Safety, Pharmacokinetics, and Drug:Drug Interaction Potential of Intravenous Durlobactam, a β-lactamase Inhibitor, in Healthy Subjects

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Running Title: Drug:Drug Interaction Potential of Intravenous Durlobactam

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Durlobactam (DUR, also known as ETX2514) is a novel β-lactamase inhibitor with broad activity against Ambler class A, C, and D β-lactamases. Addition of DUR to sulbactam (SUL) in vitro restores SUL activity against clinical isolates of *Acinetobacter baumannii*. The safety and pharmacokinetics (PK) of DUR alone and with SUL and/or imipenem/cilastatin (IMI/CIL) were evaluated in healthy subjects. This was a randomized, placebo-controlled study. In Part A, subjects including an elderly cohort (DUR 1 g) received single ascending doses of DUR 0.25-8 g. In Part B, multiple ascending dose of DUR 0.25-2 g were administered every 6 hours (q6h) for 29 doses. In Parts C and D, the drug-drug interaction (DDI) potential, including safety, of DUR (1 g) with SUL (1 g) and/or IMI/CIL (0.5/0.5 g) was investigated after single and multiple doses. Plasma and urine concentrations of DUR, SUL, and IMI/CIL were determined. Among 124 subjects, DUR was generally safe and well tolerated either alone or in combination with SUL and/or IMI/CIL. After single and multiple doses, DUR demonstrated linear dose proportional exposure across the studied dose ranges. Renal excretion was a predominant clearance mechanism. No drug:drug interaction potential was identified between DUR and SUL and/or IMI/CIL. SUL-DUR, 1 g (of each component) administered q6h with a 3 hour IV infusion, is under development for the treatment of serious infections due to *A. baumannii*. 
Acinetobacter baumannii (Ab) belongs to a cluster of bacterial species referred to as Acinetobacter baumanii-calcoaceticus complex (ABC), which are associated with serious infections including hospital-acquired and ventilator-associated bacterial pneumonia, and bloodstream, wound and complicated urinary tract infections (cUTIs) (1,2). Multi-drug resistant (MDR) isolates account for up to two-thirds of ABC infections (3-5), which are associated with high rates of morbidity (1,6-9), and mortality rates of 50% or higher (1,10-12). Multidrug resistance of ABC to antimicrobial agents is increasing with rates exceeding 50% in many parts of the world (4,13). As a consequence, an urgent need exists to identify new antimicrobial agents to treat serious ABC infections (14,15).

Durlobactam (DUR; previously ETX2514) is a novel, diazabicyclooctenone β-lactamase inhibitor (BLI) that potently inhibits Class A, C, and D β-lactamases (16-18). DUR demonstrates in vitro activity against some Enterobacteriaceae but has no in vitro activity against ABC. Sulbactam (SUL), a BLI with potent activity against Class β-lactamases exhibits in vitro activity against ABC, but its use has been limited by increasing resistance (8). In preclinical studies, the combination of sulbactam-durlobactam (SUL-DUR) exhibited potent in vitro and in vivo activity against ABC including carbapenem-resistant ABC and colistin-resistant isolates (17,19-22).

SUL-DUR is being developed for the treatment of infections caused by ABC, including MDR- and carbapenem-resistant isolates. This first-in-human Phase 1 study was
undertaken to evaluate the safety and PK of DUR after single and multiple ascending
doses and the drug-drug interaction potential of DUR when administered alone and in
combination with SUL and/or imipenem/cilastatin. In addition, the safety and tolerability
profile of DUR when co-administered with SUL and IMI/CIL, was evaluated after 11-
days of dosing. The pharmacokinetics (PK) of DUR after single and multiple-ascending
intravenous (IV) doses and in combination with SUL have also been evaluated in
healthy subjects and those with renal impairment as well as subjects undergoing
bronchial alveolar lavage (23,24).

RESULTS
A total of 124 subjects (94 DUR; 30 placebo) received ≥1 dose of study drug or placebo.
In Part B, 32 subjects were randomized, but 1 was discontinued for an infusion site
reaction and somnolence. One subject in Part D completed the study but was lost to
follow-up. All 124 subjects were included in the safety population, and all 94 who
received DUR were included in the PK population. Two other subjects completed all
study assessments, but study drug was discontinued for somnolence and nausea (1)
that occurred on Days 1 and 2 with both resolved on Day 2, and an anaphylactic
reaction due to Brazil nut allergy that occurred after eating a desert containing Brazil
nuts on Day 6 and resolved the same day (1). Subjects were generally comparable
across cohorts, except for a higher mean age in the elderly cohort (Table 1).
Part A – Single Ascending Dose

DUR demonstrated a consistent PK profile and linear increase in plasma concentrations (Figure 1) across the range of doses from 0.25 g to 8 g with mean half-life ranging from 1.5 to 2.8 hours (Table 2). A dose proportional increase in exposure (C_{max} and AUC) was observed with increasing doses (Figure 2). In Cohort 4 where DUR was administered with a 2 hour infusion, C_{max} was increased approximately 50% compared with a 3 hour infusion. In the elderly Cohort 8 administered DUR 1 g, C_{max} was increased 1.8-fold and AUC by 2-fold compared with younger subjects (Figure 1). The predominant clearance mechanism for DUR was renal excretion (~50% intact drug renally excreted). DUR demonstrated lower total and renal clearance in the elderly cohort (Cohort 8) compared with younger subjects consistent with renal clearance as the predominant mechanism of elimination (Supplemental Table).

Part B – Multiple Ascending Dose

The PK profile of DUR after multiple ascending doses of 0.25 g to 2.0 g q6h for 8 days was generally comparable to that observed after single doses with minimal accumulation after multiple dosing at Day 8 relative to Day 1 (Table 3). A dose proportional increase in exposure (C_{max} and AUC_{0-tau}) was observed across the dose range (Figure 3).

Part C – DUR-SUL Drug-Drug Interaction

Single dose co-administration of DUR and sulbactam (Cohort 13) did not alter the PK profile of DUR or SUL (Table 4). Further, co-administration had no effect on the urinary
excretion of either DUR or SUL (Supplemental Table). Single dose co-administration of 
DUR with IMI/CIL and/or SUL (Cohort 14) had no effect on the PK profile of DUR or 
IMI/CIL (Table 4). Co-administration of DUR, SUL, and/or IMI/CIL also had no effect on 
urinary excretion of DUR, and no changes were observed in urinary parameters for 
SUL, IMI or CIL (Supplemental Table).

PART D – Multiple Dose Administration of DUR, SUL, and IMI/CIL

After administration of DUR, C\text{max}, T\text{max}, and AUC\text{0-\text{tau}} were unchanged between Days 1 
and 11 (Table 5) indicating no apparent accumulation. In addition, DUR C\text{max} and T\text{max} 
obtained following multiple doses in combination with SUL and/or IMI/CIL were 
comparable to those obtained following single doses of DUR. The PK profiles of SUL, 
IMI, and CIL were unchanged between Days 1 and 11 consistent with no accumulation; 
the accumulation index was approximately 1. No apparent change in urinary parameters 
were observed for any study drug with co-administration (Supplemental Table).

Safety and Tolerability

DUR was generally safe and well tolerated. No dose-related trends were observed for 
any of the treatment-emergent adverse events (AEs), with the possible exception of 
phlebitis and catheter site phlebitis in subjects receiving multiple doses. Following a 
detailed review, there was no consistent pattern of local infusion site reactions to 
suggest a specific concern. When DUR was co-administered with SUL and IMI/CIL for 
11 days (Part D), the tolerability profile of DUR was not substantially different compared 
with multiple-dosing of DUR alone (Part B). The most common (≥5% of subjects)
treatment-emergent AEs were headache (DUR 13.8%; placebo 13.3%) and catheter site phlebitis (DUR 8.5%; placebo 3.3%). The most common (≥3% of subjects) drug-related AEs were headache (DUR 10.6%; placebo 10.0%) and catheter site phlebitis (DUR 5.3%; placebo 0%) (Table 6).

In Part B, one subject in the DUR 0.5 g DUR q6h cohort discontinued therapy for drug-related mild-moderate somnolence (mild) and nausea (moderate). The onset was on Days 1 and 2, but both events resolved by Day 2. Both events were considered possibly or probably related to therapy. In the same 0.5 g DUR q6h cohort, one subject with a known nut allergy experienced a serious AE, anaphylactic reaction to Brazil nuts, which was considered unrelated to therapy. One subject in the DUR 1 g q6h cohort discontinued for an infusion reaction (moderate, related) and somnolence (mild, unrelated) that was considered related to therapy. Both events occurred on and resolved by Day 1. The infusion site reaction was a systemic response, rather than catheter-related.

No clinically significant changes in clinical laboratory values, vital signs or ECG were observed in any subject. Decreases in mean neutrophil counts were observed in subjects receiving DUR in Part B but mean neutrophil count values remained within the reference range at all time points, and these changes were not considered clinically significant by the study investigator.

**DISCUSSION**
In the single dose phase, single doses of DUR administered across the dose range from 0.25 g to 8 g via a 3 h IV infusion demonstrated generally linear, dose proportional exposure. In the single cohort that received DUR 1 g with a 2 hour infusion, C<sub>max</sub> increased by approximately 50%. In the elderly cohort, exposure was increased by 100%, half-life was prolonged, and renal clearance and volume of distribution were reduced by approximately 50%; these observations are consistent with renal clearance as a predominant mechanism of elimination. In the multiple dose phase, DUR demonstrated linear dose proportional exposure across the dose range from 0.25 g – 2 g infused over 3 hours q6h. Minimal accumulation of DUR was observed up to Day 8, which is consistent with a short half-life. No significant effects on the PK profile of any study drug were observed with co-administration of DUR and SUL or with DUR and IMI/CIL. DUR was safe and well tolerated at single doses up to 8 g and at multiple doses up to 2 g q6h for up to 8 days. The safety profile of DUR was unchanged when co-administered as a single dose with SUL, IMI/CIL, and SUL plus IMI/CIL. DUR was associated with a low rate of discontinuation for AEs and no serious AEs.

The PK results from this study are consistent with other studies in healthy subjects where DUR administered alone and combined with SUL and/or IMI/CIL was well tolerated, including in subjects with various degrees of renal impairment (23,24). In these studies, DUR half-life ranged from 1.4 to 2.3 hours, C<sub>max</sub> from 27.0 to 33.4 mcg/mL, and AUC from 102 to 110 mcg*h/mL (23,24). The PK results are also consistent with those in patients with cUTI where no accumulation was observed with DUR following a 7 day dosing regimen (25), which is consistent with the MAD portion of
this study in healthy subjects. In the renal impairment study (23), no AEs were reported in healthy subjects, and only single AEs were reported in subjects undergoing assessment of DUR pulmonary concentrations (24). In a Phase 2 study of patients with cUTI, only 2 patients discontinued for AEs, no serious AEs were reported, and the most common AEs were headache, nausea, diarrhea, and vascular pain occurring in 3.8%-5.7% of patients (25). While renal excretion predominates as a major clearance mechanism for DUR, non-cytochrome P450-mediated hydrolytic cleavage of the diazabicyclooctenone core and bioconjugated metabolites account for the remaining clearance of DUR. Accounting for protein in human plasma (fu=0.9), and glomerular filtration rate (GFR) in healthy subjects of ~ 90 mL/min, renal clearance of DUR exceeds what would be expected via filtration and suggests an active (secretory) component. An in vitro assessment of transporter interactions with DUR has confirmed substrate affinity with the renal transporter OAT1 (data not published), confirming a role for active transport in the renal excretion of DUR.

SUL-DUR is undergoing clinical development for treating serious infections due to ABC pathogens, including treatment of hospitalized patients with pneumonia or bacteremia. Administration of SUL-DUR in an ongoing Phase 3 trial (clinicaltrials.gov: NCT03894046) is utilizing IMI/CIL as background carbapenem therapy as these serious Gram-negative infections are often polymicrobial in nature. Confirming the lack of potential DDI of SUL-DUR with IMI/CIL was an important component of the present study. Infections caused by ABC are associated with high rates of multi-drug resistance, which results in increased rates of morbidity, extended hospitalization, and higher
Currently, colistin is the only antibiotic that demonstrates consistent antimicrobial activity against ABC pathogens. Nevertheless, mortality rates are approximately 40% among patients with hospital-acquired or ventilator-associated pneumonia who are treated with colistin-based antibiotic regimens. Treatment with colistin is further complicated by dose-related toxicity, especially nephrotoxicity that occurs in 40% or more of patients. Thus, a critical unmet need remains for novel and safer treatment approaches for treating serious infections due to ABC pathogens.

Based on PK modeling conducted with this study and the renal impairment study, the dosage regimen of SUL-DUR for optimal target attainment against ABC is 1 g (of each component) administered q6h with a 3 hour IV infusion. A global Phase 3 study is evaluating the efficacy and safety of SUL-DUR for treating serious infections due to ABC in hospitalized patients.

METHODS

The study enrolled subjects at a single clinical site in Australia between September 2016 and August 2017. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. The study protocol was approved by an Institutional Review Board, and all subjects provided written informed consent prior to any study procedure. This study was registered at ClinicalTrials.gov Identifier: NCT02971423.

Study Design
This was a 4-part double-blind, placebo-controlled study (15 cohorts) of DUR administered as a 3 hour IV infusion (except for Cohort 4 where a 2 hour IV infusion was evaluated) (Table 7). Part A was a single ascending dose escalation phase that included 8 cohorts (6 active, 2 placebo subjects), including one cohort (Cohort 4) where DUR was administered with a 2 hour IV infusion and one cohort (Cohort 8) of elderly subjects age ≥65 years who received DUR 1 g via a 3 hour IV infusion. Part B was a multiple ascending dose escalation phase consisting of 4 cohorts (6 active, 2 placebo subjects) where subjects received DUR/placebo 0.25, 0.5, 1, or 2 g infused IV over 3 hours q6h for 29 doses.

Part C was a cross-over drug-drug interaction phase consisting of 2 cohorts (6 active, 2 placebo subjects). Cohort 13 was a 2-way single dose comparison between DUR 1 g and sulbactam 1 g. Cohort 14 was a 2-way single dose comparison between DUR 1 g and IMI/CIL 0.5/0.5 g. Part D was a repeat dosing phase of SUL-DUR plus IMI/CIL (10 active, 2 placebo subjects). In Cohort 15, subjects received 1 g IV DUR/placebo and 1 g IV SUL both infused over 3 hours and 0.5 g IV IMI/CIL infused over 30 minutes q6h for 41 doses.

**Subject Selection**

Healthy adult male and female subjects (age 18-55 years) and a single elderly cohort (age ≥65 years) were eligible if they were in good general health, had a body mass index of 18 to 32 kg/m² inclusive and had no clinically significant medical history. Subjects were required to have clinical laboratory values within normal limits and a
negative screen for drugs of abuse, alcohol, hepatitis B surface antigen (HBS Ag),
hepatitis C virus antibody (HCV Ab) and human immunodeficiency virus (HIV) at
screening. Female subjects were of non-childbearing potential or using a medically
acceptable contraceptive regimen and had a negative serum pregnancy test at
Screening and negative urine pregnancy test prior to study drug dosing. Male subjects
were surgically sterile or using a medically acceptable contraceptive regimen.

Subjects were excluded for hypersensitivity or allergic reaction to any beta-lactam
antibiotic; use of prescription or over-the-counter medications with 7 days of study drug
administration; participation in an investigational drug study within 30 days; current
smoker; history of major organ dysfunction; infection or underlying medical condition
that would interfere with taking study drug; history of excessive alcohol intake; or
concomitant disease or condition that could interfere with the conduct of the study.

**Study Assessments**

Routine physical examination, vital signs (supine blood pressure, heart rate, respiratory
rate, temperature), 12-lead electrocardiogram (ECG), and clinical laboratory testing
(serum chemistry, hematology, urinalysis) were performed at screening, at intervals
during the study, and at the 14 day follow-up

For Part A, plasma samples for PK analysis were collected 30 minutes prior and at 1, 2,
3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 hours after the dose except for Cohort 4 (2 h
infusion) where collection occurred at 30 minutes prior and 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 24,
36, and 48 hours after the dose. For Part B, plasma samples were collected on Day 1 at
30 minutes prior and 1, 2, 3, 3.5, 4, 5, 6 (prior to next dose), 8, 12 (prior to next dose)
hours; on Day 2 and Day 4 at 30 minutes prior to second dose; and on Day 8 at 30
minutes prior to the final dose and 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 hours after
the dose.

For Part C, Cohort 13, plasma samples were collected 30 minutes prior to the dose and
1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 (immediately prior to SUL) hours; then 1, 2, 3,
3.5, 4, 5, 6, 8, 12, 24, 36, and 48 hours (immediately prior to the SUL + DUR dose); and
then at 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 hours. For Cohort 14, plasma samples
were collected 30 minutes prior to DUR and 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48
hours (immediately prior to IMI/CIL); then 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48
hours (immediately prior to SUL + IMI/CIL); and then 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36,
and 48 hours. On Day 8, samples were collected 30 minutes prior to DUR + SUL +
IMI/CIL and 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 hours after the dose.

For Part D, plasma samples were collected on Day 1 at 30 minutes prior to the dose
and 1, 2, 3, 3.5, 4, 5, 6 (prior to next dose), 8, 12 hours (prior to next dose); 30 minutes
prior to second dose on Days 2 and 4; and on Day 11, 30 minutes prior to final dose
and at 1, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 hours.

For all cohorts, urine was collected from -12 – 0 hours prior to the start of infusion and
0-6, 6-12, 12-24, and 24-48 hours post start of infusion for determination of clearance of
In addition, urine was collected at 0-6, 6-12, 12-24, 24-48 hours post infusion on Days 8-10 for Part B; on Days 3 to 5 and 5 to 7 for Cohort 13; on Days 3 to 5, 5 to 7, and 8-10 for Cohort 14 for Part C; and Days 11 to 13 for Part D.

**Determination of DUR, SUL, CIL, and IMI plasma concentrations**

The concentrations of DUR, SUL, CIL, and IMI in plasma were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay operated in the negative ion mode (method numbers M8351072B, M8356245, and M8356242) performed at Covance (Salt Lake City, UT). A total of 2360 plasma samples were assayed between October 2016 and January 2018 (Covance Bioanalytical report 8355766). A subset of samples were retained for incurred sample assay reproducibility (ISR) testing, and the calculated assay variability values met acceptance criteria with at least two-thirds of the repeat results and original results falling within 20% of the mean of the two values. For all analytical runs, fortified calibration standards and quality controls (QCs) met acceptance criteria of within ±15% of the nominal concentration (±20% at the lower limit of quantification [LLOQ]).

Clinical samples were processed by protein precipitation with acetonitrile to isolate DUR, SUL, CIL and IMI. Stable label internal standards (ETX2514-^{13}C_{2}-^{15}N_{2}, [Lot No. AZ135725 14-015], sulbactam sodium-d{$_2$} [Lot No. 1S601], imipenem-d$_4$ [Lot No. 57513-190D1], and cilastatin $^{13}$C-$^{15}$N [Lot No. N70-63]) were utilized to establish sample and calibration analyte/internal standard peak area ratios. The blank control matrix was made up of human plasma (BioreclamationIVT) diluted 1:1 with SigmaFast.
(reconstituted protease inhibitor cocktail tablet [product S8820; Sigma-Aldrich, St. Louis, MO] in 10 mL of water) for preparation of calibration standards and QC samples.

Sample extraction of 50 µL aliquots of clinical samples, fortified standards and QC samples was completed following 50 µL addition of internal standard (250 ng/mL in 50:50 water acetonitrile). Acetonitrile (400 µL) was added and the mixture vortexed for five minutes prior to centrifugation at 3500 g for 10 minutes to separate precipitated protein from the supernatant. A100 µL aliquot of supernatant was transferred to 96-well plates. Samples were diluted further with 400 µL of water, and 5 µL of sample was injected into the LC-MS/MS system for analysis. The standard curves were linear for DUR (mean $r^2 \geq 0.996$) and CIL (mean $r^2 \geq 0.997$) over a concentration range of 5.0 to 5,000 ng/mL. The standard curves for SUL and IMI fit with quadratic regression (mean $r^2 \geq 0.997$ and $\geq 0.997$, respectively) over a concentration range of 5.0 to 5,000 ng/mL.

The respective precision and accuracy for DUR QC samples were 7.9% and -0.7% at 15 ng/mL, 6.9% and -3.0% at 175 ng/mL, 4.2% and 0.5% at 2,000 ng/mL, and 11.4% and -2.8% at 4,000 ng/mL. The respective precision and accuracy for SUL QC samples were 7.9% and -1.3% at 15 ng/mL, 4.7% and -5.1% at 175 ng/mL, 3.5% and -2.0% at 2,000 ng/mL, and 4.6% and -2.8% at 4,000 ng/mL. The respective precision and accuracy for CIL QC samples were 7.9% and 0.0% at 15 ng/mL, 8.0% and 6.3% at 175 ng/mL, 5.0% and 1.5% at 2,000 ng/mL, and 5.6% and -0.3% at 4,000 ng/mL. The respective precision and accuracy for IMI QC samples were 23.2% and -11.3% at 15 ng/mL, 4.9% and -4.6% at 175 ng/mL, 6.4% and -4.5% at 2,000 ng/mL, and 4.1% and -3.5% at 4,000 ng/mL. The LLOQ for all analytes was 5 ng/mL. Reported concentrations...
were multiplied by a factor of 2 to account for the 1:1 dilution of plasma samples with SigmaFast protease cocktail solution.

**Study Analysis**

PK parameters for the single dose arm (Part A) were peak plasma concentration ($C_{max}$); plasma concentration at time t ($C_t$); time to peak plasma concentration ($T_{max}$); area under the concentration-time curve from time 0 to 24 hours ($AUC_{0-24}$); AUC from time 0 to the last time point evaluated ($AUC_{0-t}$); AUC from time 0 and extrapolated to infinity ($AUC_{0-infty}$); elimination rate constant (kel); elimination half-life ($t_{1/2}$); clearance (CL); volume of distribution (Vd); cumulative excretion of unchanged drug in urine (Ae); urinary clearance (CLR); fraction excreted unchanged in urine (fe); and assessment of dose proportionality. For the multiple dose arms (Parts B and D), additional parameters were AUC from time 0 to the end of the dosing period ($AUC_{0-tau}$) and accumulation ratio (R0). AUC was calculated using log-linear trapezoidal rule. Half-life ($T_{1/2}$) was estimated as ln2/Kel. PK urine parameters were most accurately determined from Cohorts 6, 7, and 8, where data was available to 48 hours post-dose.

Pharmacokinetic parameters were summarized at each assessment time point using mean (± standard deviation [SD]), percent coefficient of variation (CV%), median, minimum, maximum. Single ascending dose data were assessed for dose proportionality using $C_{max}$ and AUC and accumulation ratios was determined using repeat-dose cohorts. All plasma concentrations below the limit of quantitation preceding $C_{max}$ were set to 0 and following $C_{max}$ were set to missing. Non-compartmental analysis
of PK parameters was performed using Phoenix WinNonlin v6.4 to determine PK parameters.

The intent-to-treat (ITT) population included all randomized subjects. The safety population was all randomized subjects who received any study drug. The PK population was all randomized subjects who received any study drug and had at least one quantifiable plasma concentration for the treatment received.
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**Author contribution**

All authors performed data analysis and interpretation, as well as manuscript review and approval.

**Disclosures**

At the time of this study, RI, JO, and KL were paid employees of Entasis Therapeutics, Inc., Waltham, MA. JL conducted the study on behalf of Entasis Therapeutics, Inc.
REFERENCES

1. Cai B, Echols R, Magee G, Ferreira JCA, Morgan G, Ariyasu M, Sawada T, Nagata TD. 2017. Prevalence of carbapenem-resistant Gram-negative infections in the United States predominated by Acinetobacter baumannii and Pseudomonas aeruginosa. Open Forum Infect Dis 4:ofx176.

2. Sievert DM, Rick P, Edwards JR, Schneider A, Patel J, Srinivasan A, Kallen A, Limbago B, Fridkin S. 2013. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. Infect Control Hosp Epidemiol 34:1-14.

3. Bulens SN, Yi SH, Walters MS, Jacob JT, Bower C, Reno J, Wilson L, Vaeth E, Bamberg W, Janelle SJ, Lynfield R, Vagnone PS, Shaw K, Kainer M, Muleta D, Mounsey J, Dumyati G, Concannon C, Beldavs Z, Cassidy PM, Phipps EC, Kenslow N, Hancock EB, Kallen AJ. 2018. Carbapenem-nonsusceptible Acinetobacter baumannii, 8 US Metropolitan Areas, 2012-2015. Emerg Infect Dis 24:727-734.

4. Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. 2019. Antimicrobial susceptibility of Acinetobacter calcoaceticus-Acinetobacter baumannii complex and Stenotrophomonas maltophilia clinical isolates: Results from the SENTRY Antimicrobial Surveillance Program (1997-2016). Open Forum Infect Dis 6(Suppl 1):S34-S46.

5. Lynch JP 3rd, Zhanel GG, Clark NM. 2017. Infections due to Acinetobacter baumannii in the ICU: Treatment options. Semin Respir Crit Care Med 38:311-25.
Clark NM, Zhanel GG, Lynch JP. Emergence of antimicrobial resistance among Acinetobacter species: a global threat. *Curr Opin Crit Care* 2016;22:491–499.

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

Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. 2017. Clinical and pathophysiological overview of *Acinetobacter* infections: a century of challenges. *Clin Microbiol Rev* 30:409–447.

Zilberberg MD, Kollef MH, Shorr AF. 2016. Secular trends in *Acinetobacter baumannii* resistance in respiratory and blood stream specimens in the United States, 2003 to 2012: a survey study. *J Hosp Med* 11:21–26.

Cheng A, Chuang YC, Sun HY, Sheng WH, Yang CJ, Liao CH, Hsueh PR, Yang JL, Shen NJ, Wang JT, Hung CC, Chen YC, Chang SC. 2015. Excess mortality associated with colistin tigecycline compared with colistin-carbapenem combination therapy for extensively drug-resistant *Acinetobacter baumannii* bacteremia: A multicenter prospective observational study. *Crit Care Med* 43:1194-1204.

Spellberg B, Bonomo RA. 2015. Combination therapy for extreme drug-resistant (XDR) *Acinetobacter baumannii*: Ready for prime-time? *Crit Care Med.* 43:1332-1334.

Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. 2016. Multidrug resistance, inappropriate empiric therapy, and hospital mortality in *Acinetobacter baumannii* pneumonia and sepsis. *Crit Care* 20:221.
13. Boral B, Unaldi Ö, Ergin A, Durmaz R, Eser ÖK; Acinetobacter Study Group. 2019. A prospective multicenter study on the evaluation of antimicrobial resistance and molecular epidemiology of multidrug-resistant *Acinetobacter baumannii* infections in intensive care units with clinical and environmental features. Ann Clin Microbiol Antimicrob. 18(1):19.

14. Amaya-Villar R, Garnacho-Montero J. 2019. How should we treat Acinetobacter pneumonia? Curr Opin Crit Care. 25:465-472.

15. Piperaki ET, Tzouvelekis LS, Miriagou V, Daikos GL. 2019. Carbapenem-resistant *Acinetobacter baumannii*: in pursuit of an effective treatment. Clin Microbiol Infect. 25:951-957.

16. Barnes MD, Kumar V, Bethel CR, Moussa SH, O'Donnell J, Rutter JD, Good CE, Hujer KM, Hujer AM, Marshall SH, Kreiswirth BN, Richter SS, Rather PN, Jacobs MR, Papp-Wallace KM, van den Akker F, Bonomo RA. 2019. Targeting multidrug-resistant *Acinetobacter* spp.: Sulbactam and the diazabiclooctenone β-lactamase inhibitor ETX2514 as a novel therapeutic agent. *MBio* 10: pii: e00159-19. doi: 10.1128/mBio.00159-19.

17. Durand-Réville TF, Guler S, Comita-Prevoir J, Chen B, Bifulco N, Huynh H, Lahiri S, Shapiro AB, McLeod SM, Carter NM, Moussa SH, Velez-Vega C, Olivier NB, McLaughlin R, Gao N, Thresher J, Palmer T, Andrews B, Giacobbe RA, Newman JV, Ehmann DE, de Jonge B, O'Donnell J, Mueller JP, Tommasi RA, Miller AA. 2017. ETX2514 is a broad-spectrum beta-lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including *Acinetobacter baumannii*. Nat Microbiol 2:17104.
18. Shapiro AB, Gao N, Jahic H, Carter NM, Chen A, Miller AA. 2017. Reversibility of covalent, broad-spectrum serine beta-lactamase inhibition by the diazabicyclooctenone ETX2514. *ACS Infect Dis* 3:833–844.

19. McLeod SM, Moussa S, Hackel M, Tommasi R, Miller A. 2019. The novel beta-lactamase inhibitor ETX2514 effectively restores sulbactam activity against recent global *Acinetobacter baumannii-calcoaceticus* complex clinical isolates [abstract P1185]. In: Program and abstracts of the 29th European Congress of Clinical Microbiology and Infectious Diseases.

20. McLeod SM, Roth B, Flamm R, Huband M, Mueller J, Tommasi R, Perros M, Miller A. 2017. The antibacterial activity of sulbactam and the novel beta-lactamase inhibitor ETX2514 combined with imipenem or meropenem against recent clinical isolates of *Acinetobacter baumannii and Pseudomonas aeruginosa*, [abstract Friday-82]. In: Program and abstracts of ASM Microbe (New Orleans). Washington, DC: American Society for Microbiology.

21. McLeod SM, Shapiro AB, Moussa SH, Johnstone M, McLaughlin RE, de Jonge BLM, Miller AA. 2018. Frequency and mechanism of spontaneous resistance to sulbactam combined with the novel beta-lactamase inhibitor ETX2514 in clinical isolates of *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 62:e01576-17.

22. Seifert H, Stefanik D, Muller C, Kresken M, Higgins PG, Miller A. 2019. The susceptibility of global isolates of *Acinetobacter baumannii* to ETX2514SUL and comparators [abstract P1186]. In: Program and abstracts of the 29th European Congress of Clinical Microbiology and Infectious Diseases.
23. O'Donnell D, Preston RA, Mamikonyan G, Stone E, Isaacs R. 2019. Pharmacokinetics, safety, and tolerability of intravenous ETX2514 and sulbactam in subjects with renal impairment and healthy matched control subjects. *Antimicrob Agents Chemother* 63(9). pii: e00794-19. doi: 10.1128/AAC.00794-19.

24. Rodvold KA, Gottfried MH, Isaacs RD, O'Donnell JP, Stone E. 2018. Plasma and intrapulmonary concentrations of ETX2514 and sulbactam following intravenous administration of ETX2514SUL to healthy adult subjects. *Antimicrob Agents Chemother* 62 pii: e01089-18. doi: 10.1128/AAC.01089-18.

25. Sagan O, Yakubsevitch R, Yanev K, Fomkin R, Stone E, Hines E, O'Donnell J, Miller A, Isaacs R, Srinivasan S. 2019. A double-blind, randomized, placebo-controlled study of intravenous sulbactam-durlobactam in hospitalized adults with complicated urinary tract infections, including acute pyelonephritis. *Antimicrob Agents Chemother* pii: AAC.01506-19. doi: 10.1128/AAC.01506-19.

26. Du X, Xu X, Yao J, Deng K, Chen S, Shen Z, Yang L, Feng G. 2019. Predictors of mortality in patients infected with carbapenem-resistant *Acinetobacter baumannii*: A systematic review and meta-analysis. *Am J Infect Control* 47:1140-1145.

27. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, Skiada A, Andini R, Eliakim-Raz N, Nutman A, Zusman O, Antoniadou A, Pafundi PC, Adler A, Dickstein Y, Pavleas I, Zampino R, Daitch V, Bitterman R, Zayyad H, Koppel F, Levi I, Babich T, Friberg LE, Mouton JW, Theuretzbacher U, Leibovici L. 2018. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. *Lancet Infect Dis* 18:391-400.
28. Motsch J, Murta de Oliveira C, Stus V, Köksal I, Lyulko O, Boucher HW, Kaye KS, File TM, Brown ML, Khan I, Du J, Joeng HK, Tipping RW, Aggrey A, Young K, Kartsonis NA, Butterton JR, Paschke A. 2019. RESTORE-IMI 1: A multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin Infect Dis*. pii: ciz530. doi: 10.1093/cid/ciz530.

29. Zavascki AP, Nation RL. 2017. Nephrotoxicity of polymyxins: Is there any difference between colistimethate and polymyxin B? *Antimicrob Agents Chemother*. 61(3). pii: e02319-16. doi: 10.1128/AAC.02319-16.

30. Onufrik NJ, Rubino CM, Ambrose PG, Isaacs R, Srinivasan S, O'Donnell J. 2019. Population pharmacokinetic and pharmacokinetic-pharmacodynamic target attainment analyses of ETX2514SUL to support dosing regimens in patients with varying renal function [poster P1953]. In: Program and abstracts of the 29th European Congress of Clinical Microbiology and Infectious Diseases.
| Age, years | Placebo Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4* | Cohort 5 | Cohort 6 | Cohort 7 | Cohort 8* |
|-----------|-----------------|----------|----------|-----------|----------|----------|----------|----------|
| 33 ± 16   | 24 ± 4          | 31 ± 13  | 31 ± 12  | 31 ± 8    | 21 ± 2   | 25 ± 3   | 70 ± 3   |
| Age range | 20-74           | 19-31    | 20-54    | 18-54     | 21-54    | 23-46    | 19-24    | 21-28    | 66-74    |
| Male, n (%) | 11 (70)         | 3 (50)   | 3 (50)   | 3 (50)    | 5 (83)   | 3 (50)   | 5 (83)   | 2 (33)   | 5 (83)   |
| Hispanic or latino, n (%) | 2 (13)          | 0        | 2 (33)   | 0         | 0        | 0        | 0        | 0        |
| Race, n (%) | White 15 (94)   | 4 (67)   | 3 (50)   | 5 (83)    | 6 (100)  | 4 (67)   | 2 (33)   | 5 (83)   | 5 (83)   |
| Asian     | 0               | 1 (17)   | 1 (17)   | 1 (17)    | 0        | 2 (33)   | 1 (17)   | 1 (17)   | 1 (17)   |
| Black     | 1 (6)           | 0        | 0        | 0         | 0        | 0        | 2 (33)   | 0         | 0        |
| Other     | 0               | 1 (17)   | 2 (33)   | 0         | 0        | 0        | 1 (16)   | 0         | 0        |
| Weight, kg | 77 ± 13         | 66 ± 14  | 65 ± 7   | 67 ± 8    | 72 ± 12  | 81 ± 17  | 74 ± 17  | 68 ± 16  | 85 ± 10  |
| BMI, kg/m² | 25 ± 3.4 | 22 ± 2.7 | 22 ± 1.7 | 23 ± 1.6 | 24 ± 2.7 | 27 ± 3.1 | 24 ± 2.9 | 23 ± 3.5 | 27 ± 2.4 |
|-----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|

*Cohort 4 was a 2 hour IV infusion; all other cohorts were a 3 hour IV infusion*

*Elderly subjects >65 years of age*

*Mean ± standard deviation*
Table 1 (continued). Baseline characteristics – Parts B, C, and D.

| Part B | Part C | Part D |
|--------|--------|--------|
|        | Durlobactam | Cohort 13 | Cohort 14 | Cohort 15 |
|        | Placebo | Cohort 9 | Cohort 10 | Cohort 11 | Cohort 12 | DUR 1g g + SUL + IMI/CIL | Placebo | DUR 1g g + SUL + IMI/CIL | Placebo | DUR g + SUL + IMI/CIL |
|        | (n=8)   | 0.25 g (n=6) | 0.5 g (n=6) | 1.0 g (n=6) | 2.0 g (n=6) | (n=6) | (n=6) | (n=2) | (n=2) | (n=10) |
| **Age, years** | 30 ± 1 | 28 ± 5 | 32 ± 5 | 25 ± 3 | 30 ± 6 | 27 ± 7 | 29 ± 4 | 24 ± 3 | 27 ± 1 | 28 ± 8 | 36 ± 6 |
| **Age range** | 29-33 | 19-33 | 24-38 | 23-30 | 24-40 | 20-40 | 26-32 | 21-29 | 26-27 | 21-44 | 32-40 |
| **Male, n (%)** | 6 (75) | 3 (50) | 3 (50) | 4 (67) | 5 (83) | 4 (67) | 1 (50) | 3 (50) | 1 (50) | 7 (70) | 2 (100) |
| **Hispanic or Latino, n (%)** | 0 | 0 | 1 (17) | 1 (17) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Race, n (%)** | White | 6 (75) | 5 (83) | 4 (67) | 5 (83) | 5 (83) | 0 | 5 (83) | 2 (100) | 9 (90) | 1 (50) |
|        | Asian | 1 (13) | 1 (17) | 1 (17) | 0 | 0 | 1 (17) | 2 (100) | 0 | 1 (10) | 1 (50) |
|        | Black | 0 | 0 | 1 (17) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|        | Other | 1 (13) | 0 | 0 | 1 (17) | 1 (17) | 0 | 0 | 1 (17) | 0 | 0 | 0 |
| Weight (kg) | 80 ± 13 | 64 ± 9 | 76 ± 13 | 73 ± 10 | 79 ± 17 | 81 ± 17 | 74 ± 17 | 68 ± 16 | 85 ± 10 |
|------------|---------|--------|---------|---------|---------|---------|---------|---------|---------|
| BMI (kg/m²) | 25 ± 3.5 | 23 ± 2.1 | 25 ± 3.5 | 24 ± 3.4 | 25 ± 4.3 | 27 ± 3.1 | 24 ± 2.9 | 23 ± 3.5 | 27 ± 2.4 |

Mean ± standard deviation

In parts C and D, dose of DUR and SUL was 1 g; dose of IMI/CIL was 0.5 g.
Table 2. Mean ± standard deviation PK parameters for DUR in SAD Part A (n=6 for each cohort).

| Cohort | Dose (g) | T_{1/2} (h) | T_{max} (h) | C_{max} (µg/mL) | AUC_{0-24} (h*µg/mL) | AUC_{0-t} (h*µg/mL) | CL (L/h) | Vd_{ss} (L) | K_{el} (L/h) |
|--------|---------|-------------|-------------|-----------------|----------------------|----------------------|----------|-------------|-------------|
| 1      | 0.25    | 1.5 ± 0.1   | 3.0         | 6.9 ± 1.0       | 25.5 ± 3.7           | 25.4 ± 3.7           | 10.0 ± 1.6 | 16.6 ± 3.6   | 0.5 ± 0.04   |
| 2      | 0.5     | 2.0 ± 0.4   | 3.0         | 9.9 ± 2.0       | 47.7 ± 7.5           | 47.4 ± 7.7           | 10.7 ± 1.9 | 25.8 ± 2.9   | 0.4 ± 0.07   |
| 3      | 1.0     | 2.0 ± 0.3   | 3.0         | 20.7 ± 2.8      | 76.1 ± 10.5          | 75.6 ± 10.4          | 13.4 ± 1.9 | 25.7 ± 5.0   | 0.4 ± 0.04   |
| 4*     | 1.0     | 2.2 ± 0.2   | 2.0         | 31.3 ± 6.9      | 100.8 ± 28.9         | 100.7 ± 29.0         | 10.6 ± 2.7 | 22.7 ± 6.4   | 0.3 ± 0.04   |
| 5      | 2.0     | 2.2 ± 0.2   | 2.5         | 41.5 ± 6.4      | 173.3 ± 25.6         | 173.3 ± 25.6         | 11.8 ± 1.9 | 24.3 ± 3.2   | 0.3 ± 0.03   |
| 6      | 4.0     | 2.7 ± 0.6   | 3.0         | 96.2 ± 13.6     | 367.3 ± 55.1         | 367.5 ± 55.0         | 11.1 ± 1.8 | 22.4 ± 3.6   | 0.3 ± 0.05   |
| 7      | 8.0     | 2.8 ± 0.4   | 3.0         | 175.7 ± 29.0    | 730.0 ± 164.4        | 731.3 ± 163.4        | 11.4 ± 2.3 | 28.1 ± 9.5   | 0.3 ± 0.04   |
| 8*     | 1.0     | 2.4 ± 0.3   | 3.0         | 37.8 ± 2.5      | 151.2 ± 14.0         | 151.2 ± 14.0         | 6.7 ± 0.6  | 14.5 ± 2.0   | 0.3 ± 0.03   |

* Cohort 4 was a 2 hour IV infusion; all other cohorts were a 3 hour IV infusion

b Elderly subjects >65 years of age

c Median
Table 3. Mean ± standard deviation PK parameters for DUR in MAD Part B.

| Cohort | Dose (g) | Day | T_{1/2} (h) | T_{max} (h) | C_{max} (µg/mL) | AUC_{0-\tau} (h*µg/mL) | CL (L/h) | V_{dss} (L) | Accum. Index^d |
|--------|----------|-----|-------------|-------------|----------------|------------------------|----------|------------|----------------|
| 9      | 0.25     | 1   | ND          | 3.0         | 6.9 ± 1.4      | 23.1 ± 4.9             | ND       | ND         | ND             |
|        |          | 8   | 1.9 ± 0.4   | 2.5         | 7.5 ± 1.3      | 26.2 ± 5.2             | 9.8 ± 1.7| 18.5 ± 2.9 | 1.1 ± 0.07     |
| 10a    | 0.5      | 1   | ND          | 3.0         | 14.9 ± 2.2     | 50.3 ± 9.0             | ND       | ND         | ND             |
|        |          | 8   | 2.6 ± 0.1   | 3.0         | 14.8 ± 1.1     | 53.4 ± 4.8             | 9.4 ± 0.9| 18.1 ± 1.8 | 1.3 ± 0.01     |
| 11b    | 1.0      | 1   | ND          | 2.5         | 26.9 ± 13.1    | 79.8 ± 35.9            | ND       | ND         | ND             |
|        |          | 8   | 3.5 ± 0.9   | 3.0         | 33.4 ± 6.0     | 108.7 ± 13.9           | 9.3 ± 1.1| 17.2 ± 2.0 | 1.5 ± 0.18     |
| 12     | 2.0      | 1   | ND          | 3.0         | 51.9 ± 8.0     | 179.1 ± 29.9           | ND       | ND         | ND             |
|        |          | 8   | 10.1 ± 2.9  | 3.0         | 53.3 ± 7.8     | 192.6 ± 31.2           | 10.6 ± 1.5| 21.8 ± 2.0 | 3.0 ± 0.69     |

Doses were administered q6h via a 3 hour IV infusion

ND = not determined

^a N=4; ^b N=5

c Median

d AI = 1/1 - e^{-k_{el} \tau}
Table 4. PK parameters for DUR, SUL, and IMI/CIL alone and after co-administration in Part C

| Drug Regimen          | T₁/₂ (h) | Cᵢ₅₀ (µg/mL) | AUC₀-2₄ (µg*h/mL) | CL (L/h) | Vdss (L) |
|-----------------------|----------|--------------|-------------------|----------|---------|
| Durlobactam PK – Cohort 13 |          |              |                   |          |         |
| DUR - Day 1           | 2.0 ± 0.4| 26.9 ± 3.6   | 104.4 ± 6.6       | 9.6 ± 0.6| 17.6 ± 2.0 |
| DUR + SUL - Day 5     | 2.0 ± 0.4| 28.1 ± 2.5   | 105.4 ± 6.4       | 9.5 ± 0.6| 17.4 ± 1.7 |
| Sulbactam PK – Cohort 13 |          |              |                   |          |         |
| SUL - Day 1           | 1.3 ± 0.1| 20.7 ± 0.7   | 68.5 ± 4.7        | 14.6 ± 1.0 | 18.0 ± 1.6 |
|                              | Imipenem PK Cohort 14                                                                 |                              |
|------------------------------|---------------------------------------------------------------------------------------|------------------------------|
|                              | **IMI/CIL** – **Day 3** | 1.2 ± 0.1 | 34.4 ± 5.3 | 43.7 ± 9.2 | 11.8 ± 2.1 | 14.3 ± 2.2 |
|                              | **IMI/CIL + DUR** – **Day 5** | 1.2 ± 0.2 | 31.3 ± 2.3 | 42.2 ± 5.6 | 12.0 ± 1.4 | 15.2 ± 1.2 |
|                              | **IMI/CIL + SUL** – **Day 8** | 1.2 ± 0.1 | 32.7 ± 4.0 | 45.7 ± 5.1 | 11.0 ± 1.2 | 13.9 ± 1.0 |
|                              | **Cilastatin PK Cohort 14**                                                        |                              |
|                              | **IMI/CIL** – **Day 3** | 1.2 ± 0.2 | 46.0 ± 8.3 | 49.6 ± 9.8 | 10.4 ± 1.8 | 9.6 ± 1.4 |
|                              | **IMI/CIL + DUR** – **Day 5** | 1.2 ± 0.2 | 44.0 ± 6.1 | 47.1 ± 7.2 | 10.8 ± 1.8 | 9.9 ± 1.2 |
|                              | **IMI/CIL + DUR + SUL** – **Day 8** | 1.2 ± 0.2 | 40.7 ± 4.9 | 46.9 ± 6.6 | 10.9 ± 1.6 | 10.4 ± 0.9 |

Values are mean ± standard deviation

Dose of DUR and SUL was 1 g; dose of IMI/CIL was 0.5 g
Table 5. Mean (± standard deviation) PK parameters for DUR, SUL, IMI, and CIL on Day 1 and Day 11 after co-administration in Part D (n=10).

| Cohort | Day | T1/2 (h) | Tmax (h) | Cmax (µg/mL) | AUC0-tau (h*µg/mL) | CL (L/h) | Vdss (L) | Accum. Index |
|--------|-----|----------|----------|---------------|---------------------|----------|----------|--------------|
| DUR    | 1   | ND       | 2.8 (0.5)| 27.1 ± 1.3    | 91.8 ± 5.9          | ND       | ND       | ND           |
|        | 11  | 4.3 ± 3.0| 2.4 (0.5)| 28.1 ± 8.6    | 96.3 ± 11.6         | 10.5 ± 1.2| 21.4 ± 4.9| 1.6 ± 0.7    |
| SUL    | 1   | ND       | 2.7 (0.5)| 23.9 ± 1.3    | 76.7 ± 5.8          | ND       | ND       | ND           |
|        | 11  | 2.0 ± 1.0| 2.6 (0.5)| 22.4 ± 6.1    | 67.9 ± 7.6          | 14.5 ± 1.5| 20.3 ± 5.8| 1.2 ± 0.21  |
| IMI    | 1   | ND       | 0.5 (0)  | 24.7 ± 5.2    | 35.7 ± 4.4          | ND       | ND       | ND           |
|        | 11  | 1.5 ± 0.3| 0.5 (0)  | 24.1 ± 5.3    | 33.1 ± 5.4          | 15.5 ± 2.2| 21.7 ± 3.8| 1.1 ± 0.04  |
| CIL    | 1   | ND       | 0.5 (0)  | 38.6 ± 6.0    | 45.6 ± 7.0          | ND       | ND       | ND           |
|        | 11  | 1.7 ± 0.3| 0.5 (0)  | 38.0 ± 5.6    | 39.4 ± 7.2          | 13.1 ± 2.4| 13.9 ± 2.1| 1.1 ± 0.04  |

Doses were administered q6h via a 3 hour IV infusion; Dose of DUR and SUL was 1 g; dose of IMI/CIL was 0.5 g

Accum: accumulation index; AUC0-tau: area under the concentration-time curve from time 0 to the end of the dosing period; CL: clearance; Cmax: peak plasma concentration; ND = not determined; T1/2: elimination half-life; Tmax: time to Cmax; Vdss: volume of distribution.
Table 6. Incidence of drug-related AEs occurring in >1% of subjects

| Adverse Event            | Number (%) of Subjects | All DUR (n=94) | All Placebo (n=30) | All DUR + SUL and IMI/CIL (n=10) | Placebo + SUL and IMI/CIL (n=2) |
|--------------------------|------------------------|----------------|--------------------|----------------------------------|---------------------------------|
| Abdominal pain           |                        | 0              | 0                  | 1 (50.0)                         |                                 |
| Catheter site phlebitis  | 5 (5.3)                | 0              | 0                  | 0                                |                                 |
| Dizziness                | 4 (4.3)                | 1 (3.3)        | 2 (20.0)           | 0                                |                                 |
| Dysgeusia                | 2 (2.1)                | 0              | 2 (20.0)           | 0                                |                                 |
| Headache                 | 10 (10.6)              | 3 (10.0)       | 2 (20.0)           | 0                                |                                 |
| Musculoskeletal stiffness|                        |                | 1 (10.0)           | 0                                |                                 |
| Nasal congestion         | 2 (2.1)                | 0              | 0                  | 0                                |                                 |
| Nausea                   | 2 (2.1)                | 1 (3.3)        | 0                  | 0                                |                                 |
| Pain in extremity        | 1 (1.1)                | 1 (3.3)        | 0                  | 0                                |                                 |
| Phlebitis                | 2 (2.1)                | 0              | 0                  | 0                                |                                 |
| Polydipsia               | 0                      | 0              | 1 (10.0)           | 0                                |                                 |
| Pruritus                 | 2 (2.1)                | 1 (3.3)        | 0                  | 0                                |                                 |
| Somnolence               | 1 (1.1)                | 1 (3.3)        | 0                  | 0                                |                                 |
| Upper respiratory infection | 1 (1.1)            | 1 (3.3)        | 0                  | 0                                |                                 |
| Vulvovaginal candidiasis | 2 (2.1)                | 0              | 1 (10.0)           | 0                                |                                 |
Figure 1. Mean DUR plasma concentrations for cohorts, 1, 2, 3, 5, 6, and 7 (top) and cohorts 3, 4, and 8 (bottom) during Part A single dose phase.
Figure 2. $\text{AUC}_0-\text{inf}$ and $C_{\text{max}}$ vs. dose for 3-hour infusion cohorts 1, 2, 3, 5, 6, and 7.
Figure 3. Mean ± standard deviation plasma concentrations for DUR on Day 1 and Day 8 during Part B multiple dose phase.