient received colistin in Part A and sulbactam-durlobactam in Part B and is included in summaries for both treatments. One patient received sulbactam-durlobactam in both Parts A and B of the Phase 3 trial and is counted once in Part A and Part B. If a patient experienced > 1 event within a given preferred term, that patient is counted only once for that term.
IV=intravenously; TEAE=treatment-emergent adverse event.

8.4 Treatment-Related Adverse Events

Table 24 presents a summary of treatment-related AEs that occurred in ≥ 2 patients in any treatment group in the Phase 3 trial.

In the sulbactam-durlobactam group, the incidence of treatment-related AEs was similar in Parts A and B (13.2% and 10.7%). Diarrhea, which was reported in 4 (4.4%) patients in Part A of the sulbactam-durlobactam group and 4 (4.7%) patients in the colistin group, was the only treatment-related AE reported in > 1 patient treated with sulbactam-durlobactam in the Phase 3 trial.

Table 24: Phase 3 Trial: Common Treatment-Related Adverse Events (≥ 2 Patients in Any Treatment Group; Safety Population)

	Part A		Part B
Preferred Term	Sulbactam-Durlobactam (N=91) n (%)	Colistin (N=86) n (%)	Sulbactam-Durlobactam (N=28) n (%)
Any treatment-related AE	12 (13.2)	26 (30.2)	3 (10.7)
Diarrhea	4 (4.4)	4 (4.7)	0
Acute kidney injury	0	5 (5.8)	0
Blood creatinine increased	0	4 (4.7)	0
Renal impairment	0	3 (3.5)	0
Renal failure	0	2 (2.3)	0

Note: All Phase 3 patients received background therapy of 1.0 g/1.0 g imipenem/cilastatin IV infused over 1 hour every 6 hours adjusted for renal function. One patient received colistin in Part A and sulbactam-durlobactam in Part B and is included in summaries for both treatments. One patient received sulbactam-durlobactam in both Parts A and B of the Phase 3 trial and is counted once in Part A and Part B. Related includes events reported as Related, Probably Related, and Possibly Related, as well as events with missing relationship. If a patient experienced > 1 event within a given preferred term, that patient is counted only once for that term.
AE=adverse event; IV=intravenously.

8.5 Severe Treatment-Emergent Adverse Events

Table 25 presents a summary of severe TEAEs that occurred in > 2% of patients in any treatment group in the Phase 3 trial.

Septic shock was the most common severe TEAE and occurred in 7 patients in both treatment groups. Overall, the incidence of severe TEAEs occurred at similar rates regardless of treatment, with differences in the frequency of pneumonia, acute kidney injury, and seizure, which occurred less often in the sulbactam-durlobactam group compared with the colistin group (Table 25).

Table 25: Phase 3 Trial: Common Severe Treatment-Emergent Adverse Events (> 2% of Patients in Any Treatment Group; Safety Population)

	Part A		Part B
Preferred Term	Sulbactam-Durlobactam (N=91) n (%)	Colistin (N=86) n (%)	Sulbactam-Durlobactam (N=28) n (%)
Any severe TEAE	39 (42.9)	44 (51.2)	9 (32.1)
Septic shock	7 (7.7)	7 (8.1)	0
Acute respiratory distress syndrome	3 (3.3)	2 (2.3)	0
Tracheoesophageal fistula	3 (3.3)	0	0
Multiple organ dysfunction syndrome	2 (2.2)	4 (4.7)	2 (7.1)
Cardiac arrest	2 (2.2)	4 (4.7)	1 (3.6)
Gastrointestinal hemorrhage	2 (2.2)	2 (2.3)	0
Sepsis	2 (2.2)	2 (2.3)	0
Respiratory failure	2 (2.2)	1 (1.2)	1 (3.6)
Anemia	2 (2.2)	1 (1.2)	0
Brain oedema	2 (2.2)	1 (1.2)	0
Shock hemorrhagic	1 (1.1)	0	1 (3.6)
Pneumonia	1 (1.1)	5 (5.8)	0
Acute kidney injury	1 (1.1)	4 (4.7)	0
Pulmonary embolism	1 (1.1)	2 (2.3)	0
Seizure	0	3 (3.5)	0
Renal failure	0	1 (1.2)	1 (3.6)

Note: All Phase 3 patients received background therapy of 1.0 g/1.0 g imipenem/cilastatin IV infused over 1 hour every 6 hours adjusted for renal function. One patient received colistin in Part A and sulbactam-durlobactam in Part B and is included in summaries for both treatments. One patient received sulbactam-durlobactam in both Parts A and B of the Phase 3 trial and is counted once in Part A and Part B. If a patient experienced > 1 event within a given preferred term, that patient is counted only once for that term.
IV=intravenously; TEAE=treatment-emergent adverse event.

8.6 Serious Treatment-Emergent Adverse Events

Table 26 presents SAEs that occurred in ≥ 2 patients in any treatment group of the Phase 3 trial.

Overall, there was a lower incidence of SAEs in the sulbactam-durlobactam group compared to the colistin group.

Table 26: Phase 3 Trial: Common Serious Treatment-Emergent Adverse Events (≥ 2 Patients in Any Treatment Group; Safety Population)

	Part A		Part B
Preferred Term	Sulbactam-Durlobactam (N=91) n (%)	Colistin (N=86) n (%)	Sulbactam-Durlobactam (N=28) n (%)
Any SAE	36 (39.6)	42 (48.8)	9 (32.1)
Septic shock	7 (7.7)	7 (8.1)	0
Cardiac arrest	2 (2.2)	4 (4.7)	1 (3.6)
Sepsis	2 (2.2)	3 (3.5)	0
Acute respiratory distress syndrome	2 (2.2)	2 (2.3)	0
Respiratory failure	2 (2.2)	1 (1.2)	1 (3.6)
Brain oedema	2 (2.2)	1 (1.2)	0
Gastrointestinal hemorrhage	2 (2.2)	1 (1.2)	0
Tracheo-esophageal fistula	2 (2.2)	0	0
Pneumonia	1 (1.1)	5 (5.8)	0
Multiple organ dysfunction syndrome	1 (1.1)	4 (4.7)	2 (7.1)
Pulmonary embolism	1 (1.1)	2 (2.3)	0
Acute kidney injury	1 (1.1)	2 (2.3)	0
Seizure	0	3 (3.5)	0
Anemia	0	2 (2.3)	0

Note: All Phase 3 patients received background therapy of 1.0 g/1.0 g imipenem/cilastatin IV infused over 1 hour every 6 hours adjusted for renal function. One patient received colistin in Part A and sulbactam-durlobactam in Part B and is included in summaries for both treatments. One patient received sulbactam-durlobactam in both Parts A and B of the Phase 3 trial and is counted once in Part A and Part B. If a patient experienced > 1 event within a given preferred term, that patient is counted only once for that term.
IV=intravenously; SAE=serious treatment-emergent adverse event.

8.7 Serious Treatment-Related Adverse Events

Treatment-related SAEs included pneumonia and neutropenia each in 1 patient in the sulbactam-durlobactam group (Part A/B combined) and pseudomembranous colitis and pneumonia each in 1 patient in the colistin group.

8.8 Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

In the sulbactam-durlobactam group, TEAEs leading to study drug discontinuation were reported in 10 (11%) patients in Part A and 4 (14%) patients in Part B (Table 27). The only TEAE that led to discontinuation of study drug in > 1 patient in the sulbactam-durlobactam group was hepatic function abnormal (2 patients; 1.7%); these events were

also reported as SAEs for these 2 patients and were assessed as not related to study drug.

One patient in the sulbactam-durlobactam group discontinued study drug due to a non-serious event of anaphylactic shock, which was assessed by the Investigator as moderate in severity and related to the study drug (sulbactam-durlobactam and imipenem/cilastatin); the event was reported on Day 9 of study treatment and resolved on the same day.

Table 27: Phase 3 Trial: Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (Safety Population)

	Part A		Part B
Preferred Term	Sulbactam-Durlobactam (N=91) n (%)	Colistin (N=86) n (%)	Sulbactam-Durlobactam (N=28) n (%)
Any TEAE leading to study drug discontinuation	10 (11.0)	14 (16.3)	4 (14.3)
Pneumonia bacterial	1 (1.1)	0	0
Pneumonia pseudomonal	1 (1.1)	0	0
Hepatic function abnormal	1 (1.1)	0	1 (3.6)
Shock	1 (1.1)	0	0
Shock hemorrhagic	1 (1.1)	0	0
Brain oedema	1 (1.1)	0	0
Rash	1 (1.1)	1 (1.2)	0
Acute myocardial infarction	1 (1.1)	0	0
Gastrointestinal hemorrhage	1 (1.1)	0	0
Anaphylactic shock	1 (1.1)	0	0
Hypersensitivity	1 (1.1)	0	0
Procedural hemorrhage	1 (1.1)	0	0
Electrocardiogram QT prolonged	1 (1.1)	0	0

Note: All Phase 3 patients received background therapy of 1.0 g/1.0 g imipenem/cilastatin IV infused over 1 hour every 6 hours adjusted for renal function. One patient received colistin in Part A and sulbactam-durlobactam in Part B and is included in summaries for both treatments. One patient received sulbactam-durlobactam in both Parts A and B of the Phase 3 trial and is counted once in Part A and Part B. If a patient experienced > 1 event within a given preferred term, that patient is counted only once for that term.
IV=intravenously; TEAE=treatment-emergent adverse event.

8.9 Deaths and Treatment-Emergent Adverse Events Leading to Death

8.9.1 Total Deaths

In the Phase 3 trial a total of 58 deaths occurred: 28 (23.5%) deaths in the sulbactam-durlobactam group and 30 (34.8%) deaths in the colistin group of the safety population.

This total also includes the deaths that were described in the primary efficacy analysis (Table 15).

8.9.2 Treatment-Emergent Adverse Events Leading to Death

A lower incidence of TEAEs leading to death was observed in the sulbactam-durlobactam group compared with the colistin group (Table 28). The most commonly reported TEAEs leading to death in the sulbactam-durlobactam group were septic shock, sepsis, brain oedema, respiratory failure, and multiple organ dysfunction syndrome.

No deaths at any time were assessed as related to study drug in the sulbactam-durlobactam group. One death due to pneumonia in the colistin group was assessed by the Investigator as treatment-related; this event occurred in a patient who entered the study with severe pneumonia requiring intubation. The Investigator considered the event as treatment-related because the study drug did not control the patient's pneumonia after extubation.

Table 28: Phase 3: Treatment-Emergent Adverse Events Leading to Death Within and After Day 28 (Safety Population)

	Phase 3 Parts A/B Combined			
	Sulbactam-Durlobactam (N=119) n (%)		Colistin (N=86) n (%)	
Preferred Term	**≤ 28 days**	**> 28 days**	**≤ 28 days**	**> 28 days**
Any AE leading to death	**22 (18.5)**	**6 (5.0)**	**25 (29.1)**	**5 (5.8)**
Septic shock	4 (3.4)	1 (0.8)	4 (4.7)	1 (1.2)
Multiple organ dysfunction	2 (1.7)	1 (0.8)	4 (4.7)	0
Sepsis	2 (1.7)	0	2 (2.3)	0
Respiratory failure	1 (0.8)	1 (0.8)	0	0
Brain oedema	1 (0.8)	1 (0.8)	1 (1.2)	0
Acute respiratory distress syndrome	1 (0.8)	0	2 (2.3)	0
Malignant neoplasm progression	1 (0.8)	0	1 (1.2)	0
Pleural effusion	1 (0.8)	0	0	0
Acute myocardial infarction	1 (0.8)	0	0	0
Arteriosclerosis coronary artery	1 (0.8)	0	0	0
Ventricular tachycardia	1 (0.8)	0	0	0
Hemorrhage intracranial	1 (0.8)	0	0	0
Gastrointestinal hemorrhage	1 (0.8)	0	0	0
Intra-abdominal hemorrhage	1 (0.8)	0	0	0

	Phase 3 Parts A/B Combined			
	Sulbactam-Durlobactam (N=119) n (%)		Sulbactam-Durlobactam (N=119) n (%)	
Preferred Term	**≤ 28 days**	**> 28 days**	**≤ 28 days**	**> 28 days**
Thrombosis mesenteric vessel	1 (0.8)	0	0	0
Peripheral artery thrombosis	1 (0.8)	0	0	0
Shock	1 (0.8)	0	0	0
Shock hemorrhagic	1 (0.8)	0	0	0
Cardiac arrest	0	1 (0.8)	2 (2.3)	0
Cerebral hemorrhage	0	1 (0.8)	1 (1.2)	0
Encephalitis	0	1 (0.8)	0	0
Alcohol poisoning	0	1 (0.8)	0	0
Pneumonia	0	0	5 (5.8)	0
Acinetobacter sepsis	0	0	1 (1.2)	0
Pneumonia pseudomonal	0	0	1 (1.2)	0
Concomitant disease progression	0	0	1 (1.2)	0
Cerebrovascular accident	0	0	1 (1.2)	0
Ischemic stroke	0	0	1 (1.2)	0
Intestinal ischemia	0	0	1 (1.2)	0
Weaning failure	0	0	1 (1.2)	0
Pulmonary embolism	0	0	0	2 (2.3)
Acute respiratory failure	0	0	0	1 (1.2)
Pseudomonas infection	0	0	0	1 (1.2)

Note: All Phase 3 patients received background therapy of 1.0 g/1.0 g imipenem/cilastatin IV infused over 1 hour every 6 hours adjusted for renal function. One patient received sulbactam-durlobactam in both Parts A and B of the Phase 3 trial and is counted twice.
AE=adverse event; IV=intravenously.

8.10 Primary Safety Objective: Incidence of Nephrotoxicity as Measured by Modified RIFLE Criteria

The primary safety objective of the Phase 3 trial was achieved with a significant reduction in incidence of nephrotoxicity, based on modified RIFLE criteria, in sulbactam-durlobactam-treated patients compared with colistin-treated patients in Part A with a treatment difference of 24.4% (13.2% vs 37.6%; p=0.0002; Table 29). In the colistin group, the percentage of patients was higher in the Risk (R) category, as well as in the more severe categories of Injury (I) and Failure (F). Two (2.2%) patients in the sulbactam-durlobactam group were assigned Loss (L: persistent acute renal failure or

complete loss of function for > 4 weeks) by the Investigators on Day 1 and on Day 3 of treatment.

The modified RIFLE criteria include:

- Risk (R): increased creatinine level 1.5x or glomerular filtration rate (GFR) decreased > 25%,
- Injury (I): increased creatinine level 2x or GFR decreased > 50%,
- Failure (F): increased creatinine level 3x, GFR decreased > 75%, or creatinine level ≥ 4 mg/dL,
- Loss (L): persistent acute renal failure or complete loss of function for > 4 weeks, and
- End-Stage Kidney Disease (ESKD; E): ESKD for > 3 months.

Table 29: Phase 3 Trial: Incidence of Nephrotoxicity as Measured by Modified RIFLE Criteria (Safety Population, Excluding Patients with Chronic Hemodialysis at Baseline)

	Part A			Part B
Category Modified RIFLE Criteria	Sulbactam-Durlobactam (N=91) n (%)	Colistin (N=85) n (%)	P-value[a]	Sulbactam-Durlobactam (N=26) n (%)
Patients with nephrotoxicity	12 (13.2)	32 (37.6)	0.0002	3 (11.5)
Risk (R)	6 (6.6)	13 (15.3)	-	1 (3.8)
Injury (I)	2 (2.2)	14 (16.5)	-	1 (3.8)
Failure (F)	2 (2.2)	5 (5.9)	-	1 (3.8)
Loss (L)	2 (2.2)[b]	0	-	0
ESKD (E)	0	0	-	0

a. p-value was obtained based on a Chi-Square test for treatment group differences (Part A).
b. Loss (L) was assigned by the Investigators on Day 1 and Day 3.
Note: For the patients who transferred from Part A to Part B, events that occurred before the date of transfer were summarized in Part A, and events that occurred on or after the date of transfer were summarized in Part B. All Phase 3 patients received background therapy of 1.0 g/1.0 g imipenem/cilastatin IV infused over 1 hour every 6 hours adjusted for renal function. If patients had multiple RIFLE events during post-baseline visits, the patient was counted only once at the highest severity.
GFR=glomerular filtration rate; IV=intravenously; RIFLE=Risk-Injury-Failure-Loss-End-stage kidney disease.

Consistent with the RIFLE assessment, the incidence and severity of renal and urinary disorders were lower in the sulbactam-durlobactam group for Parts A and B compared to the colistin group (Table 30).

Table 30: Phase 3 Trial: Incidence and Severity of Renal and Urinary Disorders (Safety Population)

System Organ Class Severity	Part A Sulbactam-Durlobactam (N=91) n (%)	Part A Colistin (N=86) n (%)	Part B Sulbactam-Durlobactam (N=28) n (%)
Renal and urinary disorders	9 (9.9)	27 (31.4)	3 (10.7)
Mild	4 (4.4)	12 (14.0)	1 (3.6)
Moderate	4 (4.4)	8 (9.3)	1 (3.6)
Severe	1 (1.1)	7 (8.1)	1 (3.6)

8.11 Adverse Events in Subgroups

There were no clinically relevant differences in AEs by subgroup based on analyses of age, sex, race, ethnicity, BMI, geographic region, and renal impairment.

Across treatment groups, there was a higher overall incidence of AEs in patients with moderate or severe renal impairment compared with those with no or mild renal impairment.

8.12 Adverse Events of Special Interest

In consideration of the potential risks or safety concerns based on the drug class for sulbactam-durlobactam, 7 targeted SMQs were reviewed in the Phase 3 trial. These 7 targeted SMQs included AEs identified for acute renal failure, convulsions, sepsis, infective pneumonia, drug-related hepatic disorders, hypersensitivity, and pseudomembranous colitis.

In the Phase 3 trial, the incidences of TEAEs were similar between the sulbactam-durlobactam and colistin groups based on the SMQs for infective pneumonia, drug-related hepatic disorders, hypersensitivity, and pseudomembranous colitis (Table 31). The incidences of TEAEs were lower in the sulbactam-durlobactam group compared with the colistin group based on the SMQs for acute renal failure, convulsions, and sepsis.

Table 31: Overall Summary of Targeted SMQs (Safety Population)

SMQ, n (%)	Sulbactam-Durlobactam Parts A and B	Colistin
Acute renal failure	15 (12.6)	33 (38.4)
Convulsions	3 (2.5)	6 (7.0)
Sepsis	20 (16.8)	19 (22.1)
Infective Pneumonia	30 (25.2)	20 (23.3)
Drug-related hepatic disorders	24 (20.2)	20 (23.3)
Hypersensitivity	18 (15.1)	10 (11.6)
Pseudomembranous Colitis	19 (16.0)	14 (16.3)

SMQ=Standardized Medical Dictionary for Regulatory Activities Query.

8.12.1 Acute Renal Failure SMQ

Lower incidence of TEAEs based on the acute renal failure SMQ was observed in the sulbactam-durlobactam group (15 patients, 12.6%) compared with the colistin group (33 patients, 38.4%). Acute kidney injury and blood creatinine increased were each reported in 4 (3.4%) patients in the sulbactam-durlobactam group, compared with 11 (12.8%) patients and 7 (8.1%) patients, respectively, in the colistin group. Most TEAEs in this SMQ were assessed as mild or moderate in severity, not related to study drug, and resolved with no change in study drug. One patient in the sulbactam-durlobactam and 2 patients in the colistin group had SAEs of acute kidney injury.

8.12.2 Convulsions SMQ

TEAEs based on the convulsions SMQ were reported in 3 (2.5%) patients treated with sulbactam-durlobactam and 6 (7.0%) patients treated with colistin. All of the events occurred in Part A. The incidence of seizure was higher in the colistin group (6 patients, 7.0%) compared with the sulbactam-durlobactam group (1 patients, 0.8%). Other TEAEs in this SMQ, were epilepsy and generalized tonic-clonic seizure and were reported in 1 (0.8%) patient each treated with sulbactam-durlobactam.

Three patients in the colistin group had seizures reported as a SAE; the events were assessed as mild for 1 patient and severe for the other 2 patients. In the colistin group, all seizures reported as a SAE were considered not related to study drug (but related to imipenem/cilastatin for 2 patients). Study drug was withdrawn for 2 of the patients and the events resolved (study drug action was not applicable for the other patient, and the event was reported as not resolved).

8.12.3 Emergent and Super Infections

8.12.3.1 Sepsis SMQ

The overall incidence of events in the sepsis SMQ in the sulbactam-durlobactam group (20 patients, 16.8%) was lower than that in the colistin group (19 patients, 22.1%). The most commonly reported event in this SMQ in both groups was septic shock, which was

reported in 9 (7.6%) patients in the sulbactam-durlobactam group and 8 (9.3%) patients in the colistin group. Other events in this SMQ reported in > 1 patient in either group were multiple organ dysfunction syndrome (4 [3.4%] patients in the sulbactam-durlobactam group and 4 [4.7%] patients in the colistin group), sepsis (2 [1.7%] patients in the sulbactam-durlobactam group and 3 [3.5%] patients in the colistin group), staphylococcal bacteremia (2 [1.7%] patients in the sulbactam-durlobactam group and 1 [1.2%] patients in the colistin group), and *Klebsiella* sepsis (2 [1.7%] patients in the sulbactam-durlobactam group).

Ten patients in the sulbactam-durlobactam group and 12 patients in the colistin group had SAEs based on this SMQ that led to death; all of the events were assessed as not related to study drug.

8.12.3.2 Infective Pneumonia SMQ

The overall incidences of infective pneumonia events were similar between the sulbactam-durlobactam and colistin groups (30 patients [25.2%] vs 20 patients [23.3%]). In both groups, the most commonly reported events in this SMQ were pneumonia pseudomonal (6 patients [5.0%] in the sulbactam-durlobactam group and 4 patients [4.7%] in the colistin group), and pneumonia (5 patients [4.2%] in the sulbactam-durlobactam and 5 patients [5.8%] in the colistin group).

The preferred terms of pneumonia bacterial and atelectasis each were reported in 4 patients (3.4%) in the sulbactam-durlobactam group and 3 patients [3.5%] and 0 patients, respectively, in the colistin group. *Candida* pneumonia was reported in 3 patients (2.5%) and coronavirus infection, infectious pleural effusion, pleural effusion, pneumonia *Acinetobacter*, staphylococcal infection, and staphylococcal test positive each were reported in 2 patients (1.7%) in the sulbactam-durlobactam group; coronavirus infection was also reported in 3 patients [3.5%] in the colistin group. Both patients with pneumonia *Acinetobacter* tested negative at EOT then positive during the safety follow-up. Both cases were relapse/recurrent.

No other events in this SMQ were reported in more than 1 patient in either the sulbactam-durlobactam or colistin groups. The majority of AEs in this SMQ were mild or moderate in severity and not related to study drug. One patient in the sulbactam-durlobactam group and 7 patients in the colistin group had events based on this SMQ that led to death.

8.12.4 Drug-Related Hepatic Disorders SMQ

The most commonly reported TEAEs in the drug-related hepatic disorders SMQ were ALT increased, aspartate aminotransferase (AST) increased, and blood bilirubin increased, each of which was reported in 4 (3.4%) patients treated with sulbactam-durlobactam and 2 (2.3%) patients treated with colistin. Hepatic function abnormal and gamma-glutamyl transferase (GGT) increased were each reported in 3 (2.5%) patients treated with sulbactam-durlobactam. In the colistin group, hepatic function abnormal was reported in 2 (2.3%) patients and GGT increased was reported in 1 (1.2%) patient.

Liver injury was reported in 2 (1.7%) patients treated with sulbactam-durlobactam and 4 (4.7%) patients treated with colistin. A liver function test abnormal was reported in 1 (0.8%) patient treated with sulbactam-durlobactam and 3 (3.5%) patients treated with colistin. No other TEAEs based on this SMQ were reported in > 2 patients in any treatment group.

The majority of events based on the drug-related hepatic disorders SMQ were mild or moderate in severity, non-serious, and resolved with no action taken with study drug.

8.12.5 Hypersensitivity SMQ

In the Phase 3 trial, TEAEs in the hypersensitivity SMQ were reported in 18 (15.1%) patients in the sulbactam-durlobactam group and 10 (11.6%) patients in the colistin group. The most commonly reported TEAEs in this SMQ were rash (4 patients [3.4%] in the sulbactam-durlobactam group and 2 patients [2.3%] in the colistin group), respiratory failure (3 patients [2.5%] in the sulbactam-durlobactam group and 1 patient [1.2%] in the colistin group), and conjunctivitis (3 patients [2.5%] in the sulbactam-durlobactam group).

No other TEAEs based on this SMQ were reported in > 1 patient in either treatment group. The majority of events in this SMQ were assessed as mild or moderate, unrelated to study drug and resolved.

8.12.6 Pseudomembranous Colitis SMQ

The incidences of TEAEs in the pseudomembranous colitis SMQ were similar overall between the sulbactam-durlobactam and colistin groups (19 patients [16.0%] vs 14 patients [16.3%]). Diarrhea was the most commonly reported event within this SMQ in both groups (17 patients [14.3%] in the sulbactam-durlobactam group and 9 patients [10.5%] in the colistin group). *C. difficile* colitis and antibiotic-associated colitis each were reported in 1 patient (0.8%) in the sulbactam-durlobactam group and in 3 patients (3.5%) and 2 patients (2.3%), respectively, in the colistin group. No other TEAE in this SMQ was reported in the sulbactam-durlobactam group.

8.13 QT Prolongation Assessments

Thorough QTc Study: A 24-hour Holter monitoring sub-study in healthy participants was conducted for the cardiodynamic evaluation of durlobactam on cardiac repolarization (Study CS2514-2018-0003). Durlobactam at a supratherapeutic dose of 4.0 g had no clinically relevant effects on studied ECG parameters. Based on the concentration-QTc analysis, an effect on ΔΔQTcF exceeding 10 ms can be excluded within the observed range of durlobactam plasma concentration up to approximately 190 µg/mL, which is approximately 7-fold higher than the steady state geometric mean C_{max} in patients with normal renal function.

8.14 Electrocardiogram Findings

No unexpected safety signals were observed based on longitudinal review of ECG parameters. No notable changes in ECG parameters over time were observed in patients treated with sulbactam-durlobactam versus patients treated with colistin.

Phase 3 Trial: The incidence of QTcF values > 450 msec was similar between the sulbactam-durlobactam and colistin groups. Eight of 119 (6.7%) patients in the sulbactam-durlobactam group and 6/86 (7.0%) patients in the colistin group had worst post-baseline high QTcF > 500 msec. The incidences of ECG parameter-related AEs were low. TEAEs associated with ECG abnormalities that occurred in ≥ 2% of patients in any active treatment group were atrial fibrillation and ECG QT prolonged (3/119 [2.5%] patients each) in the sulbactam-durlobactam group. In the colistin group, the most commonly reported AE associated with ECG abnormalities was atrial fibrillation in 2/86 (2.3%) patients.

QTcF increases from baseline of > 60 msec were more frequent in the sulbactam-durlobactam group of the Phase 3 trial than in the colistin group (17/119 [14.3%] patients vs 9/86 [10.5%] patients), though the incidence of QTcB values > 60 msec were similar between the groups (16/119 [13.4%] patients in the sulbactam-durlobactam group vs 11/86 [12.8%] patients in the colistin group).

8.15 Laboratory Findings

No unexpected safety signals were observed based on longitudinal review of liver function tests (LFTs), renal function tests, urinalysis, and other chemistry parameters in this critically ill population in the Phase 3 trial. Over time, no notable changes were observed in these chemistry laboratory parameters in patients treated with sulbactam-durlobactam versus colistin.

8.15.1 Liver Function

The overall incidences of shifts to elevated post-baseline LFT values were comparable for the sulbactam-durlobactam and colistin groups, although the incidence of shifts to values > 5 × upper limit of normal (ULN) tended to be higher in the sulbactam-durlobactam group. For patients with low, normal, or high values at baseline, incidences of shifts to high or higher LFT values were comparable in the sulbactam-durlobactam and colistin groups. In both treatment groups, most of the shifts in alkaline phosphatase (ALP), ALT, AST, bilirubin, and GGT were to values to ≤ 3 × ULN.

- Three (2.5%) patients in the sulbactam-durlobactam group and 1 (1.2%) patient in the colistin group met Hy's Law laboratory criteria. None were considered to be related to study drug, and in all cases in the sulbactam-durlobactam group, Hy's Law criteria was not satisfied due to plausible alternative explanations.
- The most commonly reported LFT-associated AEs in the sulbactam-durlobactam group were ALT increased, AST increased, and blood bilirubin increased in 4 (3.4%) patients each, and GGT increased in 3 (2.5%) patients. In the colistin

group, the most commonly reported AE associated with LFT abnormalities was liver function test abnormal in 3 (3.5%) patients.

8.15.2 Renal Function

Shifts in renal function parameters from baseline tended to vary between treatment groups and by study populations. A lower incidence of shifts to worse values in renal function tests was observed in the sulbactam-durlobactam group compared with the colistin group. Similar results were observed when all patients with worsening values from baseline were considered, regardless of whether the baseline value was normal.

- Among patients with normal values at baseline, shifts to low CL_{CR} values were observed in 30.0% of patients in the sulbactam-durlobactam group compared with 47.4% of patients in the colistin group. Shifts to high creatinine values were observed in 15.2% of patients in the sulbactam-durlobactam (all to ≤ 3 × ULN) group compared with 40.5% of patients in the colistin group (38.1% to ≤ 3 × ULN, 2.4% to > 3 to ≤ 5 × ULN).
- Incidences of shifts to high values for urea nitrogen also were lower in the sulbactam-durlobactam group (19.2%) compared with the colistin group (48.5%).
- Shifts to low CL_{CR} values were observed in 14.0% of patients in the sulbactam-durlobactam group compared with 48.1% of patients in the colistin group. Shifts to high creatinine values to ≤ 3 × ULN, > 3 to ≤ 5 × ULN, and > 5 × ULN, respectively, were observed in 9.5%, 2.0%, and 1.9% of patients in the sulbactam-durlobactam group compared with 28.8%, 3.8%, and 0 patients in the colistin group. The incidences of shifts to high values for urea nitrogen also were lower in the sulbactam-durlobactam group than the colistin group.
- The most commonly reported AEs associated with renal function laboratory abnormalities in the sulbactam-durlobactam group were blood creatinine increased in 4 (3.4%) patients and proteinuria in 3 (2.5%) patients.
- In the colistin group, the most commonly reported AE associated with renal function laboratory abnormalities was blood creatinine increased in 7 (8.1%) patients.

8.15.3 Other Chemistry Parameters

Shifts in other chemistry parameters from baseline tended to vary between treatment groups and by study populations. The incidence of shifts to high lactate dehydrogenase (LDH) was greater in the sulbactam-durlobactam group (65.6%) compared with the colistin group (51.6%). The incidences were lower in the sulbactam-durlobactam group compared with the colistin group for shifts to low albumin (40.0% vs 66.7%), low potassium (31.9% vs 42.6%), low protein (45.5% vs 59.1%), and low sodium (28.6% vs 44.7%). Findings were similar when including patients with worsening of abnormal baseline values in addition to those with shifts from normal baseline values.

- The most commonly reported AEs associated with other chemistry parameters in the sulbactam-durlobactam group were hypokalemia in 11 (9.2%) patients; hyponatremia and hyperkalemia in 4 (3.4%) patients each; and hypernatremia, blood albumin decreased, hypoglycemia, and hyperglycemia in 3 (2.5%) patients each.
- In the colistin group, the most commonly reported AEs associated with other chemistry parameters were hypokalemia in 9 (10.5%) patients; hyponatremia, hypomagnesemia, and hypocalcemia in 4 (4.7%) patients each; and hypernatremia and hyperchloremia in 3 (3.5%) patients each.

8.16 Safety Conclusions

The primary safety data supporting the proposed indication for sulbactam-durlobactam in adults for the treatment of HABP and VABP caused by susceptible strains of ABC is derived from the Phase 3 trial (CS2514-2017-0004) in patients with ABC infections.

No unexpected safety signals were observed based on the analyses of TEAEs. The types and incidences of TEAEs reported in the Phase 3 trial were consistent with expectations for the population of critically ill patients and were characteristic of the pharmacological class. Moreover, the overall incidence of treatment-related AEs was lower in patients treated with sulbactam-durlobactam compared to those treated with colistin (12.6% vs 30.2%). There were also fewer SAEs, and TEAEs leading to study drug discontinuation with sulbactam-durlobactam compared to colistin.

The primary safety objective for the Phase 3 trial was met and showed a statistically significant lower incidence (p=0.0002) in nephrotoxicity based on modified RIFLE criteria in patients treated with sulbactam-durlobactam compared with patients treated with colistin (13.2% vs 37.6%). Supportive safety data are derived from the 7 other clinical studies.

AESIs were assessed by SMQs for acute renal failure, convulsions, sepsis, infective pneumonia, drug-related hepatic disorders, hypersensitivity, and pseudomembranous colitis. In the Phase 3 trial, the incidences of AESIs were similar between the sulbactam-durlobactam and colistin groups based on the SMQs for infective pneumonia, drug-related hepatic disorders, hypersensitivity, and pseudomembranous colitis. The incidences of AESIs were lower in the sulbactam-durlobactam group compared with the colistin group based on the SMQs for acute renal failure, convulsions, and sepsis.

In addition, no unexpected safety signals or notable changes over time of longitudinal reviews of LFTs, renal function tests, urinalysis, other chemistry parameters, or electrocardiograms were observed. In this critically ill patient population, sulbactam-durlobactam demonstrated a favorable safety profile and was well tolerated with no major safety concerns.

9 POST-APPROVAL STUDIES

Based on an agreed pediatric study plan with the Division, pediatric studies in children 0 to < 17 years of age are deferred until efficacy and safety have been demonstrated in the adult population. Entasis proposes a Phase 1 study to assess the pharmacokinetics, safety and tolerability of sulbactam-durlobactam in children from birth to < 17 years who are receiving systemic antibiotic therapy for suspected or confirmed infection.

To support dosing in the youngest pediatric age group, birth to < 1 year of age, the Sponsor will undertake a repeat dose toxicity study in suckling rats of post-natal day age 10–11 days at study start using either daily bolus intravenous administration and/or subcutaneous administration.

10 REAL-WORLD DATA

An EAP for patients who had a documented serious and immediately life-threatening infection caused by drug-resistant *Acinetobacter* was initiated in May 2020 and is currently active. This program permits access to investigational sulbactam-durlobactam for treatment outside of the clinical trial when no comparable or satisfactory alternative therapy option was available.

All patients had severe, life-threatening polymicrobial infections. A significant proportion of patients had respiratory or multi-organ failure from Covid infection, burn, or post-surgical wound or bone infections. The length of hospital stays for these patients prior to initiation of treatment with sulbactam-durlobactam ranged from 13–116 days. Of the 12 patients treated, sulbactam-durlobactam was generally well tolerated, and no SAEs related to sulbactam-durlobactam were reported (Table 32). One event of thrombocytopenia was reported as serious and determined by the Investigator to be related to another agent. All patients in the EAP received antibiotics in addition to sulbactam-durlobactam. The maximum duration of sulbactam-durlobactam therapy was 42 days. Approximately half of the patients survived in this patient population suffering from serious and immediately life-threatening infections.

Table 32: Summary of Patients in the Sulbactam-Durlobactam Expanded Access Program

Age (Years)/Sex	Location of ABC Infection	Days of Sulbactam-Durlobactam Treatment	ABC Infection Outcome	Patient Outcome
43/Female	VABP	1	Not cleared	Expired
21/Male	VABP	3	Unknown	Comfort care, patient expired
66/Male	Pneumonia	4	Unknown	Expired
57/Female	Sternal wound	6	Unknown	Expired
70/Male	VABP, bacteremia	7	Cleared	Expired (due to COVID-19)
34/Female	VABP, bacteremia	9	Cleared	Recovering
65/Male	VABP, bacteremia	13	Cleared	Expired (due to COVID-19)
50/Male	VABP, empyema	13	Cleared	Recovered; discharged
62/Male	VABP	14	Cleared	Recovered
55/Female	VABP	14	Cleared	Recovered; discharged
44/Male	Wound, burn, bacteremia	23	Cleared	Recovered; discharged
75/Female	Surgical site	42	Cleared	Recovered; discharged

ABC=*Acinetobacter baumannii-calcoaceticus* complex; VABP=ventilator-associated bacterial pneumonia.

11 BENEFIT-RISK CONCLUSIONS

11.1 Therapeutic Context

The US Centers for Disease Control and Prevention and the World Health Organization have characterized carbapenem-resistant *A. baumannii* an urgent public health threat in US healthcare facilities and a priority pathogen for which new antibiotics are urgently needed, respectively.

The lack of safe and efficacious therapies to treat serious and life-threatening infections due to ABC is a high unmet medical need. For serious ABC infections, clinicians utilize available antibiotics at doses higher than approved for use, antibiotics that had fallen out of use due to toxicity but brought back out of lack of alternatives, and antibiotics that have not demonstrated mortality advantages, often in combination.

11.2 Benefits

Sulbactam-durlobactam provides a clinically meaningful benefit in both safety and efficacy as compared to existing therapies for the treatment of ABC infections, and therefore, has the potential to address this significant unmet need.

The primary evidence of efficacy and safety for the proposed indication is based on a rigorous, adequate, well-controlled, and pathogen-focused Phase 3 clinical trial in patients with infections caused by ABC, including MDR and carbapenem-resistant strains. The patient population included in the Phase 3 clinical trial is representative of the population that would be expected to receive sulbactam-durlobactam, if approved, and the clinical trial results are generalizable to clinical practice with this pathogen.

Sulbactam-durlobactam shows potent in vitro activity against global, contemporary ABC isolates. In addition, sulbactam-durlobactam shows a favorable microbiological response in patients dosed with sulbactam-durlobactam with ABC isolates testing with sulbactam-durlobactam MIC values of ≤ 4 µg/mL, the proposed susceptibility breakpoint. No differences in microbiological response were observed based on geographical location or site of infection.

In the active-controlled and pathogen-focused Phase 3 clinical trial in patients with ABC infections, including MDR and carbapenem-resistant strains, sulbactam-durlobactam met the primary efficacy endpoint of noninferiority for 28-day all-cause mortality in the primary analysis population. The mortality rate was 19.0% (12/63 patients) in the sulbactam-durlobactam group compared to 32.3% (20/62 patients) in the colistin group (treatment difference of −13.2%; 95% CI: −30.0%, 3.5%). All secondary endpoint analyses, including 28-day and 14-day all-cause mortality and clinical and microbiological responses at EOT, TOC, and LFU were consistent with the primary efficacy analysis across populations. In addition, subgroup analyses based on demographic and baseline characteristics consistently showed a favorable response in patients treated with sulbactam-durlobactam compared with those treated with colistin.

The primary safety objective for the Phase 3 trial was met and showed a statistically significant lower incidence (p=0.0002) of nephrotoxicity based on modified RIFLE criteria in patients treated with sulbactam-durlobactam (12/91 [13.2%]) compared with patients treated with colistin (32/85 [37.6%]). The overall incidence of treatment-related AEs in this trial was lower in patients treated with sulbactam-durlobactam (12/119 [12.6%]) compared to those treated with colistin (26/86 [30.2%]).

11.3 Risks

No unexpected safety signals were observed based on the analyses of AEs, laboratory tests, vital signs, or ECGs. The types and incidences of TEAEs reported in the Phase 3 trial were consistent with expectations for the population of critically ill patients and the β-lactam/β-lactamase inhibitor drug class.

Potential risks associated with the pharmacological class and with the use of sulbactam-durlobactam include:

- Diarrhea, including CDAD, and
- Hypersensitivity (including anaphylactic) reactions.

Diarrhea was the only treatment-related AE reported in more than 1 patient treated with sulbactam-durlobactam in Part A of the Phase 3 trial. The incidence was similar in the sulbactam-durlobactam (4/91 patients, 4.4%) and colistin (4/86 patients, 4.7%) groups.

CDAD has been reported with use of nearly all antibacterial agents, including sulbactam-durlobactam, and may range in severity from mild diarrhea to fatal colitis. In Part A of the Phase 3 trial, the incidence of at least 1 TEAE (all causality) based on the pseudomembranous colitis SMQ was 16/91 (17.6%) patients in the sulbactam-durlobactam group compared with 14/86 (16.3%) in the colistin group. Events based on this SMQ reported in the sulbactam-durlobactam group were diarrhea and antibiotic associated colitis. The incidences of these events in the sulbactam-durlobactam and colistin groups, respectively, were 15/91 (16.5%) and 9/86 (10.5%) patients for diarrhea and 1/91 (1.1%) and 2/86 (2.3%) patients for antibiotic associated colitis.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving β-lactam antibiotics. These reactions are more likely to occur in individuals with a history of β-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Hypersensitivity was observed in patients treated with sulbactam-durlobactam in clinical studies. In Part A of the Phase 3 trial, the incidence of at least 1 TEAE (all causality) based on the hypersensitivity SMQ was 15/91 (16.5%) in the sulbactam-durlobactam group and 10/86 (11.6%) in the colistin group. As described in Sections 8.6, 8.8, and 8.9, anaphylactic shock was reported in 1/91 (1.1%) patient in the sulbactam-durlobactam group which was reported on Day 9 of study treatment and resolved on the same day.

Other Information Related to Risks

The treatment-related SAEs in the sulbactam-durlobactam group in the Phase 3 trial were pneumonia in 1 patient in Part A and neutropenia in 1 patient in Part B. No treatment-related deaths were reported in patients treated with sulbactam-durlobactam.

No clinically relevant differences in TEAEs were found in subgroup analyses based on age, sex, race, ethnicity, BMI, geographic region, and renal impairment. In both the sulbactam-durlobactam and placebo/colistin groups, a higher overall incidence of TEAEs was observed for patients with moderate or severe renal impairment (CL_{CR} < 60 mL/min) compared with those with no or mild renal impairment (CL_{CR} ≥ 60 mL/min), which is consistent with the population PK analysis finding of renal function as a clinically relevant covariate. Therefore, dose adjustments are recommended in patients with CL_{CR} < 45 mL/min and those with augmented renal clearance.

Sulbactam-durlobactam is unlikely to cause DDIs related to cytochrome P450 and therefore risks for DDIs are limited.

11.4 Benefit-Risk Assessment

The pharmacology, PK, and safety of durlobactam, both alone and in combination with sulbactam, have been well characterized in a comprehensive series of in vitro and in vivo nonclinical studies. These studies have defined the key pharmacological properties of sulbactam-durlobactam, the PK, distribution, metabolism, excretion, and potential to cause DDIs, as well as the key test article-related safety findings and the reversibility of these changes. The efficacy and safety of sulbactam-durlobactam have been characterized in clinical trials. The risks identified are clinically well known, and easily diagnosed and treated in routine clinical care.

These data collectively provide sound scientific and substantial evidence of safety and efficacy of sulbactam-durlobactam for the intended and appropriate use of the product for the proposed indication. The nonclinical and clinical safety and efficacy data demonstrate a favorable benefit-risk profile and address the statutory standard for safety as outlined in the FDA August 2017 Guidance on Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases and the May 2022 Questions and Answers.

For this serious and life-threatening bacterial infection in patients with a high unmet medical need, the totality of data supports that sulbactam-durlobactam provides a clinically meaningful benefit in both safety and efficacy as compared to existing therapies for the treatment of ABC infections and therefore has the potential to address this significant unmet need.

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13 APPENDICES

13.1 Phase 3 Trial Inclusion and Exclusion Criteria

13.1.1 General Inclusion Criteria

For inclusion into the trial, patients were required to fulfill all of the following criteria, including specific inclusion criteria listed for Parts A and B. Patients must have had/been:

1. A signed informed consent;

   Note: If a study patient was unable to provide informed consent due to their medical condition, the patient's legally authorized representative may have consented on behalf of the study patient, or the decision could have been made according to the procedure permitted by local law and institutional standard operating procedures.

2. Male or female and ≥ 18 years of age;
3. A confirmed diagnosis of a serious infection and the expectation, in the judgment of the Investigator, that the patient's infection would require treatment with intravenous (IV) antibiotics;
4. A known infection caused by *Acinetobacter baumannii-calcoaceticus* complex (ABC; bacteremia, hospital-acquired bacterial pneumonia [HABP], ventilator-associated bacterial pneumonia [VABP], ventilated pneumonia [VP], complicated urinary tract infection [cUTI] or acute pyelonephritis [AP], or surgical or post-traumatic wound infections) as either a single pathogen or member of a polymicrobial infection based on evidence from culture or, if available, rapid diagnostic test from a sample collected within 72 hours prior to randomization (HABP/VABP/VP patients), and 1 of the following:

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

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

   Note: Rapid testing of respiratory specimens utilizing Biofire® FilmArray® 2.0 Pneumonia Panel (BPP) technology was recommended to enable early identification of ABC pneumonia. Patients could be randomized based on the results of the BPP rapid test while awaiting results of cultures from the local laboratory. However, if the respiratory sample did not grow ABC in the local microbiology laboratory culture, these patients were withdrawn from the study drug treatment.

   Note: Isolation of ABC from pleural effusion (empyema) was allowed, if concurrent pulmonary infiltrate was confirmed.

5. Acute Physiology and Chronic Health Evaluation (APACHE) II score between 10 and 30, inclusive, or Sequential Organ Failure Assessment (SOFA) score between 7 and 11, inclusive, at the time of diagnosis of infection. Patients who were not being treated in an intensive care unit (ICU) and could not have an APACHE II or SOFA score performed should have had a quick SOFA (qSOFA) score ≥ 2 for enrollment;
6. Expectation, in the judgment of the Investigator, that the patient would benefit from effective antibiotic therapy and appropriate supportive care for the anticipated duration of the study;
7. Women of childbearing potential (ie, not post-menopausal or surgically sterilized) must have had a negative highly sensitive urine or serum pregnancy test before randomization. Participating women of childbearing potential must have been willing to consistently use 1 highly effective method of contraception (i.e., condom, combined oral contraceptive, implant, injectable, indwelling intrauterine device, or a vasectomized partner) from Screening until at least 30 days after administration of the last dose of study drug.

13.1.1.1 Part A-Specific Inclusion Criteria

In addition to the general inclusion criteria listed above, patients may have enrolled in Part A if they met the following criteria. All patients were categorized in 1 infection type that was judged to be the primary infection by the Investigator:

1. Diagnosed with HABP, VABP, VP, and/or bacteremia, defined as:

HABP with ABC in Sputum/Respiratory Sample		
All of the following:	**And signs or symptoms evidenced by at least 2 of the following:**	**And at least 1 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 discharged from an LTAC or rehabilitation center; and • New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound was performed, a confirmatory X-ray or CT scan should have been 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).

1. Evidence of fever within 24 hours of the Screening Visit was acceptable if observed and documented by a healthcare provider.
ABC=*Acinetobacter baumannii-calcoaceticus* complex; CT=computed tomography; FiO2=fraction of inspired oxygen; HABP=hospital-acquired bacterial pneumonia; LTAC=long-term acute care; MRI=magnetic resonance imaging; pO_2=partial pressure of oxygen; WBC=white blood cell.

VABP with ABC in Sputum/Respiratory Sample		
All of the following:	**And signs or symptoms evidenced by at least 2 of the following:**	**And at least 1 of the following:**
• Onset of symptoms >48 hours after receiving ventilator support via an endotracheal (or nasotracheal) tube; • Required ventilator support; and • New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound was performed, a confirmatory X-ray or CT scan should have been 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/FiO_2 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 count (> 10,000/mm^3); • > 15% immature neutrophils (bands) regardless of total peripheral WBC count; or • Leukopenia (total WBC count < 4500/mm^3).

1. Evidence of fever within 24 hours of the Screening Visit was acceptable if observed and documented by a healthcare provider.
ABC=*Acinetobacter baumannii-calcoaceticus* complex; CT=computed tomography; FiO_2=fraction of inspired oxygen; MRI=magnetic resonance imaging; VABP=ventilator-associated bacterial pneumonia; WBC=white blood cell.

VP with ABC in Respiratory Sample		
All of the following:	**And signs or symptoms evidenced by at least 2 of the following:**	**And at least 1 of the following:**
• Required ventilator support; and • New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound was performed, a confirmatory X-ray or CT scan should have been 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).

1. Evidence of fever within 24 hours of the Screening Visit was acceptable if observed and documented by a healthcare provider.
ABC=*Acinetobacter baumannii-calcoaceticus* complex; CT=computed tomography; MRI=magnetic resonance imaging; VP=ventilated pneumonia; WBC=white blood cell.

Bacteremia with ABC	
All of the following:	**And at least 1 of the following:**
• Isolation of ABC from at least 1 blood culture collected from a peripheral vein or newly placed intravenous line.	• Fever[1] (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) or hypothermia (rectal/core temperature < 35°C [< 95°F]); • 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). • Tachycardia > 100 bpm; • Tachypnea > 25 breaths/minute; or • Hypotension, systolic < 90 mmHg.

1. Evidence of fever within 24 hours of the Screening Visit was acceptable if observed and documented by a healthcare provider.
ABC=*Acinetobacter baumannii-calcoaceticus* complex; bpm=beats per minute; WBC=white blood cell.

13.1.1.2 Part B-Specific Inclusion Criteria

Part B included patients with the following ABC infections: HABP, VABP, VP, or bacteremia who did not qualify for Part A, and cUTI/AP or surgical or post-traumatic wound infections.

1. Patients with HABP, VABP, VP, or bacteremia should have been considered for enrollment in Part B if they met ANY of the following criteria (a, b, c, or d), in addition to the general inclusion criteria listed in Appendix 13.1.1:

    a. Had an infection caused by ABC organisms known to be resistant to colistin or polymyxin B (defined as minimum inhibitory concentration [MIC] ≥4 µg/mL by a non-agar-based method);

    For known colistin- or polymyxin B-resistant infections, the following must have been satisfied:

    - Had a known resistant infection based on evidence from culture and susceptibility testing by a non-agar-based method within 72 hours prior to randomization, alone or as a single organism of a polymicrobial infection; AND received no more than 48 hours of an antimicrobial agent to which the ABC was susceptible prior to the first dose of study drug; or
    - Had documented clinical evidence of failure (i.e., clinical deterioration or failure to improve that was attributable to ABC

infection) after at least 48 hours of treatment with colistin or polymyxin B; or

b. Had known intolerance to colistin;

   Note: Patients whom the Investigator felt may have had a potential intolerance to colistin could have been enrolled in Part B on a case-by-case basis after discussion with the Medical Monitor; or

c. Had myasthenia gravis or another neuromuscular syndrome(s) that contraindicated colistin and was not ventilated;

   Note: Ventilated patients with myasthenia gravis or other neuromuscular syndromes where, in the opinion of the Investigator, colistin administration was reasonable were permitted for consideration for the study; or

d. Had acute kidney injury and was receiving renal replacement therapy at study entry.

2. Patients diagnosed with cUTI, AP, or surgical or post-traumatic wound infections may have enrolled in Part B if they met the general inclusion criteria listed in Appendix 13.1.1 as well as either a, b, c, d, or, e in addition to the indication requirements for f:

   a. Had an infection caused by ABC organisms known to be resistant to colistin or polymyxin B (defined as MIC ≥ 4 µg/mL by a non-agar-based method); or

   b. Had known intolerance to colistin;

      Note: Patients whom the Investigator felt may have had a potential intolerance to colistin could have been enrolled in Part B on a case-by-case basis after discussion with the Medical Monitor; or

   c. Had myasthenia gravis or another neuromuscular syndrome(s) that contraindicated colistin; or

   d. Had acute kidney injury and was receiving renal replacement therapy at study entry; or

   e. Had documented clinical evidence of failure (i.e., clinical deterioration or failure to improve) after at least 48 hours of treatment with a polymyxin-based regimen; and

   f. Was diagnosed with cUTI, AP, or surgical or post-traumatic wound infection, defined as:

cUTI with ABC		
At least 1 of the following:	**And at least 2 of the following signs and symptoms:**	**And at least 1 of the following:**
• Indwelling urinary catheter or intermittent bladder catheterization; • Neurogenic bladder with presence or history of urine residual volume of ≥ 100 mL; • Obstructive uropathy (e.g., nephrolithiasis, • tumor, fibrosis) that was expected to be medically or surgically treated within 48 hours post-randomization; • Azotemia due to intrinsic renal disease; or • Urinary retention in men due to previously diagnosed benign hypertrophy.	• Chills, rigors, or fever[1] (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]); • Elevated WBC count (> 10,000/mm^3) or left shift (> 15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; or • Lower abdominal pain or pelvic pain.	• Positive LCE on urinalysis; • WBC count ≥ 10 cells/mm^3 in unspun urine; or • WBC count ≥ 10 cells/hpf in urine sediment.

1. Evidence of fever within 24 hours of the Screening Visit was acceptable if observed and documented by a healthcare provider.
ABC=*Acinetobacter baumannii-calcoaceticus* complex; cUTI=complicated urinary tract infection; hpf=high-power field; LCE=leukocyte esterase; PMN=polymorphonuclear leukocyte; WBC=white blood cell.

AP with ABC	
Presence of an ascending tract infection including at least 2 of the following signs or symptoms:	**And at least 1 of the following:**
• Chills, rigors, or fever[1] (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]); • Elevated WBC count (> 10,000/mm^3) or left shift (> 15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; • Flank pain; or • Costovertebral angle tenderness on physical examination.	• Positive LCE on urinalysis; • WBC count ≥ 10 cells/mm^3 in unspun urine; or • WBC count ≥ 10 cells/hpf in urine sediment.

1. Evidence of fever within 24 hours of the Screening Visit was acceptable if observed and documented by a healthcare provider.
ABC=*Acinetobacter baumannii-calcoaceticus* complex; AP=acute pyelonephritis; hpf=high-power field; LCE=leukocyte esterase; PMN=polymorphonuclear leukocyte; WBC=white blood cell.

Surgical Wound Infection with ABC	
Superficial SSI meeting all of the following criteria:	**And at least 1 of the following regional or systemic signs of infection:**
• Followed clean surgery (elective, not emergency, nontraumatic, primarily closed, no acute inflammation, no break in technique, respiratory, gastrointestinal, biliary, and genitourinary tracts not entered); • Involved only the skin or subcutaneous tissue around the incision, did not involve fascia; • Occurred within 30 days after procedure; • Original surgical incision ≥ 3 cm; and • Purulent drainage (spontaneous or therapeutic) that was positive for ABC by culture with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2.	• Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI; • 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]); • WBC count ≥ 10,000/mm^3 or < 4000/mm^3; or • >15% immature neutrophils.

1. Evidence of fever within 24 hours of the Screening Visit was acceptable if observed and documented by a healthcare provider.
ABC=*Acinetobacter baumannii-calcoaceticus* complex; ABSSSI=acute bacterial skin and skin structure infection; SSI=surgical site infection; WBC=white blood cell.

Post-Traumatic Wound Infection with ABC	
Post-traumatic wound (including penetrating trauma) characterized by the following within 24 hours of Screening:	**And at least 1 of the following regional or systemic signs of infection:**
• Purulent drainage (spontaneous or therapeutic) that was positive for ABC by culture with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2.	• Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI; • 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]); • WBC count ≥ 10,000/mm^3 or <4000/mm^3; or • > 15% immature neutrophils.

1. Evidence of fever within 24 hours of the Screening Visit was acceptable if observed and documented by a healthcare provider.
ABC=*Acinetobacter baumannii-calcoaceticus* complex; ABSSSI=acute bacterial skin and skin structure infection; SSI=surgical site infection; WBC=white blood cell.

13.1.2 Exclusion Criteria

The following was regarded as criterion for exclusion from the trial. Patients must not have had:

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

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

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

   Note: If these organisms were identified but it was deemed by the Investigator that no treatment was warranted and their presence did not significantly change the prognosis of the patient, then the patient may have been considered for this study.

3. Pulmonary disease that precluded evaluation of a therapeutic response (such as lung cancer resulting in bronchial obstruction or on the same side as the pneumonia, active tuberculosis, cystic fibrosis, granulomatous disease, fungal

pulmonary infection, lung abscess, pleural empyema, post-obstructive pneumonia, or COVID-19 infection without clinical improvement);

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

4. Presence of suspected or confirmed deep seated bacterial infections such as bacterial Gram-negative osteomyelitis, endocarditis, or meningitis requiring prolonged therapy, as determined by history and/or physical examination;
5. Acute infective endocarditis due to Gram-positive bacteria that required urgent/emergent indication of surgery (i.e., heart failure because of valvular insufficiency or septic shock), or patients in whom surgery was contraindicated due to prohibitive risk for surgery due to comorbidities;
6. Irremovable implantable device or line thought to be the potential source of ABC infection;
7. Sustained shock with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 60 mmHg;

   Note: Patients who could maintain MAP ≥ 60 mmHg on a reasonable dose of pressors or were weaning off of pressors may have been considered. Patients who required more than the maximal dose of 2 vasopressors to maintain MAP ≥ 60 mmHg were ineligible. If vasopressors were weaned to below these levels, patient enrollment could have been reconsidered.

8. For patients to have been enrolled with the primary indication of HABP, VABP, or VP, any of the following conditions:
   a. Diagnosis of ventilator-associated tracheobronchitis; or
   b. Inability to provide proper respiratory specimens for culture. Respiratory samples from expectorated or induced sputum should have shown < 10 squamous epithelial cells and > 25 polymorphonuclear neutrophils per 100 x field.
9. For patients to have been enrolled with the primary indication of cUTI or AP, any of the following urologic conditions:
   a. Likely to receive ongoing antibacterial drug prophylaxis after treatment of cUTI (e.g., patients with vesico-uretal reflux);
   b. Suspected or confirmed prostatitis;
   c. Requirement for bladder irrigation with antibiotics or for antibiotics to be administered directly via urinary catheter;
   d. Previous or planned cystectomy or ileal loop surgery;

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

f. Complete, permanent obstruction of the urinary tract;

g. Suspected or confirmed perinephric or renal corticomedullary abscess;

h. Polycystic kidney disease; or

i. Any recent history of trauma to the pelvis or urinary tract.

10. Pregnant or breastfeeding women;

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

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

12. Receiving peritoneal dialysis;

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

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

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

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

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

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

18. Requirement for inhaled antibiotics;

19. Known history of human immunodeficiency virus infection and known recent cluster of differentiation 4 count < 200/mm^3 within the last year or presence of significant immunologic disease or dysfunction, as determined by a current diagnosis of an Acquired Immune Deficiency Syndrome-defining illness;
20. Presence of neutropenia (absolute neutrophil count < 500/mm^3) obtained from a local laboratory at Screening;
21. A QT interval corrected using Fridericia's formula (QTcF) ≥ 480 msec;
22. History of significant hypersensitivity or allergic reaction to any β-lactam, any contraindication to the use of cilastatin based on local approved prescribing information (e.g., Summary of Medicinal Product Characteristics), any contraindication to the excipients used in the respective formulations, or any contraindication to the use of β-lactam antibiotics;
23. Participation in a clinical study involving investigational medication or an investigational device within the last 30 days or 5 half-lives, whichever was longer, prior to Day 1;
24. Any condition that, in the opinion of the Investigator, would have compromised the safety of the patient or the quality of the data or required greater than 14 days of treatment with antibiotics;
25. Unable or unwilling, in the opinion of the Investigator, to comply with the Clinical Study Protocol;
26. Had previously received durlobactam in this study; or
27. For Part A only, patients with an infection known to be resistant to colistin or polymyxin B (defined as MIC ≥ 4 µg/mL by a non-agar-based method), with a known intolerance to colistin, or taking any drug that prevents them from receiving colistin.

13.2 Published Literature Supporting Non-Inferiority Margin

Table 33: Published Literature on Colistin-Based Therapy for Selection of Non-Inferiority Margin for Primary Efficacy Endpoint of the Phase 3 Trial

Treatment Reference	Population Studied	Mortality Rate
Colistin plus carbapenem		
Cheng A, Chuang YC, Sun HY, et al. Excess mortality associated with colistin-tigecycline compared with colistin-carbapenem combination therapy for extensively drug-resistant *Acinetobacter baumannii*: A multicenter prospective observational study. *Crit Care Med* 2015;43:1194-1204.	XDR; ~80% pneumonia or BSI	42%
Colistin plus carbapenem and colistin alone		
Yilmaz GR, Guven T, Guner R, et al. Colistin alone or combined with sulbactam or carbapenem against *A. baumannii* in ventilator-associated pneumonia. *J Infect Dev Countries* 2015;9(5):476-85.	MDR and XDR VAP	Colistin: 41% Colistin + carbapenem: 49%
Chuang YC, Cheng CY, Sheng WH, et al. Effectiveness of tigecycline-based versus colistin based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting; a match cohort analysis. *BMC Infectious Disease* 2014;14:102.	MDR VAP	Colistin: 50% Colistin + carbapenem: 47%
Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomized controlled trial. *Lancet Infect Dis* 2018;18:391–400.	CRAB	Colistin: 43% Colistin + meropenem: 45%
Colistin alone only		
Alvarez-Marin R, Lopez-Rojas R, Marques JA, Gomes MJ, et al. Colistin dosage without loading dose is efficacious when treating carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia caused by strains with high susceptibility to colistin. *PLoS One* 2016;11(12): e0168468. doi:10.1371/journal.pone.016846.	CRAB VAP	25%
Samrah S, Bastawi Y, Hayajneh W, et al. Impact of colistin-initiation delay on mortality of ventilator-associated pneumonia caused *A. baumannii*. *J Infect Dev Countries* 2016;10(10):1129-134.	XDR VAP	27%
Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and rifampin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: A multicenter randomized clinical trial. *Clin Infect Dis* 2013;57(3):349-58.	XDR	43%
Betrosian AP, Frantzeskaki F, Xanthaki A, et al. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multi-	MDR VAP	33%

drug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *J Infect* 2008;56:432-36.		
Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus Fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. *Antimicrob Ag Chemother* 2014;58(9):5598-601.	CRAB	57%
Zalts Ronen, Neuberger A, Hussein K, et al. Treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia: Retrospective comparison between intravenous colistin and intravenous ampicillin-sulbactam. *Am J Ther* 2016;23(1):e78-85.	CRAB VAP	26%
Garnacho-Montero J, Amaya-Villar R, Gutiérrez-Pizarraya A, et al. Vancomycin in combination with colistin in severe *A. baumannii* infections. *Chemotherapy* 2013;59:225–231.	CRAB VAP or BSI	50%

BSI=bacteremia; CRAB=carbapenem-resistant *Acinetobacter baumannii*; HAP=hospital-acquired pneumonia; MDR=multidrug-resistant; VAP=ventilator acquired pneumonia; XDR=extensively drug resistant.

Table 34: Published Literature on Untreated (Including Inappropriate Therapy) or Delayed Therapy

Reference	Population Studied	Mortality Rate
Lee HY, Chen CL, Wu SR, et al. Risk factors and outcomes analysis of *Acinetobacter baumannii* complex bacteremia in critical patients. *Crit Care Med* 2014;42:1081-88.	CRAB (~66% VAP)	87% (Inappropriate therapy)
Erbay A, Idil A, Gozel MG, et al. Impact of early appropriate antimicrobial therapy on survival in *Acinetobacter baumannii* bloodstream infections. *Int J Antimcirob Agents* 2009;34:757-79.	60% CRAB BSI (22% lung)	65%
Aydemir H, Celebi G, Piskin N, et al. Mortality attributable to carbapenem-resistant nosocomial *Acinetobacter baumannii* infections in a Turkish university hospital. *Jpn I Infect Dis* 2012;65:66-71.	CRAB (~70% pneumonia)	76%
Kwon KT, Oh WS, Song JH, et al. Impact of imipenem resistance on mortality in patients with *Acinetobacter* bacteremia. *J Antimicrob Chemother* 2007;59:525-30.	CRAB (~25% VAP)	73%

BSI=bacteremia; CRAB=carbapenem-resistant *Acinetobacter baumannii*; VAP=ventilator acquired pneumonia.