U.S. FOOD & DRUG ADMINISTRATION

Sulbactam-Durlobactam

New Drug Application 216974

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Antimicrobial Drugs Advisory Committee Meeting
April 17, 2023

Purpose of the Advisory Committee Meeting

- Today's goal is to discuss whether the data contained in the new drug application (NDA) for sulbactam-durlobactam (SUL-DUR) for injection support a favorable benefit-risk assessment for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) due to susceptible strains of *Acinetobacter* spp., including carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CRABC) organisms.

Clinical Context

- CRABC infections represent an unmet medical need in the U.S. due to the emergence and spread of *Acinetobacter* resistance and limited treatment options.[1]
- Nosocomial pneumonia is the most common disease caused by *Acinetobacter* spp. with approximately 50% of *Acinetobacter* healthcare associated infections in the United States caused by CRABC.[2]
- Patients with CRABC infections appear to have a higher risk of mortality than patients with carbapenem-susceptible *A. baumannii* infections, with overall mortality rates in HABP/VABP caused by CRABC ranging from approximately 45-60%.[3,4,5]

Regulatory Context

- The SUL-DUR development program is an example of a streamlined program for a targeted therapy for a high unmet-need pathogen, namely CRABC.
- For antibacterial drugs with the potential to treat serious infections in patients who have few or no available treatments, FDA may consider a more flexible program to facilitate development, provided there are adequate data to demonstrate that the drug is safe and effective and the statutory standards for approval are met.[6]

Phase 3 Clinical Trial Components

- Two components:
  - Part A: randomized, investigator-unblinded, assessor-blinded, non-inferiority, comparison of IV SUL-DUR versus IV colistin for treatment of HABP, VABP, ventilator pneumonia (VP) or bacteremia due to *Acinetobacter baumannii-calcoaceticus* complex organisms (ABC)
  - Part B: single-arm, evaluation of SUL-DUR for treatment of ABC-infected subjects who were resistant to colistin or who were ineligible for Part A due to other factors

Phase 3 Trial Part A: Design

- 1:1 Randomization
- Stratified by infection type, baseline disease severity, geographic region
- Background therapy: imipenem/cilastatin
- Study duration
  - Treatment period: 7 to 14 days
  - Follow-up period: 14 days
- Primary endpoint: 28-day all-cause mortality, assessed using a 20% noninferiority (NI) margin

Phase 3 Trial Part A: Results

- Part A demonstrated that SUL-DUR was non-inferior to colistin for 28-day all-cause mortality.

SUL-DUR	Colistin	Difference (95% CI)
12/63 (19.0%)	20/62 (32.3%)	-13.2% (-30.0%, **3.5%**)

- The primary analysis population was the CRABC microbiologically modified-intent to treat population (m-MITT).
- Approximately 96% of subjects in the CRABC m-MITT had HABP/VABP; only three subjects had bacteremia.

CI = confidence interval

Safety Profile

- Safety profile of SUL-DUR was generally consistent with other β-lactam/β-lactamase inhibitor drugs
- Safety database was limited in size
  - Less than 200 patients received SUL-DUR at the proposed dose and duration for the treatment of HABP/VABP
- Given the limited size of the safety database, if SUL-DUR is approved, postmarketing safety monitoring will be important in further assessing the safety profile of this product

Question for the Advisory Committee

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

References

1. CDC, 2019 AR Threats Report. www.cdc.gov/DrugResistance/Biggest-Threats.html.
2. Weiner-Lastinger, LM, S Abner, JR Edwards, AJ Kallen, M Karlsson, SS Magill, D Pollock, I See, MM Soe, MS Walters, and MA Dudeck, 2020, Antimicrobial-resistant pathogens associated with adult healthcare associated infections: Summary of data reported to the National Healthcare Safety Network, 2015-2017, Infect Control Hosp Epidemiol, 41(1):1-18.
3. Aydemir, H, D Akduman, N Piskin, F Comert, E Horuz, A Terzi, F Kokturk, T Ornek, and G Celebi, 2013, Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumanni* ventilator-associated pneumonia, Epidemiol Infect, 141(6):1214-1222.
4. Zheng, YL, YF Wan, LY Zhou, ML Ye, S Liu, CQ Xu, YQ He, and JH Chen, 2013, Risk factors and mortality of patients with nosocomial carbapenem-resistant *Acinetobacter baumannii* pneumonia, Am J Infect Control, 41(7):e59-63.
5. Lemos, EV, FP de la Hoz, TR Einarson, WF McGhan, E Quevedo, C Castaneda, and K Kawai, 2014, Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis, Clin Microbiol Infect, 20(5):416-423.
6. FDA, 2022, Draft Guidance for Industry; Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers (Revision 1).

Thank You

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Efficacy Assessment

NDA 216974

Sulbactam and Durlobactam

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Proposed Indication and Efficacy Study Reviewed

- Proposed indication
  - Treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP), caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* (ABC) complex
- Study Reviewed
  - One Phase 3 trial ATTACK (CS2514-2017-0004)
    - Part A: randomized, investigator-unblinded, assessor-blinded, non-inferiority, comparison of sulbactam (SUL)-durlobactam (DUR) versus colistin for treatment of HABP, VABP, ventilator pneumonia (VP) or bacteremia due to ABC
    - Part B: single-arm, evaluation of SUL-DUR in treatment of ABC-infected subjects who were resistant to colistin or who were ineligible for Part A due to other factors

Phase 3 Trial Part A: Study Design

- Treatment groups
  - 1.0 g SUL and 1.0 g DUR IV infused over 3 hours every 6 hours
  - 2.5 mg/kg colistin IV infused over 30 minutes every 12 hours
- Randomization: 1:1 ratio by three stratification factors
  - Infection type: HABP, VABP, VP or bacteremia
  - Baseline disease severity: APACHE 10 to 19 versus 20 to 30; or SOFA 7 to 9 versus 20 to 30; or qSOFA 2 versus 3
  - Region: mainland China versus rest of world
- Background therapy: 1.0 g imipenem/1.0 g cilastatin
- Study duration
  - Treatment period: 7 to 14 days
  - Follow-up period: 14 days

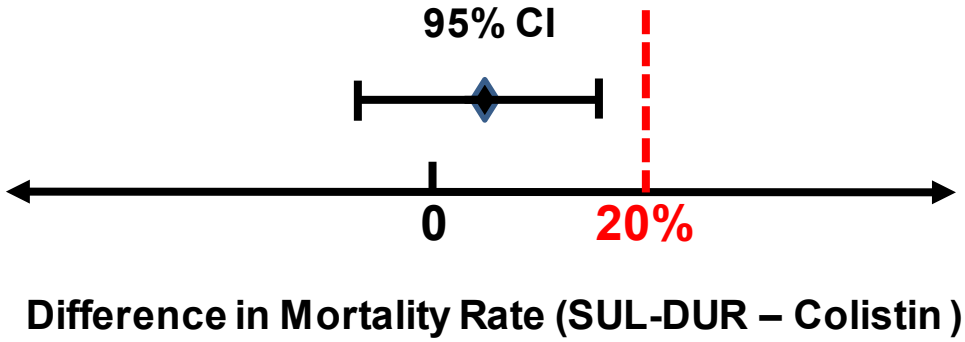
SUL = sulbactam; DUR = durlobactam; HABP = hospital-acquired bacterial pneumonia; VABP = ventilator-associated bacterial pneumonia; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; qSOFA = quick SOFA

Phase 3 Trial Part A: Efficacy Endpoints

- Primary endpoint: 28-day all-cause mortality, assessed using a 20% noninferiority (NI) margin
- Secondary endpoints
  - Clinical cure at the end of treatment (EOT), test of cure (TOC: 7 days after EOT) and late follow-up (LFU: 14 days after EOT)
  - Microbiological favorable assessment at EOT, TOC and LFU

Phase 3 Trial Part A: Justification of NI Margin

- Must determine whether SUL-DUR had unacceptably higher 28-day all-cause mortality rate than colistin, according to a pre-specified NI margin of 20%



Phase 3 Trial Part A: Justification of NI Margin

- An NI margin of 20% was accepted for this study
  - A 19% NI was estimated based on comparing mortality rates between subjects treated with colistin-based regimens versus subjects with delayed or inadequate antibacterial therapy according to literature reviews and discussion on FDA guidance for HABP and VABP

28-Day Mortality Rate (95% CI)		Effect of Colistin over Delayed or Inadequate Antibacterial Therapy
Colistin-Based Regimens	Delayed or Inadequate Antibacterial Therapy	
41% (36%, 47%)	76% (66%, 86%)	66% - 47% = 19%

  - A 20% NI margin was accepted considering high unmet medical need for antibacterial drugs to treat carbapenem-resistant ABC complex (CRABC) and trial feasibility given the COVID-19 pandemic.

Phase 3 Trial Part A: Analysis Populations

- Intent-to-treat (ITT)
  - All subjects randomized in Part A
- Microbiologically-modified intent-to-treat (m-MITT)
  - In ITT population
  - Received any amount of study drug
  - Had a baseline ABC organism isolated as the qualifying culture specimen as confirmed by the central and/or local laboratory
- Primary efficacy analysis population: CRABC m-MITT
  - In m-MITT population
  - Had HABP, VABP, VP or bacteremia
  - Had a baseline ABC organism resistant to carbapenem but not resistant to SUL-DUR and colistin
  - Had blood culture or respiratory samples collected within 72 hours before randomization
  - Not transferred to Part B

Phase 3 Trial Part A:
Reasons for Exclusion from m-MITT or CRABC m-MITT

Parameter, n (%)	SUL-DUR	Colistin
ITT	92 (100)	89 (100)
m-MITT	78 (84.8)	79 (88.8)
Exclusion from m-MITT	14 (15.2)	10 (11.2)
BPP* positive but culture negative	12 (13.0)	5 (5.6)
CRABC m-MITT	64 (69.6)	64 (71.9)
Exclusion from CRABC m-MITT	28 (30.4)	25 (28.1)
Exclusion from m-MITT due to BPP* positive but culture negative	12 (13.0)	5 (5.6)
Baseline ABC organism resistant to colistin	8 (8.7)	7 (7.9)

*BPP = Biofire FilmArray 2.0 Pneumonia Panel

Phase 3 Trial Part A: Subject Disposition

Parameter, n (%)	SUL-DUR	Colistin
ITT population	92 (100)	89 (100)
Discontinued from study treatment	24 (26.1)	31 (34.8)
Adverse event	8 (8.7)	10 (11.2)
No growth of ABC	7 (7.6)	4 (4.5)
Treatment failure	1 (1.1)	5 (5.6)
Discontinued from study	23 (25.0)	28 (31.5)
Death	15 (16.3)	21 (23.6)
Transferred to Part B	1 (1.1)	1 (1.1)

Phase 3 Trial Part A: Demographics and Clinical Factors (CRABC m-MITT Population)

Parameter, n (%)	SUL-DUR (N=64)	Colistin (N=64)
Age, mean (SD)	61.6 (16.1)	65.1 (17.0)
Gender, male	46 (71.9)	49 (76.6)
Region		
China Mainland	15 (23.4)	19 (29.7)
Rest of world	49 (76.6)	45 (70.3)
Infection type		
Bacteremia	2 (3.1)	1 (1.6)
HABP	24 (37.5)	31 (48.4)
VABP	38 (59.4)	30 (46.9)
VP	0 (0)	2 (3.1)
Baseline disease severity		
APACHE II score 10-19 / SOFA score 7-9 / qSOFA score 2	47 (73.4)	44 (68.8)
APACHE II score 20-30 / SOFA score ≥10/ qSOFA score 3	16 (25.0)	20 (31.3)

Source: Table 12 in CS2514-2017-0004 Clinical Study Report
APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; qSOFA = quick SOFA; SD = standard deviation

Phase 3 Trial Part A: Primary Endpoint
28-Day All-Cause Mortality

- Primary analysis in CRABC m-MITT population

Parameter	SUL-DUR (N=64)	Colistin (N=64)
Number of mortality / Number of subjects in analysis* (%)	12/63 (19.0%)	20/62 (32.3%)
Difference in mortality rate (SUL-DUR – colistin) (95% CI**)	-13.2% (-30.0%, **3.5%**)	

Source: Table 17 in CS2514-2017-0004 Clinical Study Report
*One subject in SUL-DUR group and two subjects in colistin group who had missing survival status at Day 28 due to withdrawal of consent were excluded from the analysis. No subjects missed survival status due to other reasons.
**The 95% CI was calculated using continuity-corrected Z-statistic.

Phase 3 Trial Part A: Primary Endpoint

- Sensitivity analyses: subjects who missed survival status at Day 28 or who received prohibited medication before Day 28 were considered as events in SUL/DUR group and nonevents in colistin group

Analysis Population	SUL-DUR n/N* (%)	Colistin n/N* (%)	Difference (95% CI**)
CRABC m-MITT	14/64 (21.9%)	20/64 (31.3%)	-9.4% (-26.2%, **7.4%**)
m-MITT excluding two subjects transferred to Part B	17/77 (22.1%)	25/78 (32.1%)	-10.0% (-25.2%, **5.2%**)
m-MITT including two subjects transferred to Part B	17/78 (21.8%)	25/79 (31.6%)	-9.9% (-24.9%, **5.2%**)
ITT excluding two subjects transferred to Part B	21/91 (23.1%)	27/88 (30.7%)	-7.6% (-21.7%, **6.5%**)
ITT including two subjects transferred to Part B	21/92 (22.8%)	27/89 (30.3%)	-7.5% (-21.5%, **6.4%**)

*n = number of mortality; N = number of subjects in the analysis
**The 95% CI was calculated using continuity-corrected Z-statistic.

Phase 3 Trial Part A: Secondary Endpoint Clinical Cure (CRABC m-MITT Population)

Assessment time	SUL-DUR (N=63)*	Colistin (N=62)*
EOT	47 (74.6%)	28 (45.2%)
TOC	39 (61.9%)	25 (40.3%)
LFU	27 (42.9%)	19 (30.6%)

Source: Table 20 in CS2514-2017-0004 Clinical Study Report
*One subject in SUL-DUR group and two subjects in colistin group withdrew consent before assessment of survival status at Day 28 were excluded from the analyses.
**The 95% CI was calculated using continuity-corrected Z-statistic.
EOT = end of treatment; TOC = test of cure; LFU = late follow-up

Phase 3 Trial Part A: Secondary Endpoint Microbiological favorable assessment (CRABC m-MITT Population)

Assessment time	SUL-DUR (N=63)*	Colistin (N=62)*
EOT		
Microbiological favorable assessment	54 (85.7%)	38 (61.3%)
Eradication	34 (54.0%)	35 (56.5%)
Presumed eradication	20 (31.7%)	3 (4.8%)
TOC		
Microbiological favorable assessment	43 (68.3%)	26 (41.9%)
Eradication	23 (36.5%)	22 (35.5%)
Presumed eradication	20 (31.7%)	4 (6.5%)
LFU		
Microbiological favorable assessment	30 (47.6%)	25 (40.3%)
Eradication	18 (28.6%)	21 (33.9%)
Presumed eradication	12 (19.0%)	4 (6.5%)

Source: Table 21 in CS2514-2017-0004 Clinical Study Report
*One subject in SUL-DUR group and two subjects in colistin group withdrew consent before assessment of survival status at Day 28 were excluded from the analyses.
**The 95% CI was calculated using continuity-corrected Z-statistic.
EOT = end of treatment; TOC = test of cure; LFU = late follow-up

Phase 3 Trial Part A: Efficacy Conclusion

- Part A demonstrated that SUL-DUR was non-inferior to colistin in the treatment of HABP/VABP caused by CRABC
  - SUL-DUR was non-inferior to colistin for 28-day all-cause mortality in the CRABC m-MITT primary analysis population

SUL-DUR	Colistin	Difference (95% CI)
12/63 (19.0%)	20/62 (32.3%)	-13.2% (-30.0%, **3.5%**)

  - Approximately 96% of subjects had HABP/VABP and only 2% (3 subjects) had bacteremia in the CRABC m-MITT population

Thank You

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Clinical Safety Assessment

NDA 216974

Sulbactam and Durlobactam

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Background

Sulbactam and durlobactam: Sulbactam, a beta-lactam antibacterial and beta-lactamase inhibitor, and durlobactam, a non-beta-lactam, beta-lactamase inhibitor. Sulbactam has intrinsic activity against *Acinetobacter spp.*

Proposed indication: Sulbactam-durlobactam is indicated in patients 18 years of age and older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex.

Proposed dose and duration: 1 gram of sulbactam and 1 g of durlobactam every 6 hours administered by intravenous infusion for 7-14 days, as guided by clinical status.

Clinical studies

Phase 2 study in complicated urinary tract infections (cUTI)

- Randomized 2:1 to SUL-DUR and placebo.
- All 80 subjects including the 53 subjects on the SUL-DUR arm received background therapy with imipenem-cilastatin.
- No patients with *Acinetobacter* infections were enrolled.
- Data from this study was used to assess safety of sulbactam-durlobactam (SUL-DUR).

Clinical studies

Single Pivotal Phase 3 study (ATTACK)

Conducted in 2 Parts

- Part A was a comparative study , randomized 1:1 to SUL-DUR (N=91) and colistin (N=86), comprised of subjects with HABP, VABP, ventilated pneumonia or bacteremia caused by carbapenem-resistant *A. baumannii* complex (CRABC). Imipenem-cilastatin was given as background therapy in both arms.
- Part B was a nonrandomized study with SUL-DUR (N=28) and included subjects who did not qualify for Part A because the baseline pathogen was known to be resistant to colistin, subjects with cUTI and acute pyelonephritis, surgical or post-traumatic wound infections.
- The study drugs were not masked for logistical reasons and the treating physician and other health care providers were not blinded in the trial except for the outcome assessor.
- The outcome assessor evaluated criteria for clinical outcomes, conducted causality assessment for adverse events, and assessed clinical signs and symptoms at study visits.
- The safety population consisted of predominantly white and Asian subjects, mostly males (70%).

Clinical Safety Database

Clinical studies	Proposed dose (N of subjects)	Proposed duration (N of subjects)	Median duration (days)
Phase 1 (6 studies) (Durlobactam up to 8 gm)	10	10	7
Phase 2	53	51	8
Phase 3 (Part A +B)	90* + 28	97	8 (Part A) 10.5 (Part B)
Total number of subjects	**181**	**158**	
Expanded access patients	12		

*1 subject was transferred to part B and was counted in both parts

Deaths

- No deaths in phase 1 or 2 studies.
- Mortality rates on SUL-DUR (26%) were numerically lower than colistin (35%) in the phase 3 study.
- Deaths were related to underlying comorbidities, complications in critically ill subjects or progression of the presenting pneumonia without apparent biologic plausibility or causal assignment to SUL-DUR.
- Most common etiologies of death in both the SUL-DUR and colistin group were septic shock and sepsis.
- Mortality rates were generally consistent with those in HABP/VABP trials and in *Acinetobacter* infections reported in the literature.

Overview of Adverse Events

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

Selected Adverse Events Occurring at >5% Safety Population, phase 3 study

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

Terms renal impairment, blood creatinine increased, toxic nephropathy, renal failure and acute kidney injury were combined to acute kidney injury

Terms liver function test abnormal, hepatic function abnormal, increased transaminases, alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased were combined to liver function test abnormal.

Adverse Events of Special Interest

- **Hypersensitivity***
  - 16.5% in SUL-DUR versus 11.5% in colistin
  - Most common drug related reaction was rash
  - One subject who received SUL-DUR had anaphylactic shock treated with steroids and resulting in treatment discontinuation
- **Pseudomembranous colitis**
  - *C. difficile* colitis, 0.8% in SUL-DUR versus 3.5% in colistin
- **Convulsions**
  - 0.8% in SUL-DUR versus 7% in colistin
- **Acute kidney injury**
- **Drug-related hepatic disorders**

* To generate the standardized medical dictionary for regulatory activities (medDRA) query of hypersensitivity, the terms rash, conjunctivitis, respiratory failure, wheezing, shock, acute respiratory failure, anaphylactic shock, conjunctival oedema, dermatitis, dermatitis allergic, dermatitis contact, distributive shock, eczema, hypersensitivity, localized oedema, pruritus generalized, respiratory distress were combined.

Safety conclusions

- The safety database was limited; however, the safety profile of SUL-DUR is consistent with the pharmacologic class.
- Hypersensitivity reactions were more frequent in the SUL-DUR group.
- Diarrhea, including *C. difficile* infections were noted among both treatment groups.
- LFT elevations were comparable between treatment groups and no specific hepatotoxicity signal was noted.
- No additional safety signals were noted from the phase 2 study.

Thank You

Clinical Microbiology Assessment

NDA 216974

Sulbactam and Durlobactam

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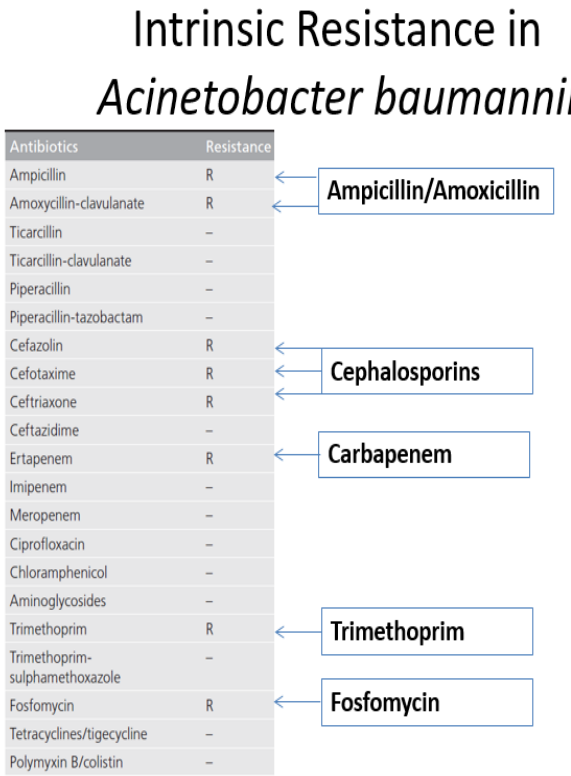
Division of Anti-Infective (DAI)

OID, CDER, FDA

Acinetobacter spp. Overview

- Complicated mechanisms of antimicrobial resistance in *Acinetobacter baumannii*
  - The interplay of both intrinsic and acquired resistance mechanisms confers various degrees of resistance to many antibacterial drugs
  - Many of the resistance genes are encoded on extra-chromosomal DNA (plasmids, transposons and insertion sequences)
- Limited therapeutic agents available on the market

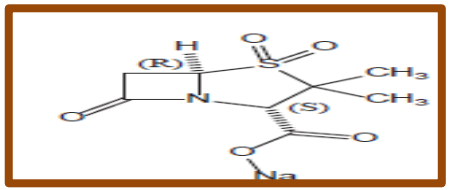
Intrinsic Resistance in *A. baumannii*



Clinical Microbiology and Infection 2011 European Society of Clinical Microbiology and Infectious Diseases, CMI, 19, 141–160

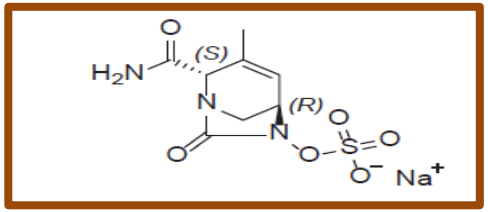
- The presence of chromosomally encoded cephalosporinases: *Acinetobacter* -derived cephalosporinases (ADCs)
  - ADCs hydrolyze β-lactams, including some cephalosporins (cefazolin, ceftriaxone) but not cefepime or imipenem
- The expression of chromosomally encoded drug efflux pumps (AdeDE efflux pump)
  - aminoglycosides, chloramphenicol, trimethoprim
- Low membrane permeability
  - $OmpA_{Ab}$; nonspecific slow porin

Mechanism of Action



Sulbactam

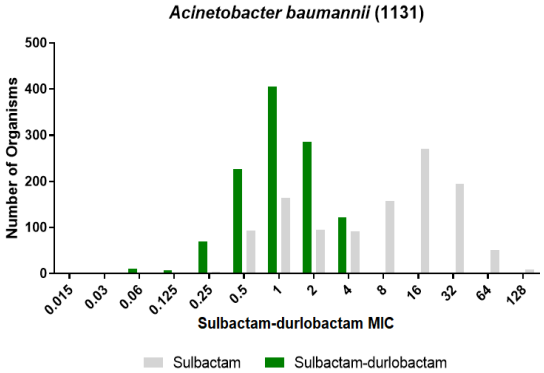
- Beta-lactam that is often used in combination as a beta-lactamase inhibitor (ampicillin-sulbactam).
  - Ampicillin has no antibacterial activity
- Against *Acinetobacter* spp.
  - Intrinsic antibacterial activity
  - Inhibits bacterial cell wall synthesis by inactivating essential penicillin-binding proteins (PBP 1 and 3)
  - Bactericidal

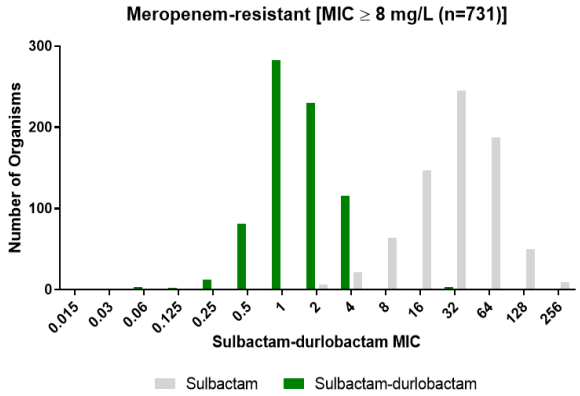


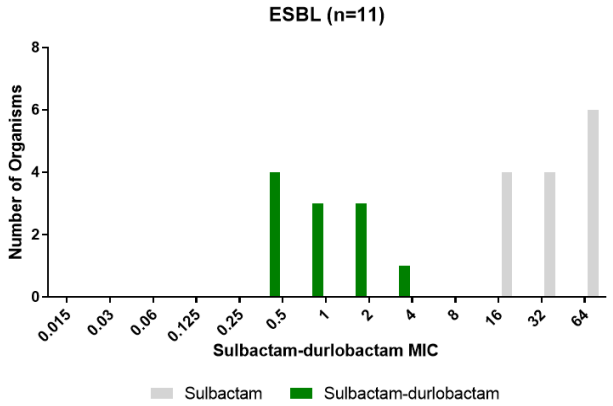
Durlobactam

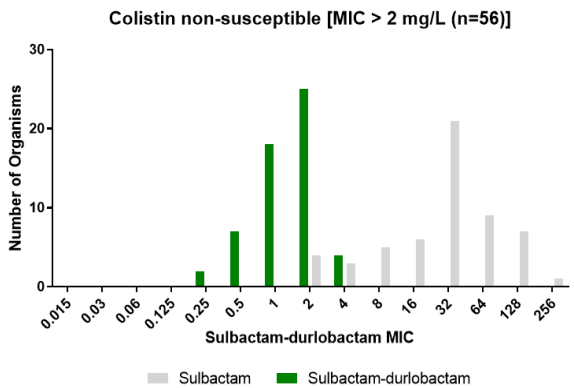
- Novel non-beta-lactam, serine β-lactamase inhibitor
- Against *Acinetobacter* spp.
  - No intrinsic antibacterial activity
  - Enhances activity of sulbactam
    - Inhibits Ambler Class A (e.g., KPC), Class C (e.g., ADC-30) and Class D (e.g., OXAs) β-lactamases.
    - No activity against metallo-β-lactamases

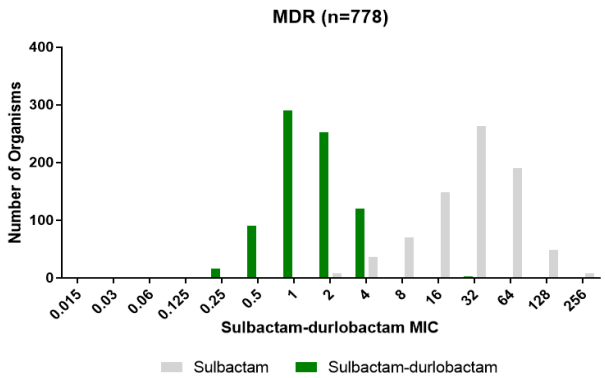
In vitro MICs against *A. baumannii calcoaceticus* complex with different resistance profiles











www.fda.gov

Source: Study Report# PC2514-2016-0008; MIC, Minimum inhibitory concentration; MDR, multi-drug resistant; ESBL, Extended-spectrum beta-lactamases

Mechanism of Resistance

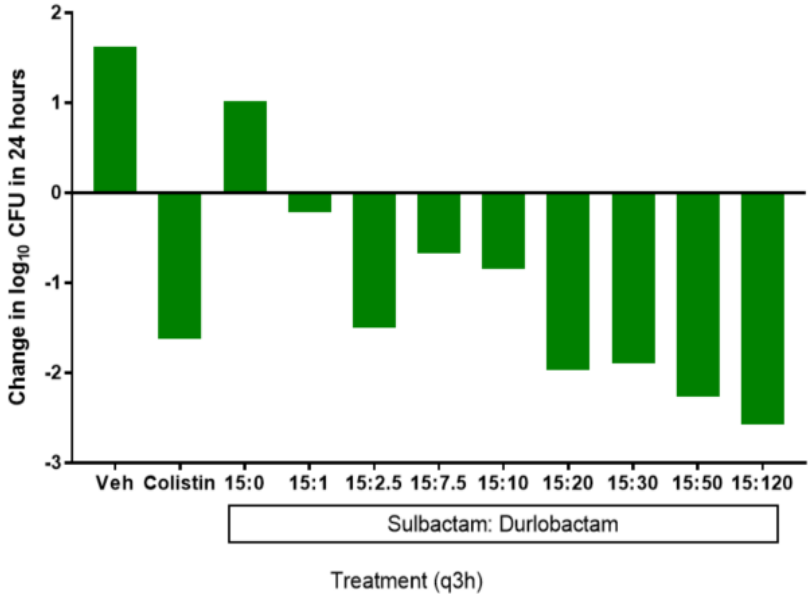
- In isolates with sulbactam-durlobactam MIC values > 4 mg/L showed:
  - Amino acid changes near the active target site of sulbactam (PBP3)
  - Organisms that express *bla*NDM-1 or any other metallo-β-lactamase.
  - Isolates that produce multiple β-lactamases and express varying levels of β-lactamases may also contribute to sulbactam-durlobactam resistance; though the combinations of these β-lactamases is unknown.

Animal Models of infection

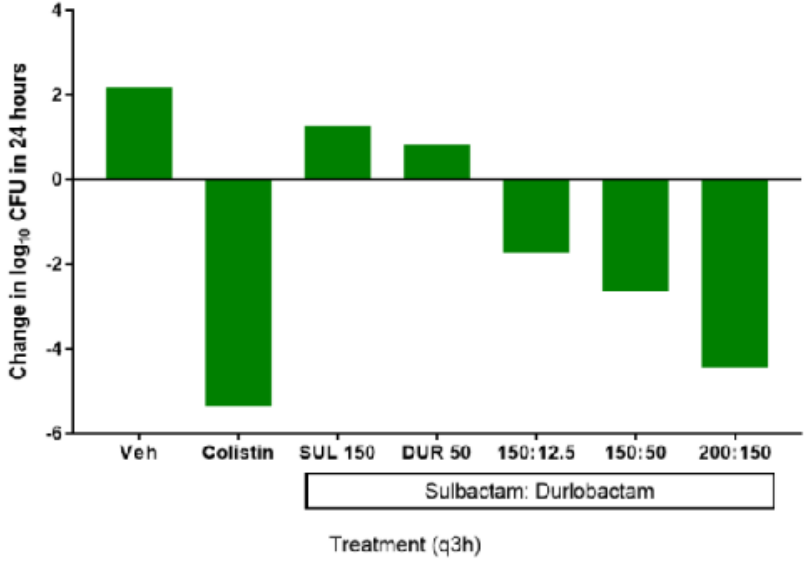
- Evaluated in murine thigh or lung infection models against 10 *A. baumannii* isolates
  - 9 isolates were MDR *A. baumannii* isolates that were sulbactam- and carbapenem-resistant characterized β-lactamases
  - Sulbactam-durlobactam MICs ranged 0.5 – 16 mg/L, sulbactam MICs 2 – 64 mg/L
- Durlobactam alone demonstrated minimal to no activity.
- Sulbactam administered at fixed concentration and varying concentrations of durlobactam showed a dose proportional reduction in bacterial burden.

Durlobactam restores activity of sulbactam in animal model of infections (neutropenic thigh infection)

ARC3486 [ADC-30, TEM-1, OXA-66, OXA-72]
Sul-Dur MIC 1 mg/L: Sul MIC 32 mg/L



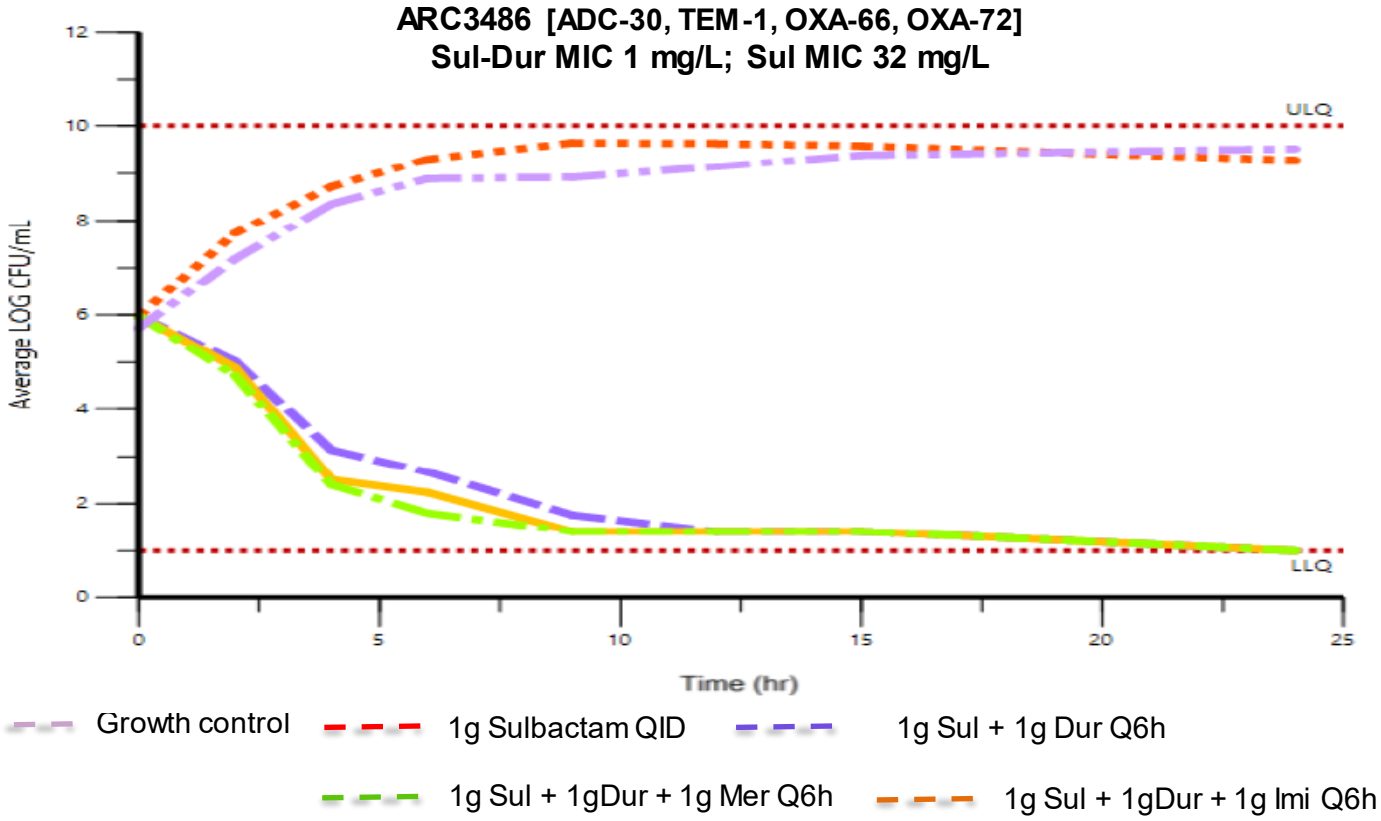
ARC5950 [ADC-11, OXA-23, OXA-69 , PBP3 (T526S)]
Sul-Dur MIC 4 mg/L; Sul MIC 64 mg/L



www.fda.gov

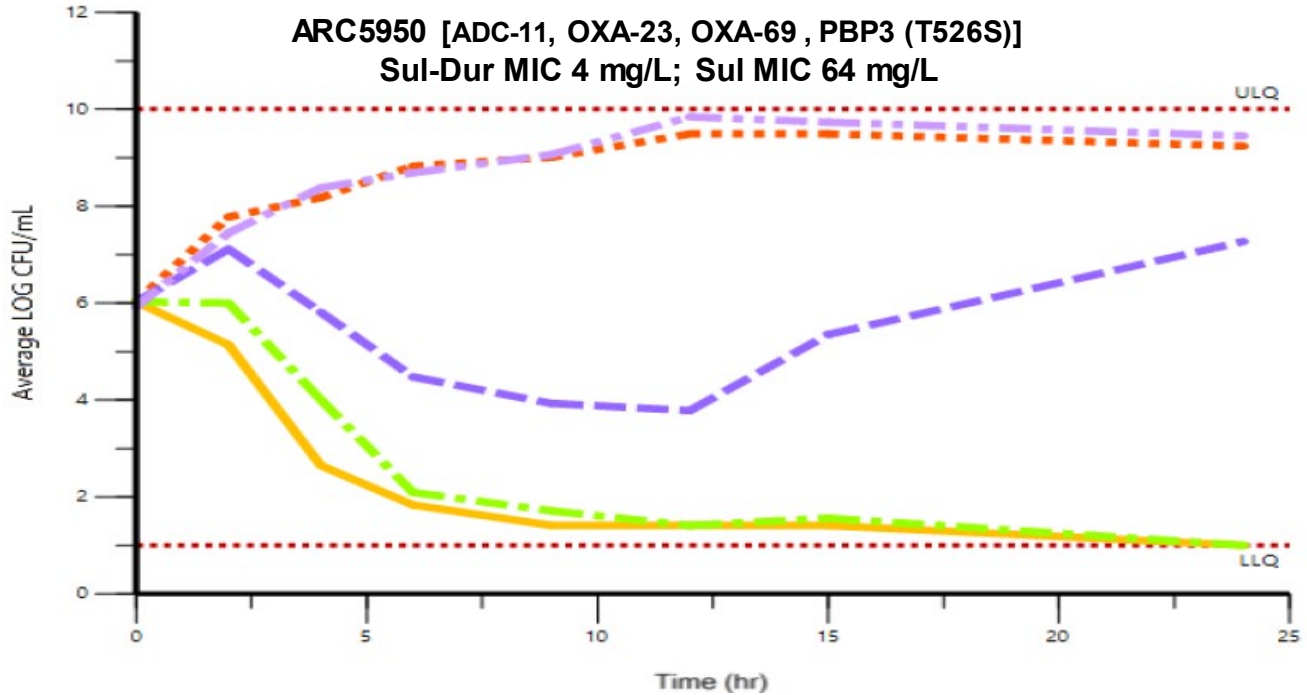
CFU: colony-forming units; Veh: Vehicle; q3h: every 3 hours

Sulbactam-Durlobactam Hollow Fiber Infection Model



Source: Study Report# PC2514-2020-0023 SUL; Sulbactam; Dur, Durlobactam; Mer, Meropenem; Imi, Imipenem; Q6h, every 6 hours; QID, every 24 hours

Sulbactam-Durlobactam Hollow Fiber Infection Model



Source: Study Report# PC2514-2020-0023 SUL; Sulbactam; Dur, Durlobactam; Mer, Meropenem; Imi, Imipenem; Q6h, every 6 hours, QID, every 24 hours

Thank You

U.S. FOOD & DRUG ADMINISTRATION

Clinical Pharmacology Assessment

NDA 216974

Sulbactam and Durlobactam

Xiaohui (Tracey) Wei, Ph.D.
Clinical Pharmacology Reviewer
Division of Infectious Disease Pharmacology
Office of Clinical Pharmacology/CDER/FDA

Pharmacokinetics (PK) Highlights

<table>
<tr><th>PK properties</th><th>Sulbactam</th><th>Durlobactam</th></tr>
<tr><td>Distribution</td><td>Plasma protein binding: 38%
AUC_{0-6} ELF/total plasma ratio: 0.5</td><td>Plasma protein binding: 10%
AUC_{0-6} ELF/total plasma ratio: 0.37</td></tr>
<tr><td>Metabolism</td><td colspan="2">Minimally metabolized</td></tr>
<tr><td rowspan="2">Elimination</td><td>CL: 9.98 L/h
T1/2: 1 to 3 hours
Excretion: 75-85% excreted unchanged in urine</td><td>CL: 9.40 L/h
T1/2: 2 to 3 hours
Excretion: 78.1% excreted unchanged in urine</td></tr>
<tr><td colspan="2">Dose normalized fold AUC Increase in Subjects with Renal Impairment Compared to Subjects with CLcr ≥90 mL/min
<table>
<tr><th>Estimated eGFR (mL/min/1.73 m^2)</th><th>Sulbactam</th><th>Durlobactam</th></tr>
<tr><td>≥60 to <90</td><td>1.4</td><td>1.4</td></tr>
<tr><td>≥30 to <60</td><td>2.0</td><td>1.9</td></tr>
<tr><td><30</td><td>4.3</td><td>3.7</td></tr>
</table></td></tr>
<tr><td>Drug-Drug interaction</td><td colspan="2">• No drug-drug interactions were observed among durlobactam, sulbactam, imipenem, and cilastatin in a clinical study in healthy subjects
• Sulbactam and durlobactam are both substrates of OAT1 based on in vitro study</td></tr>
</table>

AUC: area under the concentration-time curve; ELF: epithelial lining fluid: CL: clearance; T1/2: half-life; CLcr: creatinine clearance; eGFR: estimated glomerular filtration rate; OAT1: organic anion transporter 1

Clinical Pharmacology Considerations

- Evaluation of the proposed dose regimens: probability of pharmacokinetic/pharmacodynamic (PK/PD) target attainment (PTA) for both sulbactam (SUL) and durlobactam (DUR)
- Renal function-based dosage adjustments of SUL-DUR
- Effect of body weight on the PK of SUL and DUR

Evaluation of the Proposed Dose Regimens: PK/PD Targets

- SUL and DUR PK/PD targets were determined from murine thigh and lung infection models using a collection of ten *A. baumannii* isolates.
  - Nine isolates are sulbactam- and carbapenem-resistant.
- Sulbactam PK/PD target
  - % of dosing interval that free SUL plasma concentration remains above MIC (%*f*T>MIC): 50% for at least 1-$\log_{10}$ kill
- Durlobactam PK/PD target
  - Free-drug area under the plasma concentration-time curve (from dosing to 24-hour post-dose) to MIC ratio (*f*$AUC_{0\text{-}24}$/MIC): 10 for 1-$\log_{10}$ kill, 30 for 2-$\log_{10}$ kill

Proposed Dose Regimens by Renal Function

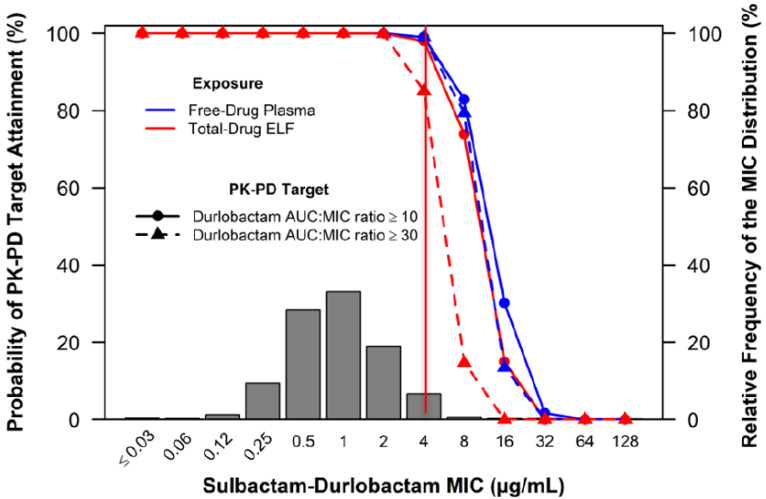
Estimated CLcr (mL/Min)	Proposed Dosage of SUL-DUR	Frequency	Infusion Time
≥130	1.5 g/1.5 g	Every 6 hours	3 hours
45-129	1 g/1 g	Every 6 hours	3 hours
30-44	1 g/1 g	Every 8 hours	3 hours
15-29	Loading dose of 1 g/1 g followed by 0.5 g/0.5 g	Every 8 hours	3 hours
<15[1]	Loading dose of 1 g/1 g followed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

[1] For patients on hemodialysis, the dose should be administered after the dialysis session has ended.

Source: Applicant's draft label for NDA 216974.
Abbreviations: CLcr, creatinine clearance (as estimated by the Cockcroft-Gault equation); DUR, durlobactam; SUL, sulbactam

Evaluation of the Proposed Dose Regimens: Probability of PK/PD Target Attainment (PTA)

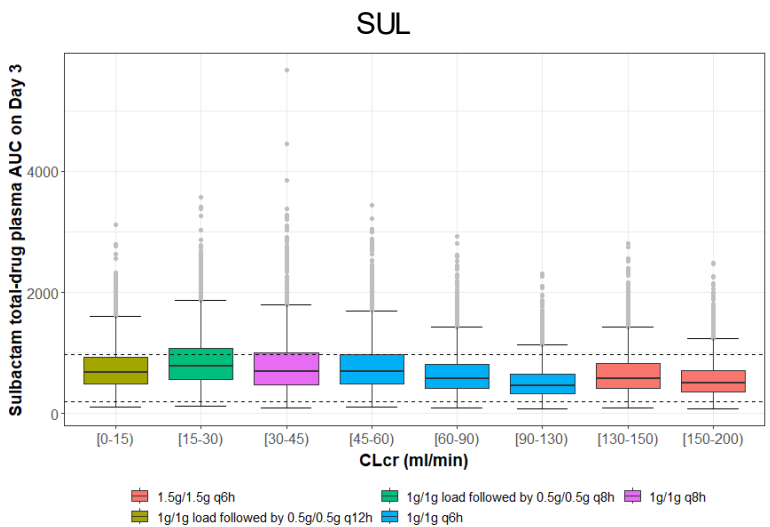
- Joint PK/PD targets: 50% *f*T>MIC for SUL + *f*AUC_{0-24}/MIC of 10 for DUR
- SUL 1 g/DUR 1 g every 6 hr by IV infusion over 3 hr and dosing regimens adjusted by renal function
- ≥ 90% PTA achieved based on plasma or ELF concentrations at MIC up to 4 µg/mL

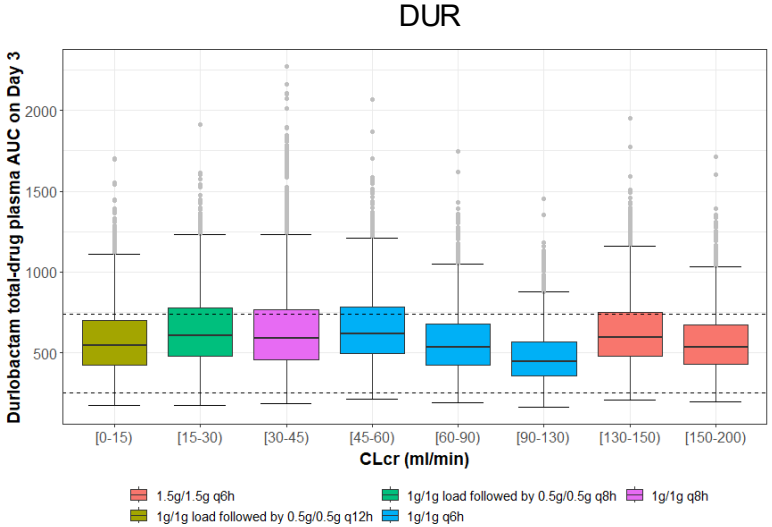


Source: Figure 62 of Applicant's module 2.7.2 Summary of Clinical Pharmacology for NDA 216974..
Abbreviations: ELF, epithelium lining fluid; MIC, minimum inhibitory concentration; IV: intravenous; PD, pharmacodynamics; PK, pharmacokinetics

Predicted Drug Exposures at the Proposed Dose Adjustments

- Predicted plasma AUCs of SUL and DUR were generally comparable across renal function categories at the proposed dose adjustments

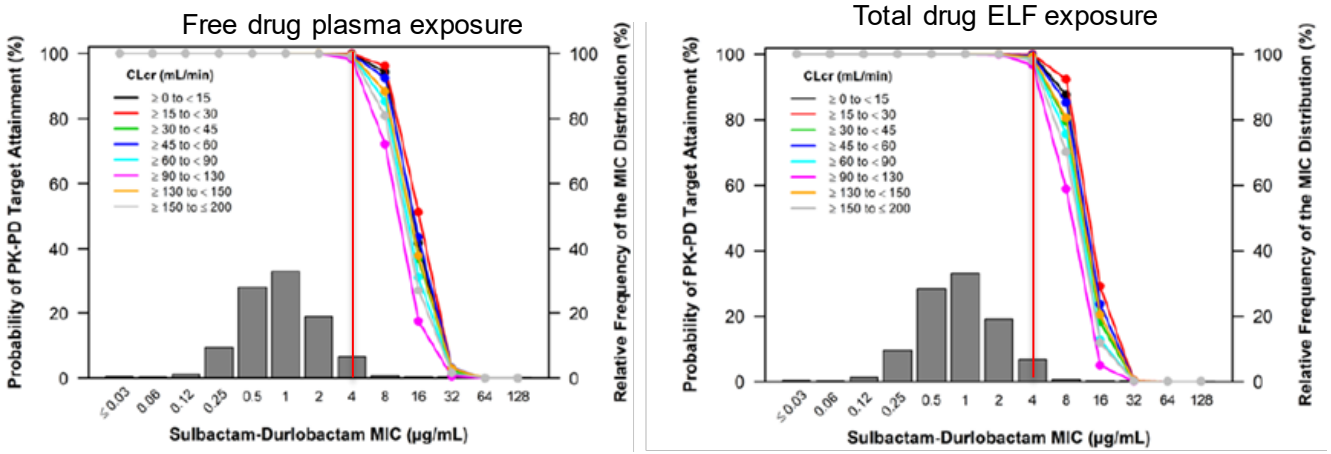




Source: Analyses by pharmacometrics review team in the FDA.
Horizontal dashed lines represent the 90% prediction interval of the CLcr ≥90 to <130 mL/min group, which is defined as the 5th and 95th percentiles for SUL or DUR plasma AUC.
Abbreviations: AUC, area under the concentration-time curve; CLcr, creatinine clearance; DUR, durlobactam; SUL, sulbactam

Probability of PK/PD Target Attainment at the Proposed Dose Adjustments

- Joint PK/PD targets: 50% *f*T>MIC for SUL + *f*AUC_{0-24}/MIC of 10 for DUR
- ≥ 90% PTA achieved based on plasma or ELF concentrations at MIC up to 4 µg/mL across renal function categories



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

Effect of Body Weight on the PK of SUL and DUR

- SUL and DUR exposures decreased as body weight (BW) increased.

Fold changes in mean AUC_{0-24} and Cmax compared to patients with BW 51 to 90 kg*

Parameter (ratio)	Sulbactam				Durlobactam			
	35 to 50 kg (n=10)	51 to 90 kg (n=121)	91 to 120 kg (n=26)	121 to 150 kg (n=5)	35 to 50 kg (n=10)	51 to 90 kg (n=121)	91 to 120 kg (n=26)	121 to 150 kg (n=5)
AUC_{0-24} Day 1	1.61	1	0.84	0.79	1.68	1	0.78	0.75
Cmax Day 1	1.55	1	0.84	0.77	1.58	1	0.79	0.73
AUC_{0-24} Day 3	2.1	1	0.93	0.97	2.03	1	1.03	1.08
Cmax Day 3	1.83	1	0.87	0.87	1.79	1	0.93	0.93

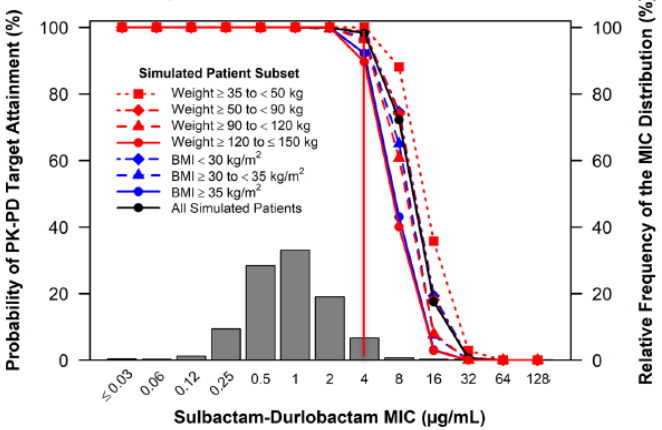
*Following 1g SUL/1g DUR q6h and dose adjustments by renal function in phase 2 and phase 3 studies; Cmax: maximum concentration

- The number of evaluable patients was limited, but the incidence of severe adverse events (SAEs) and treatment discontinuations due to AEs following SUL-DUR treatment was similar between patients with BW ≤50 kg and patients with BW> 50 kg.

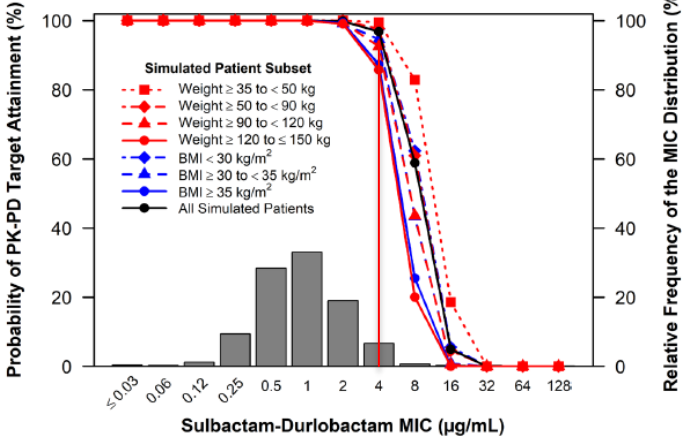
Probability of PK/PD Target Attainment Across Body Weight Bands

- Joint PK/PD targets: 50% *f*T>MIC for SUL + *f*AUC_{0-24}/MIC of 10 for DUR
- ≥ 90% PTA achieved based on plasma or ELF concentrations at MIC up to 4 µg/mL across body weight bands and renal function categories

Free drug plasma exposure
in simulated subjects with CLcr ≥90 to < 130 mL/min



Total drug ELF exposure
in simulated subjects with CLcr ≥90 to < 130 mL/min



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

Proposed Revisions on the Dose Adjustments by Renal Function

- To streamline and simplify doses to 1 g SUL/1g DUR in all renal function categories with adjustment of dosing frequency

Estimated CL_{CR} (mL/min)*	Initially Proposed Dose Regimens of SUL-DUR	Proposed Revisions on Dose Regimens of SUL-DUR
≥ 130	**1.5 g/1.5 g, every 6 hours**	**1 g /1 g, every 4 hours**
45-129	1 g/1 g, every 6 hours	Same as originally proposed doses
30-44	1 g/1 g, every 8 hours	Same as originally proposed doses
15-29	Loading dose of 1 g/1 g, followed by **0.5 g/0.5 g, every 8 hours**	**1 g /1 g, every 12 hours**
<15	Loading dose of 1 g/1 g, followed by **0.5 g/0.5 g, every 12 hours**	**1 g/1 g,** Every 12 hours for the first 3 doses (0, 12, and 24 hours), followed by every 24 hours after the third dose

*: CL_{CR} = creatinine clearance estimated by Cockcroft-Gault equation

Source: Table 3 of Applicant's response to the FDA Information Request for NDA 216974 dated on March 14, 2023

Summary of Clinical Pharmacology Assessments

- Results of population PK and probability of PK/PD target attainment analyses generally support the proposed dose regimens in the patient population for the target indication.
- The Applicant's proposed revisions on the dose adjustments in patients with altered renal function are under review.

Thank You

Charge to the Committee

NDA 216974

Sulbactam-Durlobactam

Peter Kim, M.D., M.S.
Director
Division of Anti-Infectives
Office of Infectious Diseases/CDER/FDA

Key Considerations

- This is a streamlined development program targeting a single high unmet-need pathogen.
- Part A of the phase 3 trial demonstrated that SUL/DUR was non-inferior to colistin for 28-day all-cause mortality in the CRABC m-MITT primary analysis population that mainly consisted of HABP/VABP patients.
- The safety profile of SUL-DUR appears to be generally consistent with other β-lactam/β-lactamase inhibitor drugs; however, the safety dataset is limited to less than 200 patients who received SUL-DUR at the proposed dose and duration.

Question for the Advisory Committee

VOTE: Is the overall benefit-risk assessment favorable for the use of sulbactam-durlobactam for the treatment of patients with hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex (ABC) organisms?

a. If yes, please provide your rationale.

b. If no, please provide your rationale and describe what additional studies/trials are needed.

Additional Slides Shown

Phase 3 Trial Part A: Justification of NI Margin

- Summary of mortality rates for colistin-based therapy alone or in combination with carbapenems

Reference (population studied)	Country / Year	Endpoint	Results
Cheng 2015 (XDR; ~80% pneumonia or BSI)	Taiwan / 2010-13	30-day mortality	Colistin + carbapenem: 11/26 (42%)
Yilmaz 2015 (MDR [n=41], XDR [n=29], VAP)	Turkey / 2011-13	General mortality at 28 days	Colistin + carbapenem: 16/33 (48.5%) Colistin alone: 7/17 (41.2%)
Chuang 2014 (MDR VAP)	Taiwan / 2009-10	In-hospital mortality (mean follow-up 32 days)	Colistin + carbapenem: 7/15 (46.7%) Colistin alone: 52/104 (50.0%)
Paul 2018 (CRAB)*	Multiple / 2013-16	28-day mortality	Colistin + meropenem: 94/208 (45.2%) Colistin alone: 86/198 (43.4%)
Alverez-Marin 2016 (*A. baumannii* VAP)	Spain / 2010-11	30-day mortality	Colistin alone: 14/57 (24.6%)
Samrah 2016 (All colistin-dosed VAP)	Jordan / 2009-14	30-day mortality (< 4 day trt)	Colistin alone: 7/26 (26.9%)
Durante-Mangoni 2013 (XDR *A. baumannii*)	Italy / 2008-11	30 day mortality	Colistin alone: 45/105 (42.9%)
Betrosian 2008 (MDR VAP)	Greece	28-day all-cause mortality	Colistin alone: 5/15 (33.3%)
Sirijatuphat 2014 (CRAB)**	Thailand / 2010-11	28-day all-cause mortality	Colistin alone: 27/47 (57.4%)
Zalts 2016 (CRAB in VAP)	Isreal / 2008-09	30-day mortality	Colistin alone: 17/66 (25.8%)
Garnacho-Montero 2013 (CRAB in VAP or BSI)	Spain / 2008-11	28-day mortality	Colistin alone: 14/28 (50.0%)

Source: IND131330 / SDN 21

BSI = blood stream infection; CRAB = carbapenem-resistant *A. baumannii*; MDR = multi-drug resistant; XDR = extensively drug resistant; VAP = ventilator acquired pneumonia

*only CRAB data reported from a study that enrolled subjects with carbapenem-resistant Gram negative infections. **Approximately 17% of subjects received concomitant carbapenems.

Phase 3 Trial Part A: Justification of NI Margin

- Summary of mortality rates for untreated (including inappropriate therapy) or delayed treatment

Reference (population studied)	Country / Year	Endpoint	Results
Lee 2014 (*A. baumannii* infection [~66% VAP])	Taiwan / 2009-10	30-day mortality (inappropriate therapy)	46/53 (86.8%)
Erbay 2009 (BSI [22% lung])	Turkey / 2005-08	30-day in-hospital mortality	39/60 (65%)
Aydemir 2012 (*A. baumannii* infection [~70% pneumonia])	Turkey / 2005-06	Mortality (duration of mortality assessment was not specified, but mean duration hospital stay 22 days for all versus 32 days for survivors)	35/46 (76%)
Kwon 2007 (*A. baumannii* infection [~25% VAP])	Korea / 2000-05	30-day mortality in imipenem-non-susceptible	19/26 (73%)

Source: IND131330 / SDN 21

BSI = blood stream infection; CRAB = carbapenem-resistant *A. baumannii*; VAP = ventilator acquired pneumonia