Pharmacokinetics and Tolerability of Intravenous Sulbactam-Durlobactam With Imipenem/Cilastatin in Hospitalized Adults with Complicated Urinary Tract Infections, Including Acute Pyelonephritis

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Running Title: IV Sulbactam-Durlobactam in Complicated UTI

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Durlobactam (ETX2514) is a novel β-lactamase inhibitor with broad spectrum activity against Ambler class A, C, and D β-lactamases. Durlobactam restores in vitro activity of sulbactam (SUL) against Acinetobacter baumannii-calcoaceticus complex (ABC). Sulbactam-durlobactam (SUL-DUR) is under development for treating ABC infections. Eighty patients with complicated urinary tract infection (cUTI), including acute pyelonephritis (AP) were randomized 2:1 to SUL-DUR 1 g/1 g IV or placebo every 6 hours (q6h) for 7 days and background therapy with imipenem/cilastatin (IMI) 500 mg IV q6h to evaluate the tolerability of SUL-DUR in hospitalized patients. Patients with bacteremia could receive up to 14 days of therapy. SUL-DUR tolerability and pharmacokinetic (PK) parameters were determined. Efficacy at the Test-of-Cure (TOC) visit was recorded. SUL-DUR was well tolerated with no serious adverse events (AEs) reported. Headache (5.7%), nausea (3.8%), diarrhea (3.8%), and vascular pain (3.8%) were the most common drug-related AEs with SUL-DUR of mostly of mild or moderate severity. The PK profile of DUR and SUL in hospitalized patients was consistent with observations in healthy volunteers. Overall success in the microbiological-modified intent-to-treat (ITT) population was similar between the groups as would be expected with IMI background therapy in all patients (at TOC 76.6% (n=36) with SUL-DUR and 81.0% (n=17) with placebo). SUL-DUR in combination with IMI was well tolerated in patients with cUTI. Pharmacokinetics of SUL-DUR in hospitalized patients was similar to that observed in healthy volunteers.
INTRODUCTION

*Acinetobacter baumannii* (Ab) is identified by the Centers for Disease Control and World Health Organization as a critical priority in need of new treatment options [1-3]. Ab belongs to a larger cluster of species that is referred to as *Acinetobacter baumannii-calcoaceticus* complex (ABC) that has been associated with serious infections including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, complicated urinary tract infections (cUTIs), bloodstream infections, and wound infections [4,5]. Approximately two-thirds of ABC infections are caused by multi-drug resistant (MDR) isolates [6-8]. Serious infections caused by MDR ABC are associated with high rates of morbidity [4,9-12], and mortality may range up to 50% or higher [4,13-15]. Thus, an urgent need exists to identify new antimicrobial agents to treat serious ABC infections [8,16].

Durlobactam (also known as ETX2514) is a novel, diazabicyclooctenone β-lactamase inhibitor (BLI) that exhibits potent inhibition of Class A, C, and D β-lactamases [16-18]. *In vitro*, durlobactam exhibits intrinsic antibacterial activity against some *Enterobacteriaceae* but has no significant intrinsic activity against ABC. Sulbactam (SUL), a Class A BLI, also exhibits antibacterial activity against ABC, however, its use as monotherapy has been limited by increasing resistance [11]. In preclinical studies, potent *in vitro* and *in vivo* activity against ABC is observed with sulbactam-durlobactam (SUL-DUR) [17,19,20], including carbapenem-resistant ABC, and this activity extended to isolates resistant to colistin [21,22]. SUL-DUR is being developed for the treatment of infections caused by ABC, including MDR and carbapenem-resistant isolates.
Phase 1 clinical studies in healthy subjects evaluated pharmacokinetic (PK) profiles of DUR after single and multiple-ascending intravenous (IV) doses and in combination with SUL, plasma and intrapulmonary concentrations of both components, and the drug-drug interaction potential between DUR and SUL [23-25]. SUL-DUR is being developed as for use in patients with Acinetobacter infections, the majority of whom are expected to be critically ill. Prior to dosing critically ill patients in a Phase 3 study, assessment of the PK and tolerability in a hospitalized patient population in a Phase 2 study was planned as a bridging strategy. This study evaluated the tolerability and PK of SUL-DUR in patients with cUTI, including acute pyelonephritis (AP).

**RESULTS**

Eighty patients were randomized to SUL-DUR (n=53) or placebo (n=27). Two patients discontinued due to an AE in the SUL-DUR group. One patient had moderate urticaria on Day 3 of study drug that was self-limiting. The second patient was a 82-year-old patient, who had an increased serum creatinine (69 µmol/L [normal: 55-127 µmol/L] on Day 1 to 138 µmol/L on Day 3 and 109 µmol/L on Day 5). Study drug was discontinued on Day 7 as the protocol did not allow for adjustment of dose of IMI or SUL-DUR for changes in creatinine clearance, which would have been necessary to safeguard this elderly patient.

At baseline, treatment groups were generally comparable for demographic and clinical characteristics (Table 1). Two patients had bacteremia at baseline.
Tolerability

The primary objective of this study was to assess the tolerability profile of SUL-DUR, which was generally well tolerated (Table 2). The incidence of AEs was 20 (37.7%) patients in the SUL-DUR group and 8 (29.6%) patients in the placebo group experiencing at least 1 event. The majority of AEs were mild or moderate in severity with no reported serious AEs. The most commonly reported drug-related AEs were headache, diarrhea, nausea, and phlebitis. The incidence of treatment-related AEs was similar between treatment groups: 12 (22.6%) patients with SUL-DUR and 4 (14.8%) patients with placebo. One (1.9%) patient in the SUL-DUR group had severe nausea that was considered treatment-related, but the patient continued in the study.

Two subjects discontinued treatment. A 35 year-old Caucasian female randomized to SUL-DUR experienced acute urticaria on Study Day 2. Treatment included prednisolone, diphenhydramine, and chloropyramine, and study medication was permanently discontinued on Day 3 and the subject recovered from the event on Day 5 but was discontinued from the study. The investigator considered the event moderate and related to study drug. A 82 year-old Caucasian male randomized to SUL-DUR had a central laboratory findings on Day 1 of serum creatinine 69 µmol/L (normal: 55 µmol/L-127 µmol/L) and creatinine clearance 94 mL/min (normal: >52 mL/min). There was a gradual increase in creatinine and on Day 7, creatinine was 107 µmol/L and creatinine clearance was 61 mL/min. Study medication was discontinued due to
reduced creatinine clearance on Day 7, as the protocol did not allow for dose reductions of Imipenem.

No clinically meaningful changes in safety laboratory data were noted. Compared to the placebo group, a larger change from baseline of mean leukocyte and neutrophil counts in the SUL-DUR group was observed at the LFU visit (-0.24 versus -1.42 for leukocytes and -4.96 versus -8.22 for neutrophils). However, baseline leukocyte counts in these patients with infections were high, with the median in the SUL-DUR and placebo groups being 8.1 versus 6.75. Moreover, no patients developed leukopenia or neutropenia. Mild changes from baseline were observed in patients in hepatic safety laboratory parameters in both groups at similar rates. None of these changes were clinically significant or led to discontinuation of therapy. No clinically meaningful changes in vital signs, ECG or physical findings were observed.

**Pharmacokinetics**

Plasma concentrations of durlobactam and sulbactam in Phase 2 subjects were comparable over the 6 hours sampling interval (Figure 1). Steady-state PK parameters of durlobactam and sulbactam were generally consistent when administered as a 1:1 ratio of 1000 mg +1000 mg infused over 3 hours every 6 hours (Table 3). Mean elimination half-lives of 2.2 and 1.6 h for durlobactam and sulbactam resulted in an accumulation index of 1.2 and 1.1, respectively. Mean steady-state clearance and volume of distribution of durlobactam were 10.3 L/h and 31.6 L, respectively. These values were similar to mean clearance and volume of distribution estimates for
sulbactam (13.4 L/h and 36.0 L, respectively). Variability of PK parameter estimates of clearance and volume of distribution were higher for sulbactam (62.3% and 64.9%) versus durlobactam (38.9% and 41.6%).

**Efficacy**

Overall success in the m-MITT population was similar in both groups; 36 (76.6%) patients in the SUL-DUR group and 17 (81.0%) patients in the placebo group as would be expected with a background therapy with IMI in all patients. Overall success in the ME population occurred in 36 (80.0%) patients in the SUL-DUR group and 17 (81.0%) patients in the placebo group.

Seven patients presented with a baseline IMI-non-susceptible (IMI-NS defined as MIC ≥2 mg/L) Gram-negative pathogen. For these patients, the overall success at the TOC visit occurred in 3 of 3 (100%) in the SUL-DUR group (one IMI-NS *P. mirabilis* and two IMI-NS *P. aeruginosa*) and in 3 of 4 (75%) in the placebo group (two IMI-NS *P. aeruginosa* and one of 2 (50%) IMI-NS *K. pneumoniae*).

**DISCUSSION**

This was the first study of SUL-DUR in hospitalized patients where all patients received background therapy with IMI in addition to SUL-DUR or placebo. SUL-DUR was generally well tolerated and with a tolerability profile similar to what had been observed in healthy volunteers. Previous studies have shown that DUR with and without SUL and IMI is well tolerated in healthy volunteers [23]. The majority of AEs in the SUL-DUR
group were mild or moderate in severity, with no serious AEs reported. As would be expected with a background of therapy with IMI, clinical and microbiological outcomes were comparable between treatment groups. Additionally, PK parameters in this population were similar to that observed in healthy volunteers [23,24,25]. A population pharmacokinetic (PPK) and pharmacokinetic-pharmacodynamic target attainment analysis (PK-PD TA) has recently been conducted for SUL-DUR in preparation for Phase 3 dose justification [26]. Plasma concentration data from a Phase 1 SAD/MAD and a Phase 1 renal impairment study was utilized in the construction of a DUR PPK model. For SUL a published PPK model was utilized in support of the dose justification. For both DUR and SUL, visual predictive checks (VPCs) of model-based simulations to the observed Phase 2 data presented here were used as a qualification of the base structural models and the PK-PD TA analyses. Both PPK models were found to predict the observed Phase 2 plasma SUL-DUR concentration data quite well with an excellent probability of PK-PD TA of >90% against pathogens with a SUL-DUR MIC of ≤4 mg/L.

SUL-DUR is being developed for patients with serious infections due to ABC, including HABP/VABP. For infections caused by ABC, high rates of multi-drug resistance contribute to high morbidity, extended hospitalization, and excess mortality [4,6,27]. Currently, colistin is the only antibiotic with consistent activity against ABC. Mortality rates among HABP/VABP patients treated with colistin based regimens remain high, around 40% [28] and doses are limited by toxicity issues. A critical unmet need remains for novel and safer treatment approaches for treating ABC.
Limitations of this study include the inability to comment on the efficacy of SUL-DUR. This agent is a narrow spectrum antimicrobial, designed to treat highly resistant strains of ABC infection; however as expected, no patient with ABC infection was enrolled in this study. DUR is a broad spectrum BLI and has been shown to restore IMI activity among carbapenem resistant gram negative isolates. A post-hoc sequencing analysis and susceptibility testing of the small number of IMI-NS isolates in this study revealed that six of the seven encoded one or more carbapenemase genes and addition of DUR \textit{in vitro} restored IMI susceptibility to all six. While indirect, these results support the hypothesis that \textit{β-lactamase inhibition by DUR can be clinically effective among carbapenem resistant Gram-negative pathogens.}

In conclusion, SUL-DUR was generally well tolerated in moderately ill, hospitalized adults with cUTI or AP when administered on a background therapy of IMI. Based on Phase 2 PK established in the present study and supporting PPK models, PK-PD TA analyses suggest optimal target attainment against ABC is achieved with a SUL-DUR dose of 1000 mg (of each component) q6h via a 3 hour IV infusion [26]. This dose is currently being studied in a global Phase 3 study of efficacy and safety for treating serious infections due to ABC in hospitalized patients.

**METHODS**

Patients were enrolled at 20 clinical sites in Belarus, Bulgaria, Russia, and Ukraine between January 2018 and May 2018. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. The study protocol and
amendments were approved by an Institutional Review Board for each clinical site, and all patients provided written informed consent prior to any study procedure. This study was registered at ClinicalTrials.gov Identifier: NCT03445195

**Study Design**

This was a double-blind, randomized, placebo-controlled study to evaluate the tolerability and PK of IV SUL-DUR administered with IMI in patients with cUTI, including AP, who were otherwise relatively healthy.

**Study Treatments**

Patients were randomized 2:1, to either SUL-DUR 1g/1g IV or matching placebo were reconstituted and diluted in 100 mL of 0.9% saline and infused over 3 hours administered every 6 hours (q6h) for 7 days (28 doses). All patients received background therapy with IMI 500 mg IV infused over 30 minutes q6h. Patients with bacteremia could receive up to 14 days of therapy. Randomization was stratified by baseline diagnosis (symptomatic cUTI versus AP), and at least 30% of patients were required to have a diagnosis of AP at study entry.

**Patient Selection**

Male or female patients ages 18-90 years, who were expected to require hospitalization and treatment with IV antibiotics for cUTI were eligible. Documented or suspected cUTI was defined based on the presence of at least two signs and symptoms, a urine specimen with evidence of pyuria, and the presence of at least one risk factor.
Documented or suspected AP were defined by at least two signs or symptoms and a urine specimen with evidence of pyuria. Women of childbearing potential were required to have a negative pregnancy test before randomization and to use 2 highly effective methods of contraception until at least 30 days after the last dose of study drug. Men were required to use adequate contraception for at least 90 days after the last dose of study drug. Patients were excluded for the presence of any disease or condition that could confound the assessment of efficacy including the use of any systemic antibiotic active against Gram-negative uropathogens for more than 24 hours in the 72 hour period prior to randomization.

**Study Assessments**

Tolerability was assessed from treatment-emergent adverse events (TEAEs), evaluation of changes from baseline for clinical laboratory tests (serum chemistry, hematology, urinalysis), 12-lead electrocardiogram (ECG), vital signs (heart rate, blood pressure, respiratory rate), and physical examination including weight.

Sparse sampling for PK analysis was completed with samples obtained pre-dose on Day 1, post-dose of study drug on Day 4 (±1 day) at the end of the infusion, and 0.5, 2, and 3 hours after the end of infusion (prior to the start of the next infusion). PK concentrations were analyzed using a validated LC/MS/MS assay (Data on file, Covance Laboratories, Inc.).
Clinical signs and symptoms were assessed at screening, on Days 2 through 6, end-of-treatment (EOT; 7 to 14 days after completing treatment), TOC (7 days post EOT), and late follow up visit (LFU; 7 days post TOC).

**Statistical Analysis**

No formal sample size calculation was performed. At least 80 patients were expected to be randomized 2:1 to SUL-DUR or placebo. The ITT Population included all randomized patients. The MITT Population included patients who met ITT criteria and received any Study Drug and was used as the population for the primary analysis of tolerability.

Pharmacokinetic parameters were estimated in the PK population (MITT population with at least one plasma PK sample drawn) by non-compartmental analysis was completed using Phoenix PK software (WinNonlin) version 8.1. The area under the plasma DUR or SUL concentration versus time curves (AUC) were calculated using the linear up log down method. Where the first order elimination rate constant (kel) could not be estimated, half-life, steady-state volume of distribution, and accumulation index were not reported. PK parameters included half-life, $T_{max}$, $C_{max}$, $C_{min}$, $K_{el}$, $V_{ss}$, $CL_{ss}$, $AUC_{0-tau}$, and accumulation index. PK parameters were reported using descriptive statistics.
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CONFLICTS OF INTEREST

RF, RY, OS, and KY were investigators for this study; each certifies no conflicts of interest. At the time of this work, ES, DH, JO, AM, RI, and SS, were employees of Entasis Therapeutics, Inc., Waltham, MA, and may have held stock in the company.

AUTHOR CONTRIBUTIONS

All authors performed data analysis and interpretation, as well as manuscript review and approval.
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Table 1. Baseline characteristics (ITT Population)

| Characteristic                                      | SUL-DUR + IMI (n=53) | Placebo + IMI (n=27) |
|-----------------------------------------------------|----------------------|----------------------|
| Age, years *a*                                       | 51.4 ± 17.6          | 54.9 ± 15.9          |
| Female, n (%)                                        | 27 (50.9)            | 11 (40.7)            |
| White, n (%)                                         | 53 (100.0)           | 27 (100.0)           |
| Hispanic or Latino, n (%)                            | 1 (1.9)              | 0                    |
| Body weight, kg *a*                                  | 83.8 ± 20.6          | 85.8 ± 17.9          |
| Body mass index, kg/m² *a*                           | 28.1 (6.7)           | 28.6 (5.9)           |
| Creatinine clearance, mL/min                         | 94.3 ± 23.8          | 91.7 ± 18.2          |
| Complicated UTI, n (%)                               | 31 (66.0)            | 16 (76.2)            |
| Intermittent or indwelling catheter                  | 3 (9.7)              | 2 (12.5)             |
| Functional or anatomic abnormality                   | 15 (48.4)            | 7 (43.8)             |
| Complete or partial obstructive uropathy             | 15 (48.4)            | 4 (25.0)             |
| Azotemia                                             | 3 (9.7)              | 0                    |
| Chronic urinary retention, men                       | 12 (38.7)            | 6 (37.5)             |
| Acute pyelonephritis, n (%)                          | 16 (34.0)            | 5 (23.8)             |
| Signs and Symptoms                                   |                      |                      |
| Fever with chills, rigors or warmth                  | 14 (87.5)            | 3 (60.0)             |
| Nausea/vomiting with 24 h of screening               | 11 (68.8)            | 3 (60.0)             |
| Dysuria, increased frequency or urgency              | 10 (62.5)            | 5 (100.0)            |
| Acute flank pain or costo-vertebral angle            | 15 (93.8)            | 5 (100.0)            |
| Evidence of pyuria criteria                      |         |         |
|------------------------------------------------|---------|---------|
| Positive leukocyte esterase on urinalysis       | 9 (56.3)| 2 (40.0)|
| WBC count ≥10 cells/mm³ in unspun urine         | 6 (37.5)| 0       |
| WBC count ≥10 cells/hpf in urine sediment       | 12 (75.0)| 5 (100.0)|

*a Mean ± standard deviation; hpf = high power field*
### Table 2. Summary of adverse events (safety population)

|                              | SUL-DUR+IMI (n=53) | Placebo+IMI (n=27) |
|------------------------------|---------------------|---------------------|
| Number with any AE           | 20 (37.7)           | 8 (29.6)            |
| Number with any drug-related AE | 12 (22.6)       | 4 (14.8)            |
| Number with serious AEs       | 0                   | 0                   |
| Number of deaths              | 0                   | 0                   |
| Discontinuation for AE        | 2 (3.8)             | 0                   |
| Incidence of AEs              |                     |                     |
| Abdominal pain upper          | 1 (1.9)             | 1 (3.7)             |
| Alanine aminotransferase increased | 1 (1.9)         | 0                   |
| Blood creatinine increased    | 1 (1.9)             | 0                   |
| Blood glucose increased       | 1 (1.9)             | 0                   |
| Blood pressure increased      | 1 (1.9)             | 0                   |
| Bronchitis                    | 1 (1.9)             | 0                   |
| Conjunctivitis                | 1 (1.9)             | 0                   |
| Diarrhea                      | 2 (3.8)             | 0                   |
| Duodenitis                    | 1 (1.9)             | 0                   |
| Dysbacteriosis                | 0                   | 1 (3.7)             |
| Dyspepsia                     | 0                   | 1 (3.7)             |
| Gastritis                     | 1 (1.9)             | 0                   |
| Glomerular filtration rate decreased | 1 (1.9)     | 0                   |
| Condition                                | Row 1 | Row 2 |
|-----------------------------------------|-------|-------|
| Headache                                | 5 (9.4) | 2 (7.4) |
| Infusion site reaction                  | 1 (1.9) | 0     |
| Nausea                                  | 2 (3.8) | 1 (3.7) |
| Oropharyngeal pain                      | 1 (1.9) | 1 (3.7) |
| Phlebitis                               | 3 (5.7) | 1 (3.7) |
| Pruritus                                | 0     | 1 (3.7) |
| Pseudomembranous colitis                | 0     | 1 (3.7) |
| Respiratory tract infection viral       | 1 (1.9) | 0     |
| Urticaria                               | 1 (1.9) | 0     |
| Vascular pain                           | 2 (3.8) | 0     |
| Vomiting                                | 2 (3.8) | 0     |
| Vulvovaginal candidiasis                | 1 (1.9) | 0     |
Table 3. Mean PK parameters for durlobactam and sulbactam following a 3 h IV infusion of 1000 mg.

| Parameter                        | Durlobactam     | Sulbactam      |
|----------------------------------|-----------------|----------------|
|                                  | Mean ± SD\(^a\) | CV%            | Mean ± SD | CV%            |
| \(K_{el}\), L/h\(^b\)           | 0.43 ± 0.25     | 58.0           | 0.54 ± 0.28 | 51.3           |
| Half-life, h\(^b\)              | 2.2 ± 1.6       | 72.9           | 1.6 ± 1.1 | 66.0           |
| \(T_{max}\), h                  | 3.1 ± 0.5       | 16.2           | 3.2 ± 0.6 | 17.9           |
| \(C_{max}\), mcg/mL             | 39.9 ± 38.2     | 95.8           | 39.1 ± 38.6 | 98.7           |
| \(C_{min}\), mcg/mL             | 8.9 ± 6.7       | 74.7           | 6.5 ± 7.2 | 111.9          |
| \(V_{ss}\), L                   | 10.6 ± 4.0      | 38.9           | 13.4 ± 8.4 | 62.3           |
| \(V_{ss}\), L                   | 31.6 ± 13.1     | 41.6           | 36.0 ± 23.4 | 64.9           |
| AUC\(_0\)-\(\tau\), h*mcg/mL    | 123.8 ± 85.7    | 69.2           | 107.8 ± 83.1 | 77.1           |
| Accumulation Index\(^b\)        | 1.2 ± 0.3       | 27.4           | 1.1 ± 0.2 | 18.3           |

\(^a\) Mean ± standard deviation

\(^b\) N=45, all other parameters N=52

\(K_{el}\) = first order rate constant associated with terminal (log-linear) portion of the curve;

\(T_{max}\) = time after dosing at which the maximum concentration was observed;

\(C_{max}\) = maximum observed concentration measured after dosing;

\(C_{min}\) = minimum observed concentration measured after dosing;

\(V_{ss}\) = steady state volume of distribution;

\(CL_{ss}\) = steady state clearance;

\(AUC_{0\tau}\) = steady state area under the concentration versus time curve from dosing time to dosing time plus tau, using the linear up log down method;

Accumulation index = \(1/[1-e^{-K_{el}\tau}]\)
Figure 1. Mean (standard deviation) steady-state (Day 4) plasma concentrations of durlobactam and sulbactam over 6 hour dosing interval.
