CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216974Orig1s000

<u>OTHER REVIEW(S)</u>

This is an addendum to the ARIA sufficiency memo for NDA 216974 that was checked in DARRTS on May 19, 2023 (Reference ID: 5176817).

In Section 7 of the memo, the division name was mistakenly spelled as “the Division of Antivirals”. The correct division name here should be “the Division of Anti-Infectives”.

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/s/

YAN LI
05/19/2023 03:42:51 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates

Date:	May 18, 2023
Reviewer:	Yan Li, PhD Division of Epidemiology II
Deputy Director:	Monique Falconer, MD, MS Division of Epidemiology II
Deputy Director:	Michael Blum, MD Office of Pharmacovigilance and Epidemiology
Associate Director:	Patricia Bright, PhD, MSPH Sentinel Program
Deputy Director:	Robert Ball, MD, MPH Office of Surveillance and Epidemiology
Subject:	ARIA Sufficiency Memo
Drug Name:	Xacduro (Sulbactam and Durlobactam)
Application Type/Number:	NDA 216974
Applicant/sponsor:	Entasis Therapeutics Inc
OSE RCM #:	2023-4616

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

Xacduro (Sulbactam and Durlobactam [SUL-DUR]) (NDA 216974) is a copackaged product containing sulbactam (SUL), a beta-lactam antibacterial and beta-lactamase inhibitor, and durlobactam (DUR), a novel beta-lactamase inhibitor. SUL-DUR is indicated for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP), caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex (ABC) in patients 18 years of age and older.

1.2. Describe the Safety Concern

Under 21 CFR part 312 subpart E, FDA may exercise flexibility in applying statutory standards for drugs intended to treat life-threatening and severely debilitating diseases, while preserving appropriate guarantees for safety and effectiveness. SUL-DUR was developed under a flexible development program given the unmet need for treatment options for serious and life-threatening infections caused by carbapenem-resistant isolates of ABC (CRABC).

To support the approval, the Applicant submitted a single phase 3, randomized, assessor-blinded, active-controlled (i.e., colistin) noninferiority study in 177 hospitalized adults, primarily those with HABP and VABP caused by ABC including CRABC. The safety database includes 158 subjects who received SUL-DUR at the proposed dose and duration. The overall incidence of treatment-emergent adverse events (TEAE) was 87.9% in the SUL-DUR group and 94.2% in the colistin group. There were lower incidences of serious adverse events (SAE, 39.6% vs. 48.8%) and drug-related TEAEs (13.2% vs. 30.2%) in the SUL-DUR group compared to colistin. SAEs that were higher (>1% difference) in the SUL-DUR group versus the comparator group were related to hepatobiliary (4% vs. 0%), vascular (3% vs. 1%), and respiratory, thoracic and mediastinal (9% vs. 7%) disorders.

Adverse events of special interest (AESI) monitored by the applicant during the clinical development program included hypersensitivity, drug-related hepatic disorders, acute renal failure, infective pneumonia, sepsis, pseudomembranous colitis, and convulsions. Among these, hypersensitivity reactions were more frequently in the SUL-DUR group compared to colistin (16.5% versus 11.5%), which would be expected with penicillin derivatives. The most recent draft label includes hypersensitivity reactions and *Clostridioides difficile*-associated diarrhea under the WARNINGS AND PRECAUTIONS section.

The review team concluded that no unexpected safety signal was identified in the development program. However, the safety assessment of SUL-DUR is limited by the small size of the safety database, which comprises less than 200 subjects exposed to the proposed dose and duration of therapy. In general, a safety database for a drug addressing an unmet need under a flexible development program should include approximately 300 subjects at the dose and duration of therapy proposed for marketing.[1]

A meeting of the Antimicrobial Drugs Advisory Committee was convened on April 17, 2023, to

[1] 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) (May 2022)

discuss this NDA. The committee voted unanimously to support the use of SUL-DUR for treatment of patients with HABP/VABP caused by susceptible strains of ABC organisms (12 "yes" votes, 0 "no" votes, and 0 abstentions). The committee agreed that the study demonstrated compelling results for the efficacy of SUL-DUR in reducing mortality in HABP/VABP caused by ABC but highlighted the limitations of a small safety database and recommended that augmented postmarketing surveillance be conducted to collect more safety data.

The review team determined that the limited safety database was acceptable to support the approval of SUL-DUR, given the significant unmet need for treatment options for HABP/VABP due to ABC (including CRABC), but plans to request studies to gather additional safety information upon approval.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

1.4. Statement of Purpose

The question is whether ARIA could provide additional adequate data on safety of SUL-DUR, including but not limited to the risk of hypersensitivity reactions (including anaphylaxis), in patients with ABC infections.

1.5. Effect Size of Interest or Estimated Sample Size Desired

No sample size is projected for the evaluation purpose stated in Section 1.4 given that ARIA is ultimately deemed insufficient in this memo.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

SUL-DUR will be used in adults with HABP/VABP, caused by susceptible isolates of ABC. These are critically ill patients who will be cared for in the inpatient setting and have stays in the intensive care unit.

2.2 Is ARIA sufficient to assess the intended population?

ARIA is insufficient to assess the intended population. There is no ICD-10 code for HABP and VABP. Coding guidelines suggest the use of J18.9 (pneumonia, unspecified organism) for HABP which is not specific. The code J95.851 for ventilator associated pneumonia is not specific either. Microbiology laboratory test results needed to identify the intended population are also not available in the common data model of ARIA.

3 EXPOSURES

3.1 Treatment Exposure(s)

SUL-DUR is a packaged intravenous infusion that is typically given every 6 hours.

3.2 Comparator Exposure(s)

N/A

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is insufficient to identify the exposure of interest. Patients will receive SUL-DUR in the inpatient setting. Such information is not captured in the common data model of ARIA.

4 OUTCOME(S)

4.1 Outcomes of Interest

Given the limited size of the safety database, additional study is needed to comprehensively assess the safety of SUL-DUR, including but not limited to the risk of hypersensitivity reactions (including anaphylaxis). Other outcomes of interest may include drug-related hepatic disorders, acute renal failure, infective pneumonia, sepsis, pseudomembranous colitis, and convulsions, as designated in the pre-approval clinical trial.

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA is insufficient to assess the outcomes of interest. ARIA does not have the capacity to assess several outcomes of interest. For example, ICD codes have suboptimal performance to identify anaphylaxis (positive predictive value [PPV]: 63.1%)[2], drug-induced liver injury (PPV: 66.5%)[3], and acute renal failure (PPV: 45.5% to 76.1%)[4]. Further enhancement of outcome capture would require laboratory values and clinical narratives, which are not available in the common data model of ARIA. While ICD codes may be used to identify outcomes such as sepsis, seizure, and *Clostridium difficile* infections, lack of information on the timing of exposure administration and outcome occurrence makes it difficult to make a basic causal assessment regarding whether outcomes are treatment related from a temporal perspective.

5 COVARIATES

The proposed study does not involve a comparator and is not an inferential analysis. Therefore, covariate capture is of less relevance in the ARIA sufficiency determination. Given that ARIA is insufficient to identify the population, exposure, and outcome, elaboration on covariate capture (including comorbidities, lab values, and concomitant medication use in these critically ill patients) will not be included in this memo because it will not shift the ARIA sufficiency determination.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

This will be a single-arm observational study describing the incidence of adverse events following SUR-DUL administration. While the ARIA analytic tools are sufficient for this purpose, insufficiencies in population, exposure, and outcome preclude the use of ARIA for the purpose stated in the Section 1.4.

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[2] Pharmacoepidemiol Drug Saf. 2013 Nov;22(11):1205-13.
[3] Drug Saf. 2020 Apr;43(4):371-377.
[4] Clin Kidney J. 2020 Dec; 13(6): 1083–1090.

7 NEXT STEPS

Because ARIA is deemed insufficient, the Division of Antivirals chooses to issue a postmarketing requirement (PMR) to the applicant for an observational study to gather additional safety data.

FDA PMR language includes the following:

Conduct a single-arm, open-label, prospective, observational study to assess of the safety of sulbactam-durlobactam, including (b) (4) the risk of hypersensitivity reactions (including anaphylaxis) in patients with *Acinetobacter baumannii-calcoaceticus* complex infection.

Final protocol submission: 02/2024

Study completion: 02/2029

Final report submission: 08/2029

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/s/

YAN LI
05/19/2023 11:23:21 AM

MONIQUE FALCONER
05/19/2023 11:36:10 AM

JUDITH W ZANDER on behalf of MICHAEL D BLUM
05/19/2023 12:13:13 PM

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Division of Pediatrics and Maternal Health Review

Date: May 10, 2023 **Date of Consult Request**: February 28, 2023

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatrics and Maternal Health (DPMH)

Through Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, Director, DPMH

To: Division of Anti-Infectives (DAI)

NDA Number: 216974

Drug: Xacduro (sulbactam for injection; durlobactam for injection), co-packaged for intravenous use

Applicant: Entasis Therapeutics Inc. (ETI)

Indication: Indicated in adults for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by susceptible strains of Acinetobacter baumannii-calcoaceticus complex.

Subject: Labeling review as per Pregnancy and Lactation Labeling Rule (PLLR).

Materials Reviewed

- Applicant's submission of September 29, 2022
- Division's Consult request of February 28, 2023, DARRTS Reference ID: 5133362

- Division of Pediatrics and Maternal Health Information Request (IR) dated March 8, 2023 related to the Pregnancy and Lactation Labeling Rule PLLR sections of the proposed labeling
- Applicant's response to IR of March 17, 2023

INTRODUCTION

On September 29, 2022, the applicant, ETI. submitted a new NDA 216974 for Xacduro, a co-packaged drug product of sulbactam and durlobactam for use in adults for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by susceptible strains of Acinetobacter baumannii-calcoaceticus complex. Durlobactam is a New Molecular Entity (NME), therefore this co-packaged drug product will be managed as an NME. This NDA was submitted under the 505(b)(2) pathway with drug relied upon Unasyn, NDA 050608 approved on December 31, 1986. The proposed labeling is in PLLR format. DAI has requested DPMH to ensure that the labeling complies with the PLLR content and format.

BACKGROUND

Pregnancy and Perinatal Outcomes Associated with Acinetobacter baumannii Infection

Acinetobacter species are a group of bacterial microorganisms that have emerged as significant nosocomial pathogens, with Acinetobacter baumannii being the most frequently isolated species. Acinetobacter are resistant to most antibiotics and can be found in both hospitalized patients and the community. The spectrum of clinical manifestations is broad. In general, A. baumannii mainly infects patients with impaired host defense, such as those who are in the intensive care units.[1] Although there are conflicting results regarding clinical outcomes from different clinical studies, it appears that A. baumannii infection is associated with increased mortality.[2,3] In one retrospective record review study by He M *et. al.*[4] in a 5-year period, 40 positive cultures were found, 33 cultures from adults (7 specimens from 6 patients were related to pregnancy), three cultures from newborn units, and four cultures from postmortem examinations (see Table 1). Three pregnancies with positive cultures close to the peripartum period were all associated with adverse outcomes including spontaneous abortion, preterm labor, and one full-term birth with histological chorioamnionitis. Two positive cultures were found in preterm neonates in the neonatal intensive care unit. Two of three cases of perinatal death grew pure cultures from blood and/or fetal tissue with placental or fetal examination demonstrating evidence of infection/inflammation with fetal inflammatory response. In a case report by Aivazova V *et. al.,*[5] the authors conclude that "A. baumannii can lead to premature contractions and can be associated with chorioamnionitis during pregnancy. Moreover, it can also cause septic complications in the puerperium associated with long duration of hospitalization."

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[1] Confronting multidrug-resistant Acinetobacter baumannii: a review. Neonakis I K, Spandidos D A, Petinaki E. Int J Antimicrob Agents. 2011;37:102–109

[2] Attributable mortality of Acinetobacter baumannii infections in critically ill patients: a systematic review of matched cohort and case-control studies. Falagas M E, Bliziotis I A, Siempos I I. Crit Care. 2006;10:R48.

[3] Multidrug-resistant Acinetobacter baumannii: mechanisms of virulence and resistance. Gordon N C, Wareham D W.Int J Antimicrob Agents. 2010;35:219–226.

[4] Pregnancy and Perinatal Outcomes Associated with Acinetobacter baumannii Infection. He M, Kostadinov S, Gundogan F. et. al. AJP Rep. 2013 May; 3(1): 51–56

[5] Acinetobacter baumannii infection during pregnancy and puerperium. Aivazova V, Kainer F, Friese K, Mylonas I. Arch Gynecol Obstet . 2010 Jan;281(1):171-4. doi: 10.1007/s00404-009-1107-z.

Table 1: Clinical Features of Bacterial Cultures Positive for *Acinetobacter Baumannii*

Source	Voided urine (*n* = 16)	Wound (*n* = 13)	Others (*n* = 11)
Adults (*n* = 33)			
Inpatient (*n* = 12)	5	4	3[a]
Outpatient (*n* = 21)	11	8	2[b]
Newborns (*n* = 3)	0	1	2[c]
Autopsy (*n* = 4)	0	0	4

[a]Breast milk, lung aspiration and catheter tip.
[b]Throat, sputum.
[c]Tracheal aspiration, blood from central line.

From He, M *et. al. Table 1*

Table 2: Xacduro Drug Characteristics[6]

Half Life	1-3 Hours for sulbactam 2-3 Hours for durlobactam
Molecular Weight	255.22 Daltons for sulbactam 299.23 Daltons for durlobactam
Protein bound	Approximately 38%
	Sulbactam is not mutagenic or clastogenic Durlobactam: No evidence of genetic damage
Metabolism	Metabolism is not a significant factor in the clearance of sulbactam. Durlobactam is minimally metabolized, with the primary metabolite being a hydrolysis product that is formed enzymatically in plasma, rapidly excreted in urine and further degraded via non-enzymatic, non-hepatic routes.
Administration	Intravenous (IV) infusion
Drug Class	Antibacterial drug Sulbactam, a β-lactam antibacterial, and durlobactam, a β-lactamase inhibitor.
Proposed Dosage:	A Kit containing 3 single-dose vials each containing sterile powder for reconstitution: 1 vial contains sulbactam 1 g and 2 vials each contain durlobactam 0.5 g together with sodium hydroxide and hydrochloric acid used for pH adjustment. Recommended dosage for Xacduro is 1 g sulbactam and 1 g durlobactam every 6 hours by intravenous (IV) infusion over 3 hours in adults with a creatinine clearance (CLcr) of 45 to 129 mL/min.

[6] Xacduro applicant's proposed labeling and edited by Clinical Pharmacology, Microbiology and non clinical disciplines.

Mechanism of action:
Sulbactam is a penicillin derivative that has intrinsic antibacterial activity against Acinetobacter baumannii-calcoaceticus complex (ABC). Sulbactam is bactericidal due to its inhibition of penicillin-binding proteins PBP1 and PBP3, which are essential enzymes required for bacterial cell wall synthesis. Durlobactam is a diazabicyclooctane non-beta-lactam, beta-lactamase inhibitor, that protects sulbactam from degradation by certain serine-beta-lactamases. Durlobactam alone does not have any antibacterial activity against ABC isolates.

REVIEW
Pregnancy

Non-clinical Data
Durlobactam
Daily administration of durlobactam to pregnant mice from gestation day (GD) 6 through 15 resulted in durlobactam-related, increased incidence of skeletal variations at 2- and 4 times the maximum recommended human dose based on AUC comparisons. No adverse effects on mean body weight or reproductive performance were observed for animals administered up approximately 4 times the MRHD based on body surface area comparison.

IV infusion of durlobactam to pregnant female Sprague Dawley rats from GD 6 to weaning on Lactation Day 20 at a dose level of 300 or 1000 mg/kg/day was well tolerated with no adverse maternal effects in either group. Similarly, there was no adverse effect of maternal treatment in either group on embryo-fetal, perinatal, or postnatal development up to approximately 4 times the MRHD based on body surface area comparison.

Sulbactam
As per non-clinical review by Owen McMaster, PhD., and Terry Miller, PhD., Reproduction studies have been performed in mice, rats, and rabbits at doses up to 10 times the human dose and have revealed no evidence of harm to the fetus due to ampicillin sodium/sulbactam sodium.

Clinical Data
Applicant's Review of Literature for Durlobactam
The applicant did not submit any review of literature on durlobactam. No cases of use of durlobactam in pregnancy were identified during the drug development program. There are no human data from clinical trials or review of literature with the use of durlobactam in pregnant women to evaluate a drug -associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Durlobactam is an NME.

Applicant's Review of Literature for Sulbactam
The applicant performed a search of the literature through:
- bscholar.google.com/
- Certara Library
- ECHA (https://echa.europa.eu/)
- EMA (https://www.ema.europa.eu/en/medicines?search_api_views_fulltext=sulbactam)
- JSTOR (https://www.jstor.org/)
- ScienceDirect (https://www.sciencedirect.com/)
- DOAJ (https://doaj.org/)

Search terms included: Sulbactam, sulbactam alone, reproductive development, pregnancy, teratogenicity, resorption, fetal anomalies, fetal development, birth, placenta, prenatal, neonatal, gestation, abortion.

The publications identified were PK studies of sulbactam during pregnancy. Sulbactam, like in Unasyn has been used in combination with ampicillin. In one case report, inadvertent intrauterine infusion of sulbactam (1 g) plus ampicillin (2 g) was reported in a brief communication. The antibiotic combination was being given for prophylaxis of preterm premature rupture of the membranes at 30 weeks' gestation. Apparently, the error occurred when the antibiotic was infused into an intrauterine catheter instead of the intended IV catheter. A 1690-g infant (sex not specified) was delivered by cesarean section the next day. No adverse effects of the error were observed.[7] In another publication[8], it is stated: "Sulbactam is given in combination with ampicillin. It has caused no harm in animal reproduction studies, but reports of human exposure in early gestation are lacking." However, none of the penicillins has been shown to be teratogenic. Sulbactam readily crosses the human placenta to the fetus at term. [9,10] Although no direct adverse effects of this exposure on the fetus or newborn have been reported, use of the antibiotic combination near delivery may result in superinfection with resistant bacteria in the newborn.

The combination of sulbactam and ampicillin has been used frequently in the 2nd and 3rd trimesters of pregnancy. These studies involved prophylaxis, as in cases of preterm premature rupture of the membranes, and therapy for established infections. No cases of fetal or newborn direct harm from exposure to the combination were reported.[11,12,13,14]

DPMH Review of Literature for Durlobactam

There are no human data from clinical trials or review of literature with the use of durlobactam in pregnant women to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

DPMH Review of Literature for Sulbactam

DPMH searched PubMed, Micromedex, Reprotox and GG Briggs and RK Freeman in

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[7] Inadvertent intrauterine infusion of ampicillin-sulbactam. Sigg TR, Kuhn BR. Am J Health Syst Pharm., 2000 Feb 1; 57(3):215 https://pubmed ncbi nlm nih.gov/10674773/

[8] Drugs in Pregnancy and Lactation: Tenth Edidtion https://doctorlib.info/pregnancy/drugs-pregnancy-lactation/1047 html

[9] Carroll EM, Heywood PA, Besinger RE, Muraskas JK, Fisher SG, Gianopoulos JG. A prospective randomized double-blind trial of ampicillin with and without sulbactam in preterm premature rupture of the membranes (abstract). Am J Obstet Gynecol 2000;182:S61.

[10] Smith LG Jr, Summers PR, Miles RW, Biswas MK, Pernoll ML. Gonococcal chorioamnionitis associated with sepsis: a case report. Am J Obstet Gynecol 1989;160:573–4.

[11] Smith LG Jr, Summers PR, Miles RW, Biswas MK, P

[12] Adair CD, Ernest JM, Sanchez-Ramos L, Burrus DR, Boles ML, Veille JC. Meconium-stained amniotic fluid-associated infectious morbidity: a randomized, double-blind trial of ampicillin-sulbactam prophylaxis. Obstet Gynecol 1996;88:216–20.

[13]Lovett SM, Weiss JD, Diogo MJ, Williams PT, Garite TJ. A prospective, double-blind, randomized, controlled clinical trial of ampicillin-sulbactam for preterm premature rupture of membranes in women receiving antenatal corticosteroid therapy. Am J Obstet Gynecol 1997;176:1030–8.

[14] Carroll EM, Heywood PA, Besinger RE, Muraskas JK, Fisher SG, Gianopoulos JG. A prospective randomized double-blind trial of ampicillin with and without sulbactam in preterm premature rupture of the membranes (abstract). Am J Obstet Gynecol 2000;182:S61.

Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk for use of sulbactam during pregnancy**.**

Micromedex/TERIS stated, **"**No epidemiological studies of congenital anomalies among infants born to women treated with sulbactam during pregnancy have been reported."

No adverse effect was apparent among infants born after maternal sulbactam-ampicillin treatment in the second or third trimester of pregnancy in controlled therapeutic trials[13,15,16.] Similarly, no adverse effect of peripartum maternal treatment with a sulbactam-ampicillin combination was observed among 60 newborn infants in a controlled therapeutic trial[17].
Sulbactam alone possesses little useful antibacterial activity except against the Neisseriaceae, whole organism studies have shown that sulbactam restores ampicillin activity against beta-lactamase producing strains.[18] Unasyn, (a combination of sulbactam-ampicillin) drug product for intravenous and intramuscular administration, has been used for treating gram-negative bacteria and anaerobes. The labeling for Unasyn states: "this drug should be used during pregnancy only if clearly needed." Unasyn is used mostly during the second and third trimester and the puerperium and has not shown any increased drug-associated risk associated adverse pregnancy related outcomes. There are no available data on first trimester use of Unasyn in pregnant women to assess the risk of major birth defects or miscarriage.

Reviewer Comment
All penicillins are not teratogenic. Use of sulbactam and ampicillin over the years has not shown any increased drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. This is reassuring, even though Unasyn is used mostly during the 2nd and 3rd trimesters and puerperium.

Summary
Reproduction studies have been performed in mice, rats, and rabbits at ampicillin sodium/sulbactam sodium doses up to 10 times the human dose and have revealed no evidence of harm to the fetus. There are no safety concerns with use of sulbactam in combination with ampicillin use over many years in pregnant women. There is not a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Daily subcutaneous administration of durlobactam to pregnant mice during organogenesis increased incidence of skeletal variations at 2- and 4 times the maximum recommended human dose based on AUC comparisons. No adverse effects on mean body weight or reproductive performance were observed for animals administered up approximately 4 times the MRHD based on body surface area comparison.

IV infusion of durlobactam to pregnant female Sprague Dawley rats during organogenesis and lactation

[15] Lewis DF, Adair CD, Robichaux AG, Jaekle RK, Moore JA, Evans AT, Fontenot MT: Antibiotic therapy in preterm premature rupture of membranes: are seven days necessary? A preliminary, randomized clinical trial. Am J Obstet Gynecol 188(6):1413-1417, 2003.
[16] Cox SM, Bohman VR, Sherman ML, Leveno KJ: Randomized investigation of antimicrobials for the prevention of preterm birth. Am J Obstet Gynecol 174(1 Pt 1):206-210, 1996.
[17] Adair CD, Ernest JM, Sanchez-Ramos L, Burrus DR, Boles ML, Veille J-C: Meconium-stained amniotic fluid-associated infectious morbidity: a randomized, double-blind trial of ampicillin-sulbactam prophylaxis. Obstet Gynecol 88(2):216-220, 1996.
[18] Unasyn labeling of October 9, 2020

was well-tolerated with no adverse maternal effects in either group (pregnancy or lactation). No adverse effect of maternal treatment on embryo-fetal, perinatal, or postnatal development up to approximately 4 times the MRHD based on body surface area comparison.

Lactation

Non-Clinical Data

There are no non clinical data on use of Xacduro or durlolactam in lactating animals.

Clinical Review of Data

There are no published data on the presence of Xacduro or durlobactam in human milk, on the effects on the breastfed infant or the effects on milk production. As per applicant, there were no clinical studies involving lactating females.

Applicant's Review of Literature

No publications were identified using sulbactam during lactation.

DPMH Review of the Literature

This reviewer searched PubMed, Reprotox/Micromedex, GG Briggs & RF Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, Halesmeds.com, and Drugs and Lactation Database (LactMed).

LactMed states:

Limited information indicates that ampicillin-sulbactam produces low levels in milk that are not expected to cause adverse effects in breastfed infants. Occasionally, disruption of the infant's gastrointestinal flora, resulting in diarrhea or thrush, have been reported with penicillins, but these effects have not been adequately evaluated. Ampicillin-sulbactam is acceptable in nursing mothers.

GG Briggs & RF Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk states that sulbactam is present in human breast milk. The potential effects of exposure to sulbactam on a nursing infant is unknown. The authors suggest the effects are "probably similar to those that might occur with other antibiotics: modification of bowel flora, direct effects on the infant (e.g., allergy or sensitization), and interference with the interpretation of culture results if a fever workup is required." The American Academy of Pediatrics classifies sulbactam as compatible with breastfeeding. Halesmeds.com states "The absorption of sulbactam from GI tract is poor".[19] He concludes that "Untoward effects are unlikely in a breastfeeding infant".

As per review of the literature by the Clinical Pharmacology reviewer Xiaohui (Tracey) Wei, Ph.D., sulbactam is present in breastmilk in low concentrations.[20] Published data report sulbactam in breastmilk at an estimated maximum daily infant dose of 560 mcg/kg/day (1% to 2% of adult weight-adjusted dose), assuming mean milk consumption of 200 mL/kg/day.

Summary

There are no human data on the presence of Xacduro or durlobactam in human milk, on the effects on the breastfed infant or the effects on milk production. Sulbactam is present in human milk in small amounts.

[19] Sweetman S. ed. Martindale: The Complete Drug Reference. London, England: Pharmaceutical Press;2010 Electronic version

[20] https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1038/clpt.1985.247

Therefore, the risk/benefit statement will be appropriate in the labeling, stating: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xacduro and any potential adverse effects on the breastfed child from Xacduro or from the underlying maternal condition."

Females and Males of Reproductive Potential

Non-Clinical Data

Sulbactam and durlobactam are not mutagenic or clastogenic. No adverse effects were reported on fertility, reproductive performance, fetal viability, growth, or postnatal development were observed in male and female rats, and female mice for durlobactam at 4 times the MRHD based on AUC comparisons.

No information exists on sulbactam.

Clinical Data

No information is provided by the applicant regarding the use of Xacduro in females and males of reproductive potential. No publications were identified by this reviewer.

Summary

No relevant published information was identified by either the applicant or this reviewer for Xacduro (sulbactam and durlobactam) use in patients of reproductive potential. Therefore, because neither sulbactam nor durlobactam are genotoxic, do not have any reported effects on fertility, and (based on animal studies) are not teratogenic, there is no need for pregnancy testing or contraception recommendations in labeling and subsection 8.3 Females and Males of Reproductive Potential will be omitted.

CONCLUSION

No safety concerns were identified with use of sulbactam in combination with ampicillin use over many years in pregnant women. There is not a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Daily subcutaneous administration of durlobactam to pregnant mice during organogenesis increased incidence of skeletal variations at 2- and 4 times the maximum recommended human dose but no adverse effects on mean body weight or reproductive performance were observed for animals administered up approximately 4 times the MRHD. Sulbactam is present in human milk in small amounts. No animal or human information regarding the presence of durlolactam in milk exist.

DPMH does not recommend a Post Marketing Requirement (PMR) for a descriptive pregnancy safety study or a lactation milk only study to collect safety data because such studies will be difficult to conduct in this patient population. Xacduro 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 strains of Acinetobacter baumannii-calcoaceticus complex. The information collected will be highly confounded with other medications used in the critical care setting.

DPMH LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of Xacduro labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

(b) (4)

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CHRISTOS MASTROYANNIS
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TAMARA N JOHNSON
05/10/2023 09:59:15 AM

LYNNE P YAO
05/10/2023 12:17:11 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 9, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216974
Product Name, Dosage Form, and Strength:	Xacduro (sulbactam; durlobactam) for Injection, 1 gram/1 gram per kit
Applicant/Sponsor Name:	Entasis Therapeutics, Inc. (Entasis)
TTT ID #:	2022-1984-2
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on May 9, 2023 for Xacduro. The Division of Anti-Infectives (DAI) requested that we review the revised container labels for Xacduro (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Myers, D. Label and Labeling Review Memo for Xacduro (NDA 216974). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 26. TTT ID No.: 2022-1984-1.

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DEBORAH E MYERS
05/09/2023 04:31:01 PM

VALERIE S VAUGHAN
05/09/2023 04:59:58 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 05/04/2023

To: J. Christopher Davi, Senior Regulatory Project Manager
Division of Anti-Infectives Products (DAIP)

From: Phillip Williams, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for XACDURO™ (sulbactam for injection; durlobactam for injection), co-packaged for intravenous use

NDA: 216974

Background:

In response to DAIP's consult request dated February 1, 2023, OPDP has reviewed the proposed prescribing information (PI) for the original NDA submission for XACDURO™ (sulbactam for injection; durlobactam for injection), co-packaged for intravenous use.

PI:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on April 25, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Phillip Williams at (240) 402-3974 or Phillip.Williams@fda.hhs.gov.

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PHILLIP A WILLIAMS
05/04/2023 11:44:31 AM

ADDENDUM TO

USE-RELATED RISK ANALYSIS REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 02, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216974
Product Name, Dosage Form and Strength:	Xacduro[a] (sulbactam; durlobactam) for Injection, 1 gram/1 gram per kit[b]
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Entasis Therapeutics (Entasis)
Submission Date:	September 29, 2022, November 22, 2022, December 21, 2022, February 28, 2023
OSE TTT #:	2022-2135-1
DMEPA 1 Team Leader :	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

[a] Xacduro was found to be conditionally acceptable on December 22, 2022.

[b] The Applicant states, "Xacduro for injection is supplied as a kit containing 3 single-dose vials each containing sterile powder for reconstitution" in their proposed prescribing information. We note that the Office of Pharmaceutical Quality (OPQ) will make a final determination regarding the accuracy and use of the terminology "kit" during the NDA review.

1 PURPOSE OF ADDENDUM

This memorandum serves as an addendum to the use related risk analysis (URRA) review for Xacduro (sulbactam-durlobactam) kit completed on November 09, 2022.[c]

2 BACKGROUND AND CONCLUSION

The URRA review was completed on November 09, 2022, based on Entasis confirmation that their product user interface and URRA was identical to the product user interface in their September 29, 2022, submission.[c]

Subsequently, during the label and labeling review for Xacduro (sulbactam-durlobactam) kit, it was noted that Entasis proposed different dosing regimens in their proposed prescribing information (see tables 1 and 2 below), which posed some medication error concerns due to the proposed components of the kit. The proposed kit consists of 3 vials: One (1) vial of sulbactam 1-gram sterile powder for injection and two (2) vials of durlobactam 500 mg sterile lyophilized powder for injection (See Figure 1 below).

Table 1: Recommended Dosage of XACDURO for Adults by Renal Function

Estimated CLcr (mL/min)*	Recommended Dosage of Sulbactam/Durlobactam (g)	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†	Loading dose of 1 g/1 g followed by 0.5 g/0.5 g	Every 12 hours	3 hours

*CLcr = creatinine clearance estimated by Cockcroft-Gault equation
†For patients on hemodialysis, the dose should be administered after the dialysis session has ended.

Table 2: Preparation of XACDURO by Dose

Sulbactam/ Durlobactam Dose	Sulbactam		Durlobactam	
	Number of 1 g Vials to be Reconstituted	Volume to Withdraw from Reconstituted Vial(s)	Number of 0.5 g Vials to be Reconstituted	Volume to Withdraw from Reconstituted Vials
0.5 g / 0.5 g	1 vial	2.5 mL	1 vial	2.5 mL
1 g /1 g	1 vial	5 mL	2 vials	5 mL (2.5 mL per vial)
1.5 g /1.5 g	2 vials	7.5 mL (5 mL from 1 vial, 2.5 mL from second vial)	3 vials	7.5 mL (2.5 mL per vial)

[c] Oguntimein, M. Use Related Risk Analysis Review for Xacduro (sulbactam-durlobactam) (NDA 216974). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 09. TTT No.: 2022-2135.

Figure 1. SUL-DUR Kit: Co-Packaged Sulbactam and Durlobactam Drug Product Vials

(b) (4)

[redacted]

As proposed, a user would need to use two "kits" to prepare a dosage of 1.5 g/1.5 g for patients with a CrCl ≥ 130 mL/min or half of a kit to prepare maintenance doses of 0.5 g/0.5 g for patients with impaired renal function. We were concerned this dosing introduces a new risk that was not considered in our previous review of the URRA. Specifically, the proposed dosing regimen increases the potential for wrong dose, preparation, and administration medication errors; since generally, multiple, or partial kits are not required to create a single dose.

Based on these medication error concerns, on November 17, 2022, we issued the following information request (IR):

" 1. The submitted user interface includes two additional dosing regimens, 1.5 g/1.5 g every 6 hours and 0.5 g/0.5 g every 8 or 12 hours, which was not previously identified. Furthermore, the packaging presentation (kit) containing 3 single-dose vials each containing sterile powder for reconstitution: 1 vial contains sulbactam 1 g and 2 vials each contain durlobactam 0.5 g, is not designed to allow for the labeled dosage of 1.5 g/1.5 g for patients with a CrCl ≥ 130 mL/min using a single proposed package. Instead, the proposed kit would require the health care professional (HCP) to use more than one kit to prepare a dosage of 1.5 g/1.5 g, for patients with a CrCl ≥ 130 mL/min or half of a package for patients with a CrCl of < 15 to 29 mL/min. Therefore, we request you submit an updated URRA to evaluate the potential use issues, risks, and subsequent harm related to the tasks for preparing and administering all of the potential dosing regimens.

2. As previously described, the proposed packaging presentation (kit) would require use of two proposed kits to prepare a single dose of 1.5 g/1.5 g for patients with a CrCl ≥ 130 mL/min or half of a kit to prepare a dosage of 0.5 g/0.5 g for patients with a CrCl of < 15 to 29 mL/min. We have medication error concerns about the risk of potential wrong dose, preparation, and administration medication errors. Therefore, your URRA should include your plans to mitigate

the potential medication error risks. For example, consider developing packaging presentations (kits) for each of the proposed dosing regimens." [d]

On November 22, 2022, Entasis indicated they will send an updated URRA by end of December 2022.[e]

On December 12, 2022, the 74-day letter included the aforementioned November 17, 2022,IR.[f]

On December 21, 2022, Entasis sent an updated URRA, planned risk mitigation strategies and summary of human factor (HF) formative data and provided the following[g] [h]:

- The updated URRA included all the use tasks, risks, and subsequent harms related with all the proposed dosing regimen (0.5 g/0.5 g, 1.0 g/1.0 g and 1.5 g/1.5 g) for Xacduro.
- Planned Risk Mitigation Strategies: specific design of package kit and instructions for use with ample warnings and reminders that a specific number of vials are required to provide a single dose of SUL-DUR for each of the three dose regimens. Entasis stated that these warnings inadvertent omission (or inclusion) of 1 or 2 vials in the kit during the preparation of the final IV bag for administration are consistent with labeling provided in several commercial products.
- Entasis conducted one HF formative study:
  -First Formative Study: Preparation of a single recommended dosage (1 g sulbactam /1 g durlobactam) was conducted to evaluate the mitigation strategies proposed.
  - Participants: 9 HCPs (4 hospital-based pharmacists/ pharmacy technicians and 5 intensive-care unit (ICU) nurses)

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[d] Davi, C. FDA Communication: Information Request for Sulbactam and Durlobactam (NDA 216974). Silver Spring (MD): FDA, CDER, OND, DAI (US); 2022 NOV 17. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80699abf.

[e] Clinical Information Amendment Response to IR URRA 17NOV2022 for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2022 NOV 22. Available from: \\CDSESUB1\EVSPROD\nda216974\0011\m1\us\111-info-amend\clinical-information-amendment-response-to-ir-urra-17nov2022.pdf.

[f] Davi, C. FDA Filing Communication – Filing Review Issues Identified for Xacduro (sulbactam-durlobactam (NDA 216974). Silver Spring (MD): FDA, CDER, OND, DAI (US); 2022 DEC 12. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806a14f7.

[g] Use-Related Risk Analysis for SUL-DUR (3-VIAL) Kit (Rev. 01) for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2022 Dec 21. Available from: \\CDSESUB1\EVSPROD\nda216974\0016\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acinetobacterbaumanniiinfection\5354-other-stud-rep\urra\use-related-risk-analysis.pdf.

[h] Multiple Module Information Amendment Day-74-URRA-Impurities 12DEC2022 for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2022 Dec 21. Available from: \\CDSESUB1\EVSPROD\nda216974\0016\m1\us\111-info-amend\multiple-module-information-amendment-day-74-ir-urra-impurit.pdf.

- Results: None of the recorded use errors were due to the multi-vial nature of the Xacduro kit. For more details regarding the results see appendix 2 of the URRA. Based on the use errors, close calls and use difficulties and subjective feedback additional mitigations were made such as; increasing prominence of storage information; clarifying the wording in the important safety information to users not to use non-kit components if they are dropped on a hard surface and damaged.

- Entasis indicated they planned to conduct a second formative study assessing the preparation of the recommended dosage (including the 1.0g/1.0g dosage, and the upper (1.5g/1.5g) and lower (0.5g/0.5g) dosing regimens). Entasis indicated they planned to submit the study results and updated URRA at the end of February 2023.

On February 28, 2023, Entasis submitted the second HF formative data and their updated URRA which listed the associated risks with the use of the Xacduro kit for all proposed dosing regimens.[i]

-Second Formative Study: Preparation of the recommended dosage upper (1.5g/1.5g) and lower (0.5g/0.5g) dosage was conducted to evaluate the mitigation strategies proposed.

- Participants: 12 HCPs (6 hospital-based pharmacists/ pharmacy technicians and 6 intensive-care unit (ICU) nurses)

- Results: None of the recorded use errors were due to the multi-vial nature of the Xacduro kit. For more details regarding the results see appendix 4 of the URRA.

Additionally, included in this February 28, 2023, submission, Entasis noted "*It is acknowledged that an alternate dosing regimen to eliminate the need for a 1.5g/1.5 g dosage was proposed by Entasis in NDA amendment (SN 0025[j]). Additionally, Entasis has performed further modeling and plans to submit a new proposal shortly to the NDA, which could also eliminate the need for a 0.5g/0.5g dosage.*"[k] Furthermore, Entasis eliminated the 1.5 g/1.5 g and 0.5 g/0.5 g doses in their revised labeling. According to the label and labeling review, the Division of Anti-infectives (DAI) concurred with Entasis' proposal to eliminate the proposed 1.5 /1.5 g and 0.5 g/0.5 g doses. Specifically, the Revised Label and Labeling Review dated April 26, 2023, stated the following; "*Subsequently DAI has concurred with Entasis' proposal to eliminate the proposed 1.5*

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[i] Use-Related Risk Analysis for SUL-DUR (3-VIAL) Kit (Rev. 02) for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2023 FEB 28. Available from: \\CDSESUB1\EVSPROD\nda216974\0034\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acinetobacterbaumanniiinfection\5354-other-stud-rep\urra\use-related-risk-analysis.pdf.

[j] Clinical Information Amendment ClinPharm Dosing 19JAN2023 for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2023 FEB 02. Available from: \\CDSESUB1\EVSPROD\nda216974\0025\m1\us\111-info-amend\clinical-information-amendment-clinpharm-dosing-19jan2023.pdf.

[k] Clinical Information Amendment URRA Follow Up for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2023 FEB 28. Available from: \\CDSESUB1\EVSPROD\nda216974\0034\m1\us\111-info-amend\clinical-information-amendment-urra-follow-up.pdf.

gram/1.5 gram and 0.5 gram/0.5 gram doses. From the aforementioned perspective, we find the proposed Instructions for Use (IFU), that only includes dose preparation instructions for the 1 gram/1 gram dose, acceptable from a medication error perspective. We also find the revised carton labeling acceptable from a medication error perspective."[1]

Based on the aforementioned information regarding Entasis's proposal to eliminate the 1.5 g/1.5 g and 0.5 g/0.5 g doses and DAI's concurrence with this proposal, we have determined that our aforementioned medication error concerns have been addressed and we maintain that Entasis does not need to submit human factors validation study results with their marketing application for the proposed 1 g/1 g dosing regimen.

[1] Myers D. Review of Revised Label and Labeling for Xacduro (NDA 216974). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 26. TTT No.: 2022-1984-1.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 26, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216974
Product Name, Dosage Form, and Strength:	Xacduro (sulbactam; durlobactam) for Injection, 1 gram/1 gram per kit[a]
Applicant/Sponsor Name:	Entasis Therapeutics, Inc. (ETI)
TTT ID #:	2022-1984-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader (Acting):	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised Instructions for Use (IFU), container labels, and carton labeling received on April 21, 2023 for Xacduro. The Division of Anti-Infectives (DAI) requested that we review the revised IFU, container labels, and carton labeling for Xacduro (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

We note that the submitted revised labeling includes revisions based on recommendations made by the Office of Pharmaceutical Quality (OPQ). Thus, we defer to OPQ to determine if these revisions are acceptable.

[a] The Applicant states, "Xacduro for injection is supplied as a kit containing 3 single-dose vials each containing sterile powder for reconstitution" in their proposed prescribing information. We note that the Office of Pharmaceutical Quality (OPQ) will make a final determination regarding the accuracy and use of the terminology "kit" during the NDA review.

[b] Myers, D. Label and Labeling Review for Xacduro (NDA 216974). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 29. TTT ID No.: 2022-1984.

Additionally, in our previous label and labeling review[c] we discussed inclusion of the proposed 1.5 gram/1.5 gram and 0.5 gram/0.5 gram doses [redacted] (b) (4). However, subsequently DAI has concurred with Entasis' proposal to eliminate the proposed 1.5 gram/1.5 gram and 0.5 gram/0.5 gram doses. From the aforementioned perspective, we find the proposed Instructions for Use (IFU), that only includes dose preparation instructions for the 1 gram/1 gram dose, acceptable from a medication error perspective. We also find the revised carton labeling acceptable from a medication error perspective.

However, the revised container labels are unacceptable from a medication error perspective. Thus, we provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 3 for Entasis Therapeutics, Inc.

3 RECOMMENDATIONS FOR ENTASIS THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	We previously noted that the strength statements (i.e., "0.5 g/vial" and "1 g/vial") appear in the same font color.	The use of the same color font for the product's strength statements minimizes the differentiation between the strengths, and in this case also active ingredients, which may lead to confusion or preparation errors.	We previously recommended that you revise the font color of one of the strength statements (i.e., "0.5 g/vial" or "1 g/vial"), so that the strength statements appear in their own unique color and the color does not overlap with any other colors utilized in highlighting the strengths. Included in your Information Response, last column in the table which represents your response to FDA recommendations, is the statement "*Change is identified as B4 on the attached pdf*." However, the strength statements (i.e., "0.5 g/vial" or "1 g/vial") appear to be same

[c] Myers, D. Label and Labeling Review for Xacduro (NDA 216974). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 29. TTT ID No.: 2022-1984.

Table 1. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			font color. Thus, we recommend that you revise the font color of one of the strength statements (i.e., "0.5 g/vial" or "1 g/vial"), so that the strength statements appear in their own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.
2.	As currently presented, the text (b) (4) [redacted] (b) (4) are duplicative.	Presenting duplicative information may hinder the readability of other important information on the label. In this case the strength statement also acts as the net quantity statement. Additionally, the presentation of the statements (b) (4) [redacted] (b) (4) in two different font colors provides unnecessary prominence.	Remove the duplicative statements (b) (4) [redacted] (b) (4) as they are unnecessary.
3.	Xacduro (sulbactam; durlobactam) is a co-packaged product. The kit contains 2 vials of durlobactam and 1 vial of Sulbactam. However, there is no mention of "Xacduro" on the container labels.	Medication errors could occur if the vial(s) was to be unintentionally separated from the carton (e.g., restocking medication error) with no identification regarding the source of the vial (i.e., "Xacduro® kit."	To provide clarity we recommend the inclusion of the statement "For use as part of Xacduro® kit" on the container label.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 21, 2023

Instructions for Use (IFU) (Image not shown) available at the following link: \\CDSESUB1\EVSPROD\nda216974\0045\m1\us\114-labeling\114a-draft-label\draft-instruction-for-use-xacduro-20apr2023.pdf.

Container labels

(b) (4)

Carton labeling

(b) (4)

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 29, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216974
Product Name and Strength:	Xacduro (sulbactam; durlobactam) for Injection, 1 gram/1 gram per kit[a]
Product Type:	Multiple Ingredients Co-packaged Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Entasis Therapeutics, Inc. (ETI)
FDA Received Date:	September 29, 2022
TTT ID #:	2022-1984
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

[a] The Applicant states, "Xacduro for injection is supplied as a kit containing 3 single-dose vials each containing sterile powder for reconstitution" in their proposed prescribing information. We note that the Office of Pharmaceutical Quality (OPQ) will make a final determination regarding the accuracy and use of the terminology "kit" during the NDA review.

1 REASON FOR REVIEW

As part of the approval process for Xacduro (sulbactam; durlobactam) for Injection, the Division of Anti-Infectives (DAI) requested that we review the proposed Xacduro prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND/REGULATORY HISTORY

NDA 216974 is a 505(b)(2) NDA and the listed drug product is Unasyn, NDA 050608.

The Use-Related Risk Analysis (URRA) Review, dated December 7, 2021, determined that that Entasis does not need to submit human factors (HFs) validation study data with your marketing application for Sulbactam-durlobactam, to be used by healthcare professionals.[b]

The subsequent URRA Review dated November 9, 2022, again maintained that the Applicant does not need to submit human factors validation study results with their new drug application under NDA 216974 for Sulbactam-durlobactam 1 g /1 g per vial, injection.[c]

On November 17, 2022, DMEPA sent an information request (IR) to Entasis.[d]

On November 22, 2022, Entasis indicated they will send an updated URRA by end of December 2022.[e]

On December 12, 2022, the 74-day letter was sent to Entasis, in which DMEPA provided potential review issues.[f]

On December 21, 2022, Entasis submitted an updated URRA and noted their plans to conduct a new formative study to include the 1.0 g/1.0 g dosage, and the upper (1.5 g/1.5 g) and lower

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[b] Oguntimein, Murewa. Use-Related Risk Analysis Review for SUL-DUR (IND 131330). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 DEC 07. OSE RCM No.: 2021-1771.

[c] Oguntimein, Murewa. Use-Related Risk Analysis Review for Sulbactam-durlobactam (NDA 216974). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 NOV 09. OSE RCM No.: 2022-2135.

[d] Davi, C. FDA Communication: Information Request for Sulbactam and Durlobactam (NDA 216974). Silver Spring (MD): FDA, CDER, OND, DAI (US); 2022 NOV 17. NDA 216974. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80699abf.

[e] Clinical Information Amendment Response to IR URRA 17NOV2022 for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2022 NOV 22. Available from: \\CDSESUB1\EVSPROD\nda216974\0011\m1\us\111-info-amend\clinical-information-amendment-response-to-ir-urra-17nov2022.pdf.

[f] Davi, C. FDA Filing Communication – Filing Review Issues Identified for Xacduro (sulbactam-durlobactam (NDA 216974). Silver Spring (MD): FDA, CDER, OND, DAI (US); 2022 DEC 12. NDA 216974. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806a14f7.

0.5 g/0.5 g) dosing regimens that were not included in the first formative study. These results will be submitted by end of February 2023.[g,h]

On February 28, 2023, Entasis submitted their updated URRA which lists the associated risks with the use of the sulbactam-durlobactam kit for all proposed dosing regimens.[i] Also included in this February 28, 2023 submission, Entasis notes "*It is acknowledged that an alternate dosing regimen to eliminate the need for a 1.5 g/1.5 g dosage was proposed by Entasis in NDA amendment (SN 0025[j]). Additionally, Entasis has performed further modeling and plans to submit a new proposal shortly to the NDA, which could also eliminate the need for a 0.5 g/0.5 g dosage.*"[k]

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A

[g] Multiple Module Information Amendment Day-74-URRA-Impurities 12DEC2022 for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2022 Dec 21. Available from: \\CDSESUB1\EVSPROD\nda216974\0016\m1\us\111-info-amend\multiple-module-information-amendment-day-74-ir-urra-impurit.pdf.

[h] Use-Related Risk Analysis for SUL-DUR (3-VIAL) Kit (Rev. 01) for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2022 Dec 21. Available from: \\CDSESUB1\EVSPROD\nda216974\0016\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acinetobacterbaumanniiinfection\5354-other-stud-rep\urra\use-related-risk-analysis.pdf.

[i] Use-Related Risk Analysis for SUL-DUR (3-VIAL) Kit (Rev. 02) for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2023 FEB 28. Available from: \\CDSESUB1\EVSPROD\nda216974\0034\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acinetobacterbaumanniiinfection\5354-other-stud-rep\urra\use-related-risk-analysis.pdf.

[j] Clinical Information Amendment ClinPharm Dosing 19JAN2023 for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2023 FEB 02. Available from: \\CDSESUB1\EVSPROD\nda216974\0025\m1\us\111-info-amend\clinical-information-amendment-clinpharm-dosing-19jan2023.pdf.

[k] Clinical Information Amendment URRA Follow Up for Sulbactam-durlobactam (NDA 216974). Waltham (MA): Entasis Therapeutics, Inc.; 2023 FEB 28. Available from: \\CDSESUB1\EVSPROD\nda216974\0034\m1\us\111-info-amend\clinical-information-amendment-urra-follow-up.pdf.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 DISCUSSION

In reviewing the proposed labels and labeling received on September 29, 2022, we identified concern with Entasis proposal to supply Xacduro as a single kit consisting of one vial containing sulbactam 1 gram and two vials each containing durlobactam 0.5 gram, for a total of 1 gram/1 gram per kit, which would be incongruent with some of the proposed dosages (i.e., 1.5 gram/1.5 gram and 0.5 gram/0.5 gram) described [redacted] (b) (4) (See Figure 1).

Figure 1. Proposed Recommended Dosage for Xacduro for Adults by Renal Function

Estimated CLcr (mL/min)*	Recommended Dosage of Sulbactam/Durlobactam (g)	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†	Loading dose of 1 g/1 g followed by 0.5 g/0.5 g	Every 12 hours	3 hours

*CLcr = creatinine clearance estimated by Cockcroft-Gault equation
†For patients on hemodialysis, the dose should be administered after the dialysis session has ended.

As proposed, there is an increased risk for preparation and dosage errors if 1½ kits are needed to prepare a 1.5 gram/1.5 gram dose.[I] Similarly, there is an increased risk of error if only a portion of one kit is intended to be used to prepare a 0.5 gram/0.5 gram dose. Our concerns were shared with the review team and Entasis.

Following notification of the Agency's concern with dosing errors, Entasis submitted proposals to revise the 1.5 gram/1.5 gram and 0.5 gram/0.5 gram doses [redacted] (b) (4) [redacted] (b) (4) (See Figure 2).

[I] Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors. Food and Drug Administration. 2016. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf.

Figure 2. Revised Proposed Recommended Dosage for Xacduro for Adults by Renal Function

Estimated CL_{CR} (mL/min)*	Recommended Dosage of Sulbactam/Durlobactam (g)	Frequency	Infusion Time
≥ 130	1 g/1 g	Every 4 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	1 g/1 g	Every 12 hours	3 hours
< 15‡	1 g/1 g	For initiation of treatment: Every 12 hours for the first 3 doses (0, 12, and 24 hours), followed by every 24 hours after the third dose† For all other treatment course: Every 24 hours	3 hours

*CL_{CR} = creatinine clearance estimated by Cockcroft-Gault equation
‡For patients on hemodialysis, the dose should be administered after the dialysis session has ended.
† This is equivalent to 1 g sulbactam/1 g durlobactam q12h on Day 1 followed by 1 g sulbactam/1 g durlobactam every 24 hours

At the time of this review, Entasis's proposals are still under review. However, should either of the 1.5 gram/1.5 gram and 0.5 gram/0.5 gram doses be retained [redacted] (b) (4), we have the following recommendations to minimize medication errors:

- We considered that the risk of preparation and dosage error could be mitigated through the introduction of additional kit(s) that correspond to each prescribed dose. For example, a kit containing a total of 0.5 grams of sulbactam and 0.5 grams of durlobactam.
- As currently presented, we note the inclusion of "Vial numbers" ("1", "2", and "3") in the [redacted] (b) (4) container labels and carton labeling. The current "Vial numbers" could lead to dose errors given that each total dose would not require the use of both vials 1 and 2 of durlobactam. For example, only vial 1 or 2 of durlobactam would be needed to prepare a 0.5 gram/0.5 gram dose. Moreover, one additional vial each of durlobactam (vials 1 or 2) and sulbactam (vial 3) would be required to prepare a 1.5 gram/1.5 gram dose. To avoid confusion, we recommend removal of the "Vial numbers" ("1", "2", and "3") from the [redacted] (b) (4) container labels, and carton labeling.
- As currently presented, the proposed Instructions for Use (IFU) only includes dose preparation instructions for the 1 gram/1 gram dose. [redacted] (b) (4) (b) (4)

4 CONCLUSION AND RECOMMENDATIONS

Independent of the final acceptability of the labeled doses as described in Section 3, the proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 for the Division and in Section 6 for Entasis Therapeutics, Inc.

5 RECOMMEDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented, throughout the prescribing information the text "vial(s)" appears without the preceding package type term (e.g., Highlights of Prescribing Information, Dosage Forms and Strengths, subsection 2.4 *Preparation of Xacduro for Intravenous Administration*, subsection 3 *Dosage Forms and Strengths*, subsection 16.1 *How Supplied*.	Omission of an appropriate package type term can result in the remaining contents of the vial being "saved" for future use resulting in deteriorated drug product medication errors.	Where missing, we recommend adding the package type term "single-dose" prior to the text "vial(s)."
Highlights of Prescribing Information			
1.	As currently presented, under the heading "*Dosage and Administration*", the text "…patients with CLcr<45 ml/min…" includes the symbol "<" prior to "45 ml/min" within the text.	The symbols '<' and '>' are error-prone[m] because these symbols are often mistaken and used as opposite of intended. Use of these symbols in the Dosage and Administration sections of the "Highlights" and "Dosage and Administration" sections of Prescribing Information, could lead to medication errors.	To provide clarity, we recommend replacing the symbol "<" with the intended meaning "less than."

[m] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2022 JUN 13]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 *Dosage and Administration*			
1.	As currently presented, in subsection 2.1 *Recommended Dosage* we note use of the abbreviation "g" which is not defined.	Abbreviations can be a source of misinterpreted and result in confusion if not appropriately defined.	To minimize the potential for misinterpretation, replace the first occurrence of the abbreviation "g" with the word "gram" followed by the abbreviation "g" enclosed in parentheses. For example, "The recommended dose of XACDURO is 1 gram (g) of…"
2.	As currently presented, in subsection 2.1 *Recommended Dosage* and subsection 2.2 *Recommended Dosage Adjustments by Renal Function*, the text "…patients with CLcr<45 mL/min." includes the symbol "<" prior to "45 mL/min" within the text.	The symbols '<' and '>' are error-prone because these symbols are often mistaken and used as opposite of intended. Use of these symbols in the Dosage and Administration sections of the "Highlights" and "Dosage and Administration" sections of Prescribing Information, could lead to medication errors.	To provide clarity, we recommend replacing the symbol "<" with the intended meaning "less than."
3.	As currently presented, in subsection 2.2 *Recommended Dosage Adjustments by Renal Function*, Table 1 "Recommended Dosage of XACDURO for Adults by Renal Function" at the bottom of the first column "Estimated CLcr (ml/min)*" includes the text "<15" which includes the symbol "<"	The symbols '<' and '>' are error-prone because these symbols are often mistaken and used as opposite of intended. Use of these symbols in the Dosage and Administration sections of the "Highlights" and "Dosage and Administration" sections of Prescribing Information, could lead to medication errors.	To provide clarity, we recommend replacing the symbol "<" with the intended meaning "less than."

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	prior to the number "15" within the text.		
4.	As currently presented, under the subheading "*Items required by Pharmacy to prepare XACDURO*" located in subsection 2.4 *Preparation of XACDURO for Intravenous Administration*, we note the package term (b) (4) (b) (4)	The package type term, (b) (4) is not considered an appropriate package type term.[n] Also, omission of an appropriate package type term can result in the remaining contents of the vial being "saved" for future use resulting in deteriorated drug product medication errors.	Revise the package type term (b) (4) to "single-dose vial."
5.	As currently presented, within the text associated with the number "1", under the subheading "*Preparation of XACDURO*", located in subsection 2.4 *Preparation of XACDURO for Intravenous Administration*, the statement "Each reconstituted vial contains 1 g of sulbactam per 5.0 mL of clear…" contains a trailing zero.	The use of trailing zeros could result in numeric misinterpretation (e.g., 50 mL).	To avoid numeric misinterpretation, we recommend the removal of the trailing zero from the statement "Each reconstituted vial contains 1 g of sulbactam per 5.0 mL of clear…". For example, "Each reconstituted vial contains 1 g of sulbactam per 5 mL of clear…"
6.	As currently presented, in subsection 2.6 *Storage of Prepared Solution in Infusion Bag,* the storage statement (i.e., "…in the	The lower temperatures in the ranges may be overlooked, resulting in medication errors such as administration of	To provide clarity, add the degree and centigrade symbols (°C) following the number "2" and the degree and Fahrenheit symbols (°F) following the

[n] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from https://www.fda.gov/media/117883/download.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	refrigerator at 2-8 °C (36 -46°F)…") is missing the degree symbol (°) and the units of measurement (Centigrade and Fahrenheit, respectively) following the first temperature in the ranges.	deteriorated product medication errors. Additionally, when a hyphen is included in a range instead of the word "to," the hyphen can be overlooked.	number "36" within the storage statement. Additionally, we also recommend replacing the hyphen with its intended meaning "to." For example, "…in the refrigerator at 2°C to 8 °C (36°F to 46°F)…"
Full Prescribing Information – Section 3 *Dosage Forms and Strengths*			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	A description of identifying characteristics is required per 21 CFR 201.57(c)(4)(ii) and can be used to help mitigate the risk of administering deteriorated or contaminated drug for this product.	We recommend that the description of identifying characteristics of the dosage form, such as color or any other identifying characteristics to facilitate identification, be added in accordance with 21 CFR 201.57(c)(4)(ii).
Full Prescribing Information – Section 16 *How Supplied/Storage and Handling*			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	A description of identifying characteristics can be used to help identify the product and is required per 21 CFR 201.57(c)(17)(iii).	We recommend that the description of identifying characteristics of the dosage form, such as color, clarity of solution, or any other identifying characteristics to facilitate identification, be added in accordance with 21 CFR 201.57(c)(17)(iii).
2.	As currently presented in subsection 16.1 *How Supplied*, bullet points for the "1 g durlobactam" and 1 g sulbactam" includes (b) (4) (b) (4)	As both the durlobactam and sulbactam drug products are a dry powder formulation, the inclusion of (b) (4) (b) (4) could be misinterpreted (b) (4) (b) (4)	We recommend removing the (b) (4) (b) (4) to avoid misinterpretation or confusion that could lead to medication errors.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(b) (4) (b) (4), which could cause confusion and lead to medication errors.	

6 RECOMMENDATIONS FOR ENTASIS THERAPEUTICS, INC.

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The format for expiration date is defined as "YYYY MM DD." However, it is unclear how the month will be expressed.	Clearly defining the expiration date will minimize confusion and the risk for use of deteriorated drug medication errors. For example, presenting the month as 'MA' or 'JU' does not clearly communicate whether 'MA' or 'JU' is for the months of March or May and June or July, respectively.	Clarify how you intend to express the month within the expiration date statement. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			used to separate the portions of the expiration date.
2.	As currently presented, the route of administration is stated as (b) (4) (b) (4)" However, according to the proposed Prescribing Information (PI) subsections 2.1 *Recommended Dosage* and 2.3 *Administration* this product is intended for administration via intravenous infusion.	We are concerned that the drug could be inadvertently administered as an intravenous bolus. Additionally, to avoid medication errors involving wrong route of administration, the route of administration statement should be prominently displayed on the PDP of both the container labels and carton labeling. Furthermore, this product requires dilution prior to administration.	To help avoid medication errors involving wrong route of administration and wrong preparation, revise the route of administration statement from (b) (4)" to instead "For intravenous infusion after dilution" on the PDP of the container labels and carton labeling. Additionally, ensure the route of administration (i.e., "For intravenous infusion after dilution.") is prominently displayed on the carton labeling.
3.	As currently presented, the "Recommended Dosage" statement is not included on the proposed container labels and carton labeling.	21 CFR 201.55 requires "...labels for prescription drugs bear a statement of the recommended or usual dosage."	Add your intended "Recommended Dosage" statement on the container labels and carton labeling. For example, "Recommended Dosage: See prescribing information."
Container Labels			
1.	Each vial label of the individual components of the drug product prominently includes the (b) (4)	(b) (4) (b) (4) The current presentation (b) (4) (b) (4) could result in misinterpretation (b) (4) (b) (4)	We recommend removing the (b) (4) (b) (4) from each container label. Ensure the respective established name and corresponding strength are presented as the most prominent critical information on the PDP of each vial.

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(b) (4). Additionally, the (b) (4) (b) (4) on the container label could be misinterpreted (b) (4) (b) (4).	
2.	The individual vials do not include a statement to clarify that sulbactam must be administered with durlobactam and vice versa.	This product is not a fixed-dose combination product. Both active ingredients are not contained in a single vial but are required to be administered for a complete dose.	We recommend adding to the sulbactam vial, "Must be administered with durlobactam" and to the durlobactam vial, "Must be administered with sulbactam".
3.	As currently presented, there is no linear barcode included on the container labels.	The drug barcode is often used as an additional verification during dose preparation and before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the product's linear barcode to each individual container label as required per 21 CFR 201.25(c)(2). We recommend that the container label linear barcode be oriented in a vertical position to improve scannability of the barcode, as barcodes placed in a horizontal position may not scan due to the curvature of the container. Additionally, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
4.	As currently presented, the strength statements (i.e., "0.5 g/vial" and "1 g/vial") appear in the same font color.	The use of the same color font for the product's strength statements minimizes the differentiation between the	Revise the font color of one of the strength statements (i.e., "0.5 g/vial" or "1 g/vial"), so that the strength statements appear in their own unique

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		strengths, and in this case also active ingredients, which may lead to confusion or preparation errors.	color and the color does not overlap with any other colors utilized in highlighting the strengths.
5.	As currently presented, the dosage form is not included on the PDPs.	Dosage form is critical information and should be prominent on the PDP. See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Errors. Food and Drug Administration* (May 2022).[o]	Add the dosage form (i.e., "for Injection") on the PDPs.
6.	As currently presented, the package type term (i.e., "Single-Dose Vial") is not included on the container labels (i.e., the one vial of sulbactam 1 g/vial and two vials of durlobactam 0.5 g/vial).	The unused contents of the reconstituted product vials could be inadvertently "saved" for future use and result in use of deteriorated drug product medication errors. Including the package type term helps facilitate proper handling of products.	Add the appropriate package type term (i.e., "Single-Dose Vial") to all three container labels (i.e., the one vial of sulbactam 1 g/vial and two vials of durlobactam 0.5 g/vial). Additionally, we recommend that the package type term (i.e., "Single-Dose Vial") be followed by the statement "Discard Unused Portion." Furthermore, to increase the prominence of this important information we recommend locating this statement to the PDP and using bold font of the statement "Discard Unused Portion."

[o] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			For example: "Single-Dose Vial – Discard Unused Portion"
7.	As currently presented, the top of each vial's side panel includes the text [redacted] (b) (4) and [redacted] (b) (4) respectively. However, the [redacted] (b) (4) statement lacks the corresponding active ingredient.	Clearly defining the appropriate active ingredient will minimize the risk for confusion and wrong preparation medication errors.	To provide clarity we recommend adding the appropriate active ingredients to the statements [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) For example, "Contains Durlobactam 0.5 g/vial." and "Contains Sulbactam 1 g/vial."
8.	As currently presented, the storage statement, including temperature range, is missing on the container vials.	Clearly defining the storage temperature will minimize confusion and risk for deteriorated drug medication errors.	Add the storage statement, including temperature range, on the container labels.
Carton Labeling			
1.	As currently presented, the strength statement is [redacted] (b) (4)	Xacduro for injection is supplied as a kit containing 3 single-dose vials each containing sterile powder for reconstitution.	We recommend that the strength statement [redacted] (b) (4) [redacted] (b) (4) be revised to "1 g/1 g per kit."
2.	Each panel that includes the proprietary name and total strength per kit does not clearly denote that the carton consists of each active ingredient supplied in separate vials and co-packaged within the kit.	There is potential for preparation errors if each vial is assumed to contain both active ingredients. Additionally, the "3 vials" descriptor could be misinterpreted as "3 vials each containing both active ingredients".	We recommend including a statement on the PDP and top panel of the carton to denote that this kit consists of sulbactam co-packaged with durlobactam. For additional clarity, we recommend adding the net quantity of contents statement (i.e., "Each carton contains…" statement) in place of the "3 vials" descriptor. The net quantity of contents statement should clarify that there is one (1) single-dose vial

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			of sulbactam containing 1 gram/vial and two (2) single-dose vials of durlobactam each containing 0.5 gram/vial. Furthermore, we recommend including a statement to convey that sulbactam must be administered with durlobactam.
3.	As currently presented, the human-readable and machine-readable (2D data matrix barcode) product identifier is missing.	The Drug Supply Chain Security Act (DSCSA) requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to the smallest saleable unit (usually the carton) of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (July 2021).[p] Additionally, if the product identifier requirements apply to your product, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.
4.	As currently presented on the side panel, the text states (b) (4)	Dry powder parenteral products should express the product strength in terms	On the side panel, revise the statement "Single-dose kit." Additionally, revise the

[p] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	[redacted] (b) (4)	of the total amount of drug per vial (e.g., XX mg/vial or XX mg per vial). Additionally, the descriptor "Single-dose kit" can be revised to better express a declaration of net quantity of contents in accordance with 21 CFR 201.1(g).	strength statement from [redacted] (b) (4) (b) (4) to, for example: Each carton contains: **Durlobactam** Two amber vials 0.5 g/vial each **Sulbactam** One clear vial 1 g/vial
5.	As currently presented on the back panel, the text associated with the vial images includes (b) (4) [redacted] (b) (4)	The final volumes in each vial will be more than (b) (4) [redacted] (b) (4), respectively, when accounting for the volume contributed by the powder. As such, to provide clarity, generally, the amount per milliliter concentration is included to minimize the risk of the entire contents being withdrawn from the vial.	We recommend revising to cite the resultant concentration (i.e., 0.2 g/mL). For example: For durlobactam, revise to: "The resultant solution contains 0.2 g/mL durlobactam" and For sulbactam: "The resultant solution contains 0.2 g/mL of sulbactam" See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*[q]

[q] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Xacduro that Entasis Therapeutics, Inc. submitted on September 29, 2022.

<table>
<tr><th colspan="2">Table 4. Relevant Product Information for Xacduro</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>sulbactam; durlobactam</td></tr>
<tr><td>Indication</td><td>Indicated in adults for the treatment of infections due to Acinetobacter baumannii-calcoaceticus complex including multidrug-resistant and carbapenem-resistant strains.</td></tr>
<tr><td>Route of Administration</td><td>Intravenous infusion</td></tr>
<tr><td>Dosage Form</td><td>for injection</td></tr>
<tr><td>Strength</td><td>1 gram/1 gram per kit[r]</td></tr>
<tr><td>Dose and Frequency</td><td>
Recommended Dosage of XACDURO for Adults by Renal Function
<table>
<tr><th>Estimated CLcr (mL/min)*</th><th>Recommended Dosage of Sulbactam/Durlobactam (g)</th><th>Frequency</th><th>Infusion Time</th></tr>
<tr><td>≥ 130</td><td>1.5 g/1.5 g</td><td>Every 6 hours</td><td>3 hours</td></tr>
<tr><td>45-129</td><td>1 g/1 g</td><td>Every 6 hours</td><td>3 hours</td></tr>
<tr><td>30-44</td><td>1 g/1 g</td><td>Every 8 hours</td><td>3 hours</td></tr>
<tr><td>15-29</td><td>Loading dose of 1 g/1 g followed by 0.5 g/0.5 g</td><td>Every 8 hours</td><td>3 hours</td></tr>
<tr><td>< 15†</td><td>Loading dose of 1 g/1 g followed by 0.5 g/0.5 g</td><td>Every 12 hours</td><td>3 hours</td></tr>
</table>
*CLcr = creatinine clearance estimated by Cockcroft-Gault equation
†For patients on hemodialysis, the dose should be administered after the dialysis session has ended.
</td></tr>
<tr><td>How Supplied</td><td>Kit containing 3 single-dose vials each containing sterile powder for reconstitution: 1 vial contains sulbactam 1 g and 2 vials each contain durlobactam 0.5 g.</td></tr>
<tr><td>Storage</td><td>Refrigerate at 2°C to 8°C (36°F to 46°F); (b) (4) permitted (b) (4) [see USP Controlled Cold Temperature]. Store prepared XACDURO in the refrigerator.</td></tr>
<tr><td>Container Closure</td><td>The stopper is (b) (4) (b) (4) no natural rubber. The stopper is (b) (4). The seal is (b) (4) (b) (4) flip-off cap.</td></tr>
</table>

[r] The Applicant states, "Xacduro for injection is supplied as a kit containing 3 single-dose vials each containing sterile powder for reconstitution" in their proposed prescribing information. We note that the Office of Pharmaceutical Quality (OPQ) will make a final determination regarding the accuracy and use of the terminology "kit" during the NDA review.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 9, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "IND 131330" and "NDA 216974." Our search identified five previous reviews[s,t,u,v,w], and we considered our previous recommendations to see if they are applicable for this current review.

[s] Myers, D. Proprietary Name Review for Xacduro (IND 131330). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 03. OSE RCM No.: 2018-27822110.

[t] Myers, D. TAM Cheatsheet for IND 131330. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 29. OSE RCM No.: 2019-2207.

[u] Oguntimein, Murewa. Use-Related Risk Analysis Review for SUL-DUR (IND 131330). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 DEC 07. OSE RCM No.: 2021-1771.

[v] Oguntimein, Murewa. Use-Related Risk Analysis Review for Sulbactam-durlobactam (NDA 216974). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 NOV 09. OSE RCM No.: 2022-2135.

[w] Myers, D. Proprietary Name Review for Xacduro (NDA 216974). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 21. PNR ID#: 2022-1044724790.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[x] along with postmarket medication error data, we reviewed the following Xacduro labels and labeling submitted by Entasis Therapeutics, Inc.

- Container labels received on September 29, 2022
- Carton labeling received on September 29, 2022
- Instructions for Use received on September 29, 2022, available from \\CDSESUB1\EVSPROD\nda216974\0001\m1\us\114-labeling\114a-draft-label\draft-instruction-for-use-xacduro.pdf.
- Prescribing Information (Image not shown) received on September 29, 2022
    - Cleaned proposed (Draft) PI available at the following link: \\CDSESUB1\EVSPROD\nda216974\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-word-20sep22.docx.
    - Annotated Draft PI available at the following link: \\CDSESUB1\EVSPROD\nda216974\0001\m1\us\114-labeling\114a-draft-label\annotated-draft-labeling-text.pdf.

F.2 Label and Labeling Images

(b) (4)

[redacted]

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[x] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS
03/29/2023 02:21:06 PM

VALERIE S VAUGHAN
03/29/2023 02:51:41 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 216974
Submission Number	0001
Submission Date	9/29/2022
Date Consult Received	1/23/2023
Drug Name	Xacduro (Sulbactam-Durlobactam); Durlobactam also referred to as ETX2514
Indication	Treatment of infections due to Acinetobacter baumannii-calcoaceticus complex including multidrug-resistant and carbapenem-resistant strains, in adults
Therapeutic Dose	1 gram over 3 hours every 6 hours for up to 14 days for creatinine clearance (CrCl) 45 to 129 mL/min. Adjusted dosing for CrCl <45 and CrCl>129 mL/min.
Clinical Division	DAI
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 1/23/2023 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Thorough QT Study Report, CS2514-2018-0003 (NDA 216974 / SDN 1; link);
- Previous IRT review under IND 131330 dated 10/16/2018 in DARRTS;
- Sponsor's response to IR dated January 23, 2023 (NDA 216974 / SDN 24; link);
- Sponsor's response to IR dated January 23, 2023 (NDA 216974 / SDN 29; link);
- Sponsor's response to IR dated February 13, 2023 (NDA 216974 / SDN 30; link);
- Draft labeling (NDA 216931 / SDN 1; link);
- Investigator's brochure (NDA 216974 / SDN 24; link); and
- Highlights of Clinical Pharmacology and Cardiac Safety (NDA 216974 / SDN 24; link).

1 SUMMARY

ETX2514 did not prolong the QTcF interval in this thorough QT study – see Table 1 for overall results.

The clinical study CS2514-2018-0003 was a thorough QT study. The highest dose provided 1.4-fold high clinical exposure. Data were analyzed using by-time analysis as the primary analysis, which did not suggest that ETX2514 is associated with significant QTc

prolonging effect. The findings of the primary analysis are further supported by the lack of QTc prolongation in nonclinical data and exposure-response analysis (section 4.5).

Table 1 : Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☒ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• According to the sponsor, the adjusted dosing regimen in subjects with severe renal impairment provides steady state Cmax of 70 µg/mL. This is expected to be the high clinical Cmax (section 3.1)
• The supratherapeutic dose in the TQT study provided Cmax of 96.2 µg/mL which covers high clinical Cmax by 1.4-fold.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Time (h)</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>ΔΔQTcF</td><td>4 g ETX2514 IV</td><td>6.0</td><td>1.8</td><td>(-1.0, 4.5)</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td rowspan="2">Integrated nonclinical risk assessment was not conducted since the QT assessment pathway is a thorough QT study</td></tr>
<tr><td>In vivo findings</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to eCTD 0001 (link) from the CSS-IRT.

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Additionally, we are omitting section x, as we do not have any edits to that section. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (4)

[redacted]

(b) (4)

[redacted]

3 SPONSOR'S SUBMISSIOND

3.1 OVERVIEW

Sulbactam and durlobactam is proposed in combination to treat infections due to Acinetobacter baumannii-calcoaceticus complex including multidrug-resistant and carbapenem-resistant strains. The proposed dosing regimen is 1 gram each of sulbactam and durlobactam over 3 hours every 6 hours for up to 14 days in patients with CrCl between 45 and 129 mL/min. The dosing regimen is adjusted for CrCL <45 and >129 mL/min.

Sulbactam is approved in combination with ampicillin for the treatment of infections due to susceptible strains as described in the product label (Unasyn). The maximum approved dose of sulbactam is 1 gram every 6 hours infused over 10 – 30 minutes.

We previously reviewed a study protocol for a TQT study for durlobactam monotherapy and found it overall acceptable as the exposure to sulbactam is expected to be less than that of the currently maximum approved dosing regimen (i.e., due to a shorter dosing regimen), and there is no evidence of pro-arrhythmic effects of sulbactam. (DARRTS 10/16/2018)

The current review focuses on the TQT study report for durlobactam (ETX2514). There are no significant changes between the final study protocol and the study protocol previously reviewed.

3.1.1 Clinical pharmacology

See the Highlights of Clinical Pharmacology and Cardiac Safety table.

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	1-gram ETX2514 infused over 3 hours every 6 hours for up to 14 days	39.9 µg/mL
Sponsor's High clinical exposure scenario	Patients with severe renal impairment received the adjusted dosage of 1g/1g Sulbactam/ ETX2514 Q12h	70 µg/mL
Highest dose in QT assessment	Single infusion: 4 grams ETX2514 over 3 hours	96.2 ug/mL
C_{max} Ratio	1.4	

3.1.2 Nonclinical Safety Pharmacology Assessments

A non-GLP in vitro study of the effects of ETX2514 on cardiac ion channels was conducted using electrophysiologic measurement of ion flux through recombinant voltage-gated channels expressed in mammalian cells. The channels tested (and the current they are believed to conduct in cardiac cells, shown in brackets) were: hCav1.2/β2/α2δ (ICaL),

hCav3.2 (ICaT), hHCN4 (IF), hKv1.5 (IKUR), hKv11.1 (hERG; IKR), hKv4.3/hKChIP2.2 (ITO), hKv7.1/hKCNE1 (IKS) and hNav1.5 (INa). ETX2514 did not produce >50% inhibition of ion channel activity for any of the 8 human cardiac channels evaluated at up to the maximum concentrations tested, 100 to 1000 µM.

Potential in vivo cardiovascular effects of ETX2514 were evaluated in a group of 4 male beagle dogs given a single 2-hour IV infusion at a dose volume of 10 mL/kg at a rate of 5 mL/kg/hour of vehicle (0.9% sodium chloride for injection) or ETX2514 at 500, 1000 and 2000 mg/kg.

Animals were dosed using a Latin Square crossover design, and the study was conducted in compliance with United States Food and Drug Administration GLP for Nonclinical Laboratory Studies. Each animal received each treatment with 3 4 days between doses. Surgically implanted telemetry devices continuously monitored the following parameters for 90 minutes before and at least 20 hours after the start of infusion: hemodynamic parameters (body temperature, heart rate, diastolic, systolic, mean arterial blood pressure, and arterial pulse pressure) and ECG parameters (PR, QTc and QRS intervals).

Assessment of the general health of the animals was based on mortality, clinical observations, body weight, and body temperature (via telemetry). Administration of 500, 1000 and 2000 mg/kg ETX2514 to male beagle dogs did not result in any ETX2514 related deaths or body weight changes. When dosed with 2000 mg/kg, 3 of 4 animals were observed with vomitus containing food, which was considered ETX2514 related.

No qualitative ECG effects or changes in PR interval, QRS duration, QT interval, QTc interval, heart rate or arterial pressures were attributed to ETX2514, up to 2000 mg/kg. Administration of ≥1000 mg/kg ETX2514 was associated with a small elevation in body temperature during the light phase (within the 12-hour light period). Peak body temperature increases of 0.6 and 1.1°C occurred in animals dosed with 1000 and 2000 mg/kg ETX2514.

In summary, there were no ETX2514 related adverse effects on cardiovascular function in male beagle dogs given single doses up to 2000 mg/kg via intravenous infusion. Systemic exposures were not assessed in this study. However, in the 14-day repeat dose toxicology study in dogs Day 1 Cmax and AUC0-24h in males at 2000 mg/kg were 2465 ± 151 µg/mL and 6177 ± 787 h*µg/mL, respectively.

Reviewer's Comment: *The results of nonclinical testing are consistent with the lack of QTc effect observed in humans.*

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

In the sponsor's by-time analysis, ETX2514 4 g IV excluded the 10 msec threshold at the supratherapeutic dose level for ΔΔQTcF.

Sponsor presented by-time analysis for all intervals (QTcF, HR, PR and QRS).

Reviewer's comment: *FDA reviewer's analysis results are similar to the sponsor's results. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *FDA reviewer's analysis results also show that assay sensitivity was established by the moxifloxacin arm. The results of the sponsor's exposure-response analysis also indicate that the study demonstrated assay sensitivity. Please see Section 4.3.1.1 and 4.5.1.1 for additional details.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (>100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis also shows the similar results. Please see section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

The sponsor used the model recommended in the white paper.

ETX2514 4.0 g IV infused over 3 hours was selected as the supratherapeutic dose for the TQT study (NCT03985410). This dose has a Cmax of 96.2±13.6 µg/mL, which represents a 3.4-fold increase above the Cmax at the clinical dose and a 1.4-fold increase above the maximum predicted Cmax in patients with severe renal impairment.

At baseline, data were available from 31 subjects on active treatment, 31 subjects on moxifloxacin, and 30 subjects on placebo.

ETX2514 at the studied dose did not have a clinically relevant effect on HR. Mean ΔHR on active treatment closely followed the pattern observed on placebo. As a result, mean ΔΔHR was small across postdose time points, varying between −2.6 bpm at 3 hours post-SOI and −0.2 bpm at 4 hours post-SOI.

Mean ΔQTcF on ETX2514 closely followed the placebo pattern across post-dose time points. Mean ΔΔQTcF varied between 0.0 ms at 24 hours post-SOI and 1.8 ms at 6- and 8-hours post-SOI. In the concentration-QTc analysis, a linear model with a treatment effect-specific intercept was fitted for ETX2514 plasma concentrations and represented the data in an acceptable way. The estimated slope of ETX2514 plasma concentration in the concentration-QTc relationship was shallow and not statistically significant (−0.0000019 ms per ng/mL [90% CI: −0.0000232 to 0.0000194]) with a positive and not statistically significant treatment effect-specific intercept 0.6 ms. The predicted QT effect (ΔΔQTcF) at the observed geometric mean ETX2514 Cmax (106 µg/mL) was 0.43 ms (90% CI: −1.38 to 2.23). Based on this concentration-QTc analysis, an effect on ΔΔQTcF exceeding 10 ms can be excluded up to ~190 µg/mL

The same linear model with a treatment effect-specific intercept as in the concentration-QTc analysis was used in the assay sensitivity analysis for moxifloxacin. The treatment effect-specific intercept was small, 0.4 ms, and not statistically significant. The slope of

the relationship was positive and statistically significant: 0.0065 ms per ng/mL (90% CI: 0.00544 to 0.00750), and the lower bound of the 2-sided CI of the predicted QT effect (13.99 ms [90% CI: 12.27 to 15.71]) at the geometric mean peak moxifloxacin concentrations (2103.4 ng/mL) was above 5 ms, thereby demonstrating assay sensitivity.

Reviewer's comment: *The sponsor's concentration-QTc analysis suggests a lack of significant QTc prolongation. This analysis is supportive of the primary by-time analysis.*

In the Highlights of Clinical Pharmacology and Cardiac Safety table, the sponsor states that the Cmax of 96.2±13.6 µg/mL represents a 3.4-fold increase above the Cmax at the clinical dose. This estimate relates to the Cmax observed as described below:

At the time of the last dose of ETX2514SUL 1 g/1 g, co-administered with IMI, every 6 hours for 11 days, the ETX2514 Cmax is 28.1±8.6 µg/mL. The maximum ETX2514 Cmax at steady state is predicted to be ~70 µg/mL in patients with severe renal impairment. The maximum clinical dose proposed for ETX2514SUL 1.5 g/1.5 g is in patients with augmented renal clearance; the Cmax in these patients, however, is only ~14.0 µg/mL.

A separate section of the Highlights of Clinical Pharmacology table states:

For normal renal function 1g IV q6h infused over 3 hours. This dose was used in the Phase 2 cUTI trial. Mean (CV%) Cmax and AUC0-6h at steady state were 39.9 (38.2) µg/mL and 123.8 (69.2) h•µg/mL, respectively (NCT03445195).

To be conservative, the higher estimate of Cmax (i.e., 39.9 µg/mL), not the lower estimate of Cmax (i.e., 28.1 µg/mL), was used in Table 2 of this review as the steady state exposure expected when the therapeutic dose was administered.

3.2.4 Safety Analysis

There were no deaths, serious AEs in the study, or AEs leading to discontinuation. Two subjects discontinued the study due to withdrawal of consent (01011) or lost to follow-up after having their infusion interrupted or completed on day 1 (01058).

No cardiac-related AEs were observed in the study.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to the subject, visit, and treatment allocation. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT

measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 By-Time Analysis

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and a compound symmetry covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 3.

Figure 1: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

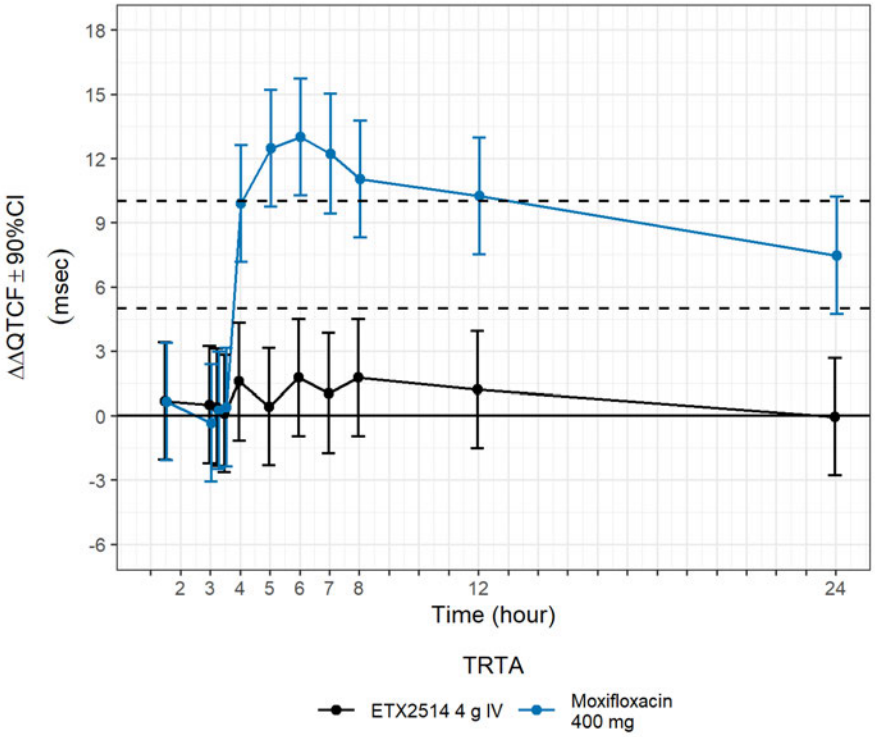


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Treatment	Nact / Npbo	Time (hour)	ΔΔQTCF (msec)	90.0% CI (msec)
ETX2514 4 g IV	31 / 30	6.0	1.8	(-1.0 to 4.5)

4.3.1.1 Assay Sensitivity

The statistical reviewer used the same linear mixed model as treatment arm to analyze the moxifloxacin effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The time-course of changes in ΔΔQTcF is shown in Figure 1 with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 4). Figure 1 shows a delayed ΔΔQTcF increase in moxifloxacin arm and the maximum ΔΔQTcF effect occurred at hour 6 (i.e., 3 hours after moxifloxacin administration) because oral moxifloxacin was administered after 3 hours of placebo ETX2514 infusion. Thus, the time profile of moxifloxacin is consistent with historical profile.

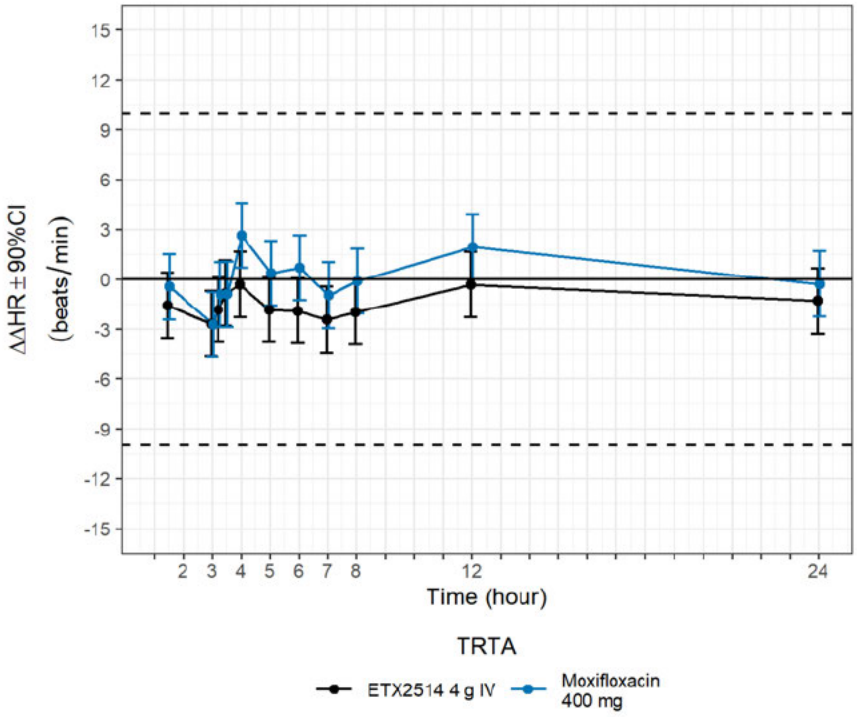
Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Treatment	Nact / Npbo	Time (hour)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	31 / 30	6.0	13.0	(10.3 to 15.7)	(9.3 to 16.7)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

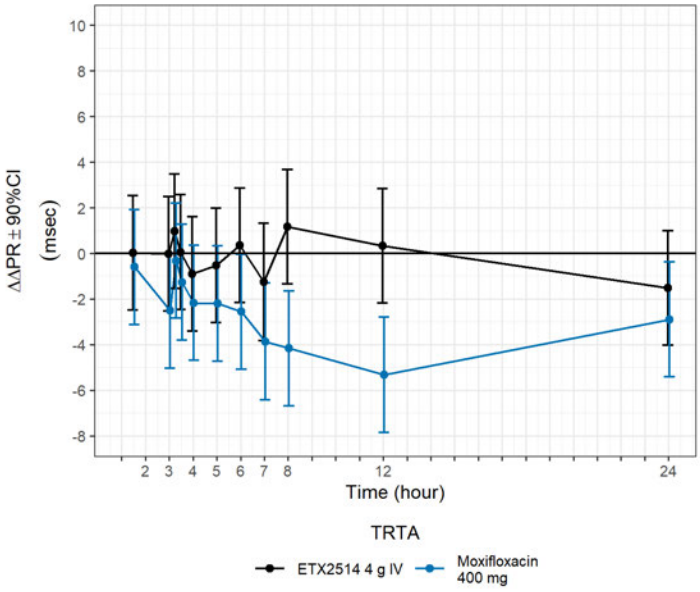
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

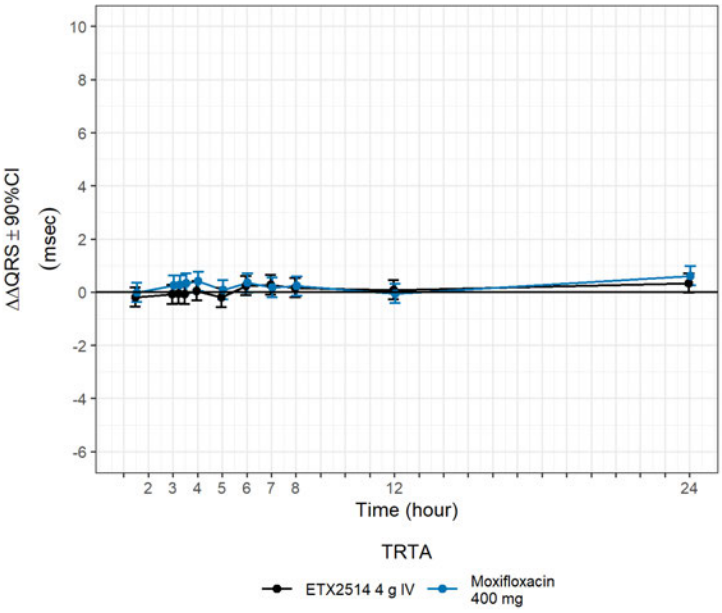
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects experienced QTcF values >480 msec with or without a change from baseline >60 msec. None of the subjects experienced ΔQTcF >30 msec for ETX2514 4 g IV.

4.4.2 HR

None of the subjects experienced HR >100 beats/min for ETX2514 4 g IV.

4.4.3 PR

None of the subjects experienced PR >220 msec; with and without 25% increase over baseline for ETX2514 4 g IV.

4.4.4 QRS

None of the subjects experienced QRS >120 msec; with and without 25% increase over baseline for ETX2514 4 g IV.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]

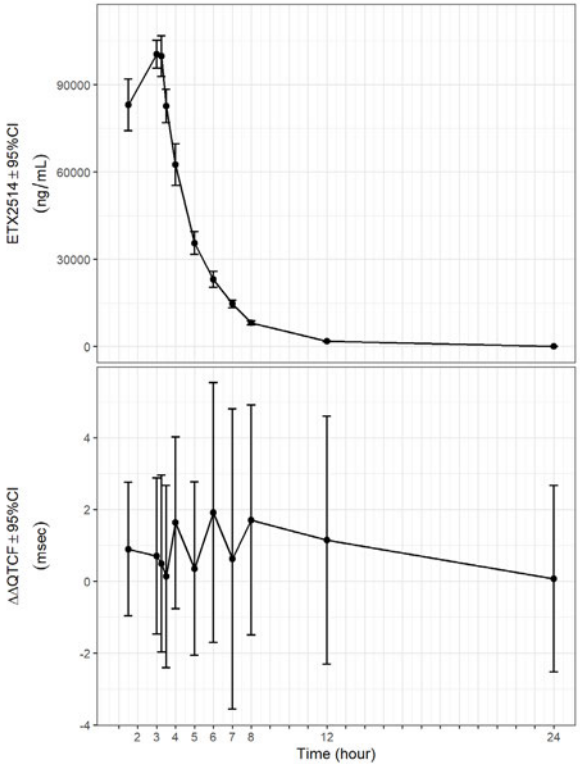
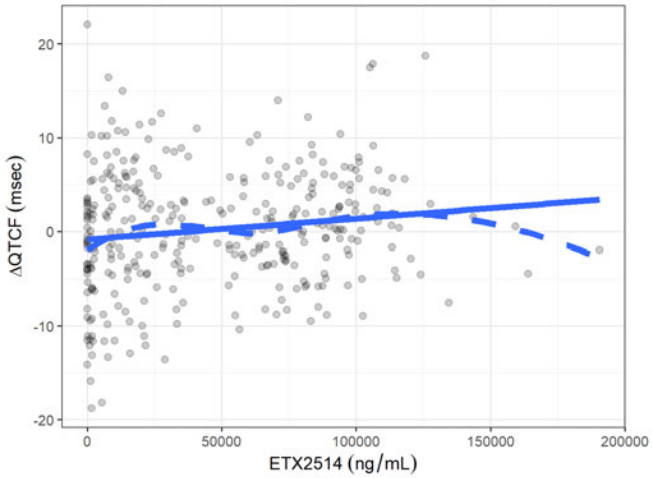


Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 5.

[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 7: Goodness-of-fit Plot for QTcF

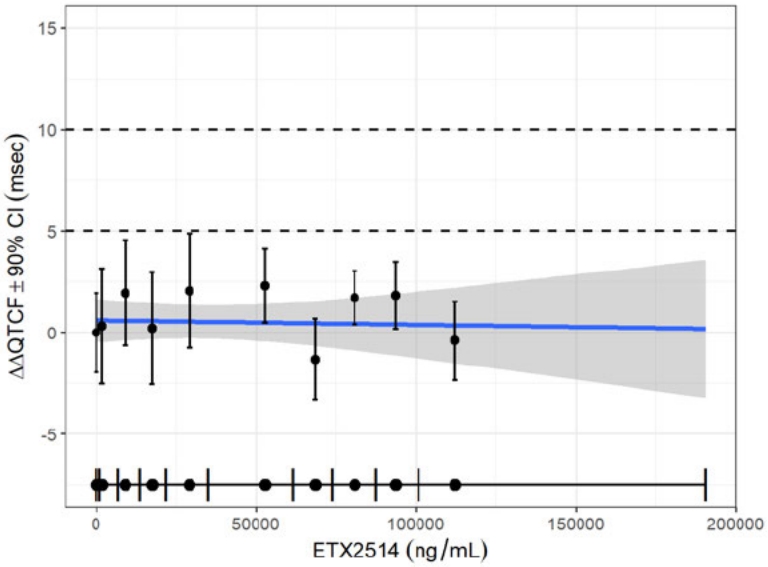


Table 5: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	ETX2514 (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
ETX2514 4 g IV	1	106,474.6	0.4	(-1.4 to 2.1)

4.5.1.1 Assay Sensitivity

When the same linear mixed effect model is applied, the goodness-of-fit plot for moxifloxacin is shown in Figure 8, and the predicted QTcF at the geometric mean Cmax is listed in Table 6. The predicted QTcF effect (i.e., the lower bound of the 2-sided 90% confidence interval) was above 5 msec at the observed geometric mean Cmax of 400 mg moxifloxacin. Thus, assay sensitivity was demonstrated.

Figure 8: Goodness-of-fit plot of ΔΔQTcF for Moxifloxacin

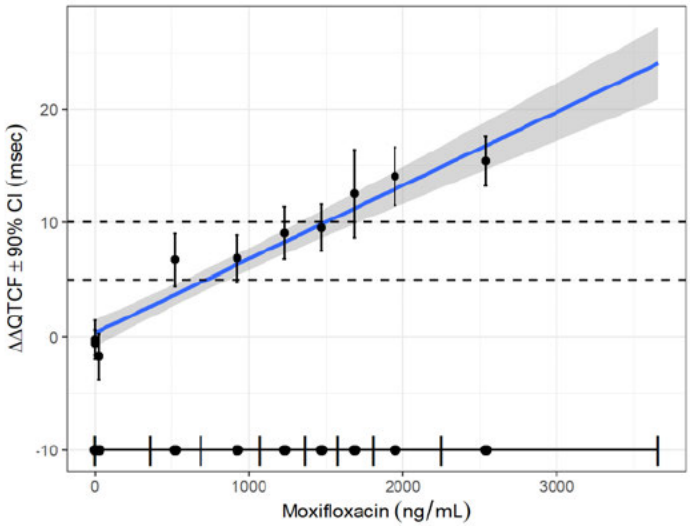


Table 6: Predictions from Concentration-QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	2,103.4	13.9	(12.2 to 15.7)

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

Protocol previously reviewed under IND 131330 (DARRTS 10/16/2018).

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DEVI KOZELI on behalf of MICHAEL Y LI
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Signing on behalf of Mike as he is OOO

LARS JOHANNESEN
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CHRISTINE E GARNETT
03/15/2023 08:15:44 AM

Clinical Inspection Summary

Date	March 2, 2023
From	Cheryl Grandinetti, Pharm.D. Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Christopher Davi, Senior RPM Mayurika Ghosh, M.D., Medical Reviewer Dmitri Iarikov, M.D., Ph.D. Medical Team Leader Peter Kim, MD, Division Director, Division of Anti-Infectives (DAI)
NDA #	216974
Applicant	Entasis Therapeutics, Inc.
Drug	Xacduro (sulbactam-durlobactam)
NME	Yes
Proposed Indication	Treatment of infections due to Acinetobacter baumannii-calcoaceticus complex including multidrug-resistant and carbapenem-resistant strains in adults
Consultation Request Date	October 31, 2022
Summary Goal Date	March 17, 2023
Action Goal Date	May 29, 2023
PDUFA Date	May 29, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Lin, Marchaim, and Vasquez were inspected in support of NDA 216974, covering one clinical trial, CS2514-2017-004, Part A.

During the clinical investigator inspections, the source records documenting (1) the primary efficacy endpoint of 28-day all-cause mortality; (2) key secondary endpoint of clinical cure at the Test of Cure (TOC) visit; and (3) inclusion in the carbapenem-resistant ABC microbiologically modified intent-to-treat (m-MITT) population were reviewed and verified against the sponsor's data line listings for the 23 randomized subjects at the 3 sites inspected. These source records included records documenting survival status; microbiology culture testing results from the local and central laboratory at the Screening/Baseline Visit; investigator and blinded assessor-reported signs and symptoms of infection at Baseline and TOC Visits and concomitant gram-negative antimicrobial medications received up to the TOC visit.

The inspection of Dr. Vasquez (Site 604-001) found a significant data reliability concern

involving data (i.e., investigator and blinded-assessor assessments of signs and symptoms of the presenting infection) collected to support a key secondary efficacy endpoint of clinical cure at the TOC visit. The protocol required that investigators and blinded assessors assign each sign and/or symptom of the presenting indication a classification of absent, mild, moderate, or severe at various time points in the study. During review of the source records supporting these assessments of signs and symptoms of infection, it was observed that the source record made no distinction when "absent" meant that investigators and blinded assessors either:

1. Evaluated signs and symptoms of infection, and that sign or symptom was not present in the subject or
2. Did not evaluate the sign/symptom of infection in the subject (e.g., data missing or assessment not performed per protocol)

Therefore, it was not possible to verify the source data against the applicant's data line listings when the signs and symptoms of infection assessment was categorized as "absent" at this site.

The inability to distinguish when the assessment of "absent" meant that the infection sign/symptom was assessed but not present in the subject or the infection sign/symptom was not assessed is concerning. In an email to the DAI review team, dated Feb 22, 2023, OSI recommended that a sensitivity analysis be conducted regarding this key secondary efficacy endpoint data for the 9 randomized subjects at this site.

Notwithstanding the data reliability concern involving the key secondary endpoint data of clinical cure noted during the inspection of Dr. Vasquez, the data otherwise generated by the 3 clinical investigator sites inspected appear acceptable in support of the respective indication.

II. BACKGROUND

NDA 216974 was submitted to support the use of sulbactam-durlobactam for the treatment in adults with infections due to Acinetobacter baumannii-calcoaceticus complex (ABC), including multidrug-resistant and carbapenem-resistant strains. The pivotal study supporting the application was the following:

- CS2514-2017-0004, "A Randomized, Active-Controlled Study to Evaluate the Efficacy and Safety of Intravenous Sulbactam-ETX2514 in the Treatment of Patients With Infections Caused by Acinetobacter baumannii-calcoaceticus Complex"

Protocol CS2514-2017-0004 was a 2-part study as follows:

- Part A was the pivotal, assessor-blinded, randomized, comparative portion of the study in subjects with documented ABC hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), ventilated pneumonia (VP), or bacteremia.

- Part B was the open-label, supportive portion of the study that included subjects known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms that are known to be resistant to colistin or polymyxin B, those failing a colistin or polymyxin B regimen prior to study entry or are on acute renal replacement therapy, and subjects with infections due to colistin- or polymyxin B-resistant ABC with sources of infection other than HABP, VABP, VP, and/or bacteremia, as detailed in the inclusion criteria.

Inspections were conducted on subjects enrolled in part A of the study.

The primary objectives of this study were to compare the following:

- The efficacy of sulbactam-durlobactam plus imipenem/cilastatin to colistin plus imipenem/cilastatin in subjects with carbapenem-resistant ABC (CRABC) infections in Part A
- The incidence of nephrotoxicity, as measured by the Risk–Injury–Failure–Loss–End-stage renal disease (RIFLE) criteria, of sulbactam-durlobactam to colistin in subjects with ABC infections in Part A

Subjects:

- For part A, a total of 181 subjects were randomized (i.e., 92 to sulbactam-durlobactam and 89 to colistin); Of the subjects who were randomized, 177 subjects were treated (i.e., 91 subjects in the sulbactam-durlobactam group and 86 subjects in the colistin group)
- For Part B, a total of 28 subjects were enrolled in the open-label sulbactam-durlobactam group, which included 2 subjects who were transferred from Part A because the local microbiology laboratory susceptibility results indicated that the screening ABC isolates were colistin-resistant

Sites: There were 85 clinical sites who participated in the trial; 71 clinical sites screened subjects and 59 clinical sites randomized/enrolled subjects

Study initiation and completion dates: September 5, 2019 (study initiation) to Dec 16, 2021 (study completion date)

Database Lock Date: September 21, 2021; with an unlock on December 16, 2021

Study Unblinding: September 21, 2021

Part A consisted of the following:

- Screening/Baseline Visit (-48 hours to Day 1, the first dose of study drug)
- Treatment Period (Day 1 though End of Treatment (EOT), ≥7 days and ≤14 days)
- Test of Cure (TOC, Study days >14 days to ≤ 21 days)
- Late Follow-Up (LFU) and Day 28 Visit or Early Termination Visit (ET) (Study days >21 days to ≤ 28 days)

Subjects were stratified and then randomized in a 1:1 ratio to one of the following treatment groups on Day 1 as follows:

Stratification Factors:

- By indication (i.e., HABP/VABP/VP versus bacteremia)
- By severity of illness based on:
  - Acute physiology and chronic health evaluation (APACHE) II of 10 to 19 versus 20 to 30; or
  - Sequential organ failure assessment (SOFA) of 7 to 9 versus ≥10; or
  - Quick SOFA (qSOFA) of 2 versus 3 score at Screening
- By geography (i.e., China Mainland versus Rest of World)

In the situation where a subject has more than one score reported, the scores will be used in the following order: APACHE, SOFA, and qSOFA.

Randomized Treatment Groups:

- Group 1: sulbactam 1 gram IV plus durlobactam 1 gram IV infused over 3 hours every 6 hours plus imipenem/cilastatin 1 gram IV infused over 60 minutes q6h
- Group 2: colistin 2.5 mg/kg IV infused over 30 minutes every 12 hours (q12h) plus imipenem/cilastatin 1 gram IV infused over 60 minutes q6h

Subjects were enrolled in the study for approximately 28 days, with a maximum duration of 32 days. The Treatment Period began on Day 1, and study drug was administered for 7 days with a prolongation of therapy of up to 14 days if clinically indicated. The Test of Cure (TOC) Visit was completed 7 days (+/-2 days) after the EOT Visit for all subjects. The LFU Visit was completed 14 days (+/-2 days) after the EOT Visit for all subjects. For subjects with an LFU Visit occurring before Day 28, a telephone call to assess survival was made on Day 28 or anytime thereafter. Every attempt was made to record survival status at Day 28 or anytime thereafter for all randomized subjects (including HABP/VABP/VP subjects who were randomized to Part A based on a positive BPP rapid test, but who subsequently did not have growth of ABC in their respiratory sample culture), regardless of their status of treatment, as long as the subject has not withdrawn consent from participation in the study.

No dosing regimen changes, other than those specified in the protocol for renal insufficiency or for subjects on imipenem who developed a seizure that was thought to be directly related to imipenem, could occur without discussion with the Medical Monitor. If changes to the regimen were needed due to unsatisfactory clinical response, subjects should have been classified as clinical failures and discontinued from study drug. All subjects should have received at least 48 hours of IV study drug before the Investigator considered the subject to be a clinical failure and discontinued the subject from study drug therapy.

The ***primary efficacy endpoint*** was 28-day all-cause (ACM) mortality in the carbapenem-resistant (MIC to imipenem/meropenem ≥8 mg/L) ABC microbiologically modified-intent-to-treat (m-MITT) population in Part A.

The m-MITT Population included all subjects randomized to study drug treatment (sulbactam-durlobactam plus imipenem/cilastatin or colistin plus imipenem/cilastatin) who received study drug, and who had an ABC organism isolated as the qualifying culture specimen, as confirmed by the central and/or local microbiology laboratory. Subjects were excluded from the

carbapenem-resistant ABC m-MITT Population if they have isolates that are deemed by the central laboratory to be resistant to sulbactam-durlobactam (MIC >4 mg/L) or colistin (MIC ≥4 mg/L), if their blood culture or respiratory samples are collected more than 72 hours prior to randomization, if they are transferred from Part A to Part B, or if they are enrolled with infections other than ABC pneumonia or bloodstream infection (i.e., ABC infections other than HABP, VABP, VP, and bacteremia).

A ***key secondary efficacy endpoint*** was clinical cure at Test-of-Cure (TOC) in the carbapenem-resistant ABC m-MITT Population. The TOC will occur 7 days after the EOT visit.

- **Clinical cure** was defined as complete resolution or significant improvement of signs and symptoms that were present at baseline and no new symptoms, such that no additional Gram-negative antimicrobial therapy was warranted.

- **Clinical failure** was defined as symptoms present at study entry that did not significantly improve or completely resolve, or new symptoms that developed and required the initiation of a non-study Gram-negative antibacterial drug therapy, death, or intolerance to study drug leading to discontinuation from the study treatment.

- **Clinical indeterminate** was defined as determination cannot be made because of missing data or the subject was lost to follow-up.

Blinded Assessors:

In Part A, assessment data was collected and handled as if it were a blinded study. Each site assigned a blinded assessor, in addition to the unblinded Investigator, to evaluate criteria for clinical outcomes, conduct causality assessment for adverse events, and assess clinical signs and symptoms at study visits where an endpoint is evaluated.

The blinded assessor and the unblinded investigator assessed clinical signs and symptoms of the presenting indication at Screening, Day 5, Day 7, EOT, TOC, LFU and ET. Clinical outcome assessments (i.e., clinical cure, clinical failure, and clinical indeterminant) were performed by a blinded assessor, in addition to the unblinded Investigator at Day 5, Day 7, EOT, TOC, LFU and ET. If there was a discrepancy between the assessment of the blinded assessor and unblinded Investigator, the assessment from the blinded assessor was used. If there was a missing assessment from either the blinded assessor or unblinded Investigator, the other available assessment was to be used.

Microbiology Testing:

Local laboratories performed gram-staining, species identification, and susceptibility testing using procedure approved by Entasis. Two copies of each isolate were frozen, and the primary culture was shipped monthly from the site to the following central microbiology laboratory, depending on the site location:

(b) (4)

[redacted] (b) (4)

[redacted] (b) (4) central laboratory then shipped frozen isolates in batches to [redacted] (b) (4) a second central laboratory, monthly for confirmation testing. On the rare occasion where both the primary and backup cultures were lost or non-viable, results from the local laboratory for bacterial species and susceptibility to carbapenems and colistin were used for enrollment decisions. If an isolate for testing at the central laboratory was not available, the local laboratory data was used to confirm the presence of ABC organism, as long as the local laboratory used modern methods of diagnosis such as molecular-based tests, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, Vitek, Phoenix, etc. (i.e., not conventional biochemical or manual phenotypic methods).

Rationale for Site Selection

The clinical sites were selected based on enrollment, site specific efficacy, and previous inspection history.

III. RESULTS (by site):

1. **Dror Marchaim, MD**
   Site #376-004
   Unit of Infectious Diseases
   Zerifin, N/A 70300, Israel
   PDUFA Inspection Dates: January 15 to 19, 2023

At this site, 6 subjects were screened, 6 were randomized in Part A of the study, and 5 subjects completed the study. Per the applicant's data line listings, Subject [redacted] (b) (6) (randomized to colistin) died on Study Day 24.

A full audit of the study records for the 6 subjects randomized in Part A was conducted. Records reviewed during the inspection included those related to the study protocol and amendments; Ethics Committee submissions, approvals, and correspondence; eligibility criteria; informed consent process and forms; source records documenting the primary and key secondary efficacy endpoints of 28-day all-cause mortality, clinical cure at the TOC visit, and use of concomitant gram-negative antimicrobial medications (other than anti-microbial agents permitted in the protocol) as well as inclusion in the carbapenem-resistant ABC m-MITT population; processes and procedures related to use of blinded assessors and maintenance of the study blind; adverse event reporting; protocol deviations; drug accountability, monitor logs and follow-up letters; and other regulatory documentation.

There was no evidence of under-reporting of adverse events. The source records documenting 28-day all-cause mortality, clinical cure at the TOC visit and inclusion in the carbapenem-resistant ABC m-MITT population were reviewed and verified against the

sponsor's data line listings for the 6 randomized subjects.

These source records included records documenting survival status; microbiology culture and susceptibility testing results from the local laboratory at Screening/Baseline Visit; investigator and blinded assessor-reported signs and symptoms of infection at Screening/Baseline and TOC Visits; and concomitant gram-negative antimicrobial medications received up to the TOC. No discrepancies were noted. Of note, the source records that documented the microbiology culture testing results from the central laboratory for the 6 randomized subjects were not available for review and verification during inspection.

Reviewer's comment: *In a 27 Jan 2022 response to an Information Request (IR), the applicant submitted certified copies of the microbiology culture testing results from the central laboratory. These certified copies of the testing results were reviewed and verified against the sponsor's data listings at Screening/Baseline by this reviewer for the 6 randomized subjects. No issues or discrepancies were noted.*

In addition, qualification of blinded assessors and processes and procedures related to use of blinded assessors and maintaining the blind was reviewed. No issues or cases of inadvertent unblinding of blinded assessors were observed.

2. Yu-Chao Lin, MD
Site #158-001
No 2, Yuh-Der Road Taichung
N/A 404, Taiwan
PDUFA Inspection Dates: January 16 to 19, 2023

At this site, 72 subjects were screened, 8 were randomized in Part A of the study, and 6 subjects completed the study. Subject [redacted] (b) (6) (randomized to sulbactam-durlobactam) withdrew consent on Study Day 13 and subsequently died after withdrawal from the study on Study Day 25 and Subject [redacted] (b) (6) (randomized to sulbactam-durlobactam) withdrew consent on Study Day 14 and subsequently died after withdrawal from the study on Study Day 17.

A full audit of the study records for the 8 subjects randomized in Part A was conducted. Records reviewed during the inspection included those related to the study protocol and amendments; Ethics Committee submissions, approvals, and correspondence; eligibility criteria; informed consent process and forms; source records documenting the primary and key secondary efficacy endpoints of 28-day all-cause mortality, clinical cure at the TOC visit, and use of concomitant gram-negative antimicrobial medications (other than anti-microbial agents permitted in the protocol) as well as inclusion in the carbapenem-resistant ABC m-MITT population; processes and procedures related to use of blinded assessors and maintenance of the study blind; adverse event reporting; protocol deviations; drug accountability, monitor logs and follow-up letters; and other regulatory documentation.

There was no evidence of under-reporting of adverse events. The source records

documenting 28-day all-cause mortality, clinical cure at the TOC visit, and inclusion in the carbapenem-resistant ABC m-MITT population were reviewed and verified against the sponsor's data line listings for the 8 randomized subjects.

These source records included records documenting survival status; microbiology culture testing results from the local and central laboratory at Screening/Baseline Visit; and investigator and blinded assessor-reported signs and symptoms of infection at Screening/Baseline and TOC Visits. No discrepancies were noted.

In addition, qualification of blinded assessors and processes and procedures related to use of blinded assessors and maintaining the blind was reviewed. No issues or cases of inadvertent unblinding of blinded assessors were observed.

3. Luis E. Hercilla Vasquez, MD
Site #604-001
Jr. Colina 1081, Bellavista, Callao, Peru
Callao, Callao 7016, Peru
PDUFA Inspection Dates: January 30 to February 3, 2023

At this site, 28 subjects were screened, 9 were randomized in Part A of the study, and 6 subjects completed the study. Per the applicant's data line listings, Subjects [redacted] (b) (6) (randomized to sulbactam-durlobactam), [redacted] (b) (6) (randomized to sulbactam-durlobactam), and [redacted] (b) (6) (randomized to colistin) died on Study Days 27, 23, and 9, respectively.

A full audit of the study records for the 9 subjects randomized in Part A was conducted. Records reviewed during the inspection included those related to the study protocol and amendments; Ethics Committee submissions, approvals, and correspondence; eligibility criteria; informed consent process and forms; source records documenting the primary and key secondary efficacy endpoints of 28-day all-cause mortality and clinical cure at the TOC visit as well as inclusion in the carbapenem-resistant ABC m-MITT population; processes and procedures related to use of blinded assessors and maintenance of the study blind; protocol deviations; monitor logs and follow-up letters; and other regulatory documentation. Of note, due to inspection time constraints, a comprehensive review of drug accountability, adverse event reporting, and use of concomitant gram-negative antimicrobial medications (other than anti-microbial agents permitted in the protocol) administered to the 9 randomized subjects during the conduct of the trial was not performed.

The source records documenting 28-day all-cause mortality, clinical cure at the TOC visit and inclusion in the carbapenem-resistant ABC m-MITT population were reviewed and verified against the sponsor's data line listings for the 9 randomized subjects.

These source records included records documenting survival status; microbiology culture testing results from the local and central laboratory at the Screening/Baseline visit in the ITT population; and investigator and blinded assessor-reported signs and symptoms of

infection at baseline and TOC visit. The following issues and discrepancies were noted:

1. The protocol required that the assessors assign each sign and symptom of the presenting indication a classification of absent, mild, moderate, or severe at various time points in the study. Discrepancies were observed in Subject [redacted] (b) (6) such that the investigator signs and symptoms for cough, respiratory rate, and dyspnea were assessed as "absent" in the source record but were not among the signs and symptoms listed as assessed in the data line listings at the TOC Visit. The site staff explained that the investigator and blinded assessors at this site used the categorization of "absent" to mean either of the following:

   - That the sign/symptom was assessed but not present in the subject
   - That the sign/symptom was not assessed (e.g., the data are missing or assessment not performed per protocol)

   In further review of these source records and other source records at the site (e.g., medical record), this distinction (i.e., that the sign/symptom was assessed and determined not to be present in the subject or sign/symptom was not assessed in the subject) was not documented in the source records. Thus, it was not possible to verify the signs and symptoms of infection data against the applicant's data line listings the sign/symptom was assessed by the investigators and blinded-assessors as absent.

Reviewer's comment: *The inability to distinguish when the assessment of "absent" meant that the infection sign/symptom was assessed but not present in the subject or the infection sign/symptom was not assessed (e.g., resulting in missing data) is concerning. OSI recommends that a sensitivity analysis be conducted regarding this key secondary efficacy endpoint data for the 9 randomized subjects at this site.*

2. In addition to the larger issue of the two meanings of the assessment of "absent" on the source records for the investigator and blinded assessor assessment of signs and symptoms of infection, there were minor discrepancies observed in 4 subjects at the Screening/Baseline and TOC Visits. These minor discrepancies were assessed by this reviewer to have no impact on both the subject's outcome (e.g., clinical cure, clinical failure) and the primary and key secondary efficacy endpoints.

Also, as noted previously, due to time-constraints during inspection, the source records that documented concomitant gram-negative antimicrobial medications received up to the TOC Visit for the 9 randomized subjects were not reviewed and verified against the applicant's data line listings.

In addition, qualification of blinded assessors and processes and procedures related to use of blinded assessors and maintaining the blind was reviewed. No issues or cases of inadvertent unblinding of blinded assessors were observed.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist
Good Clinical Practice Assessment Branch
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cc:
Central Doc. Rm. NDA 216974
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DAI/Medical Reviewer/Mayurika Ghosh
DAI/Medical Team Leader/Dmitri Iarikov
OSI/Office Director/David Burrow
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Branch Chief/Jenn Sellers
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/ GCP Program Analysts/Yolanda Patague

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/s/

CHERYL A GRANDINETTI
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JENN W SELLERS
03/02/2023 02:41:39 PM

MEMORANDUM

USE-RELATED RISK ANALYSIS REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 09, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216974
Product Name, Dosage Form, and Strength:	Sulbactam-durlobactam injection, 1 g / 1 g per vial
Device Constituent:	Sterile Powder for Injection
Product Type:	Drug Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Entasis Therapeutics (Entasis)
FDA Received Date:	September 29, 2022, October 14, 2022
OSE RCM #:	2022-2135
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director of Human Factors:	Jason Flint, MBA, PMP

1 REASON FOR REVIEW

On September 29, 2022, the Applicant submitted New Drug Application (NDA) 216974 that included a use-related risk analysis (URRA) and justification for not submitting further human factors (HF) data to support their marketing application for Sulbactam-durlobactam 1 g / 1 g per vial, injection.

2 BACKGROUND AND CONCLUSION

On August 27, 2021, under IND 131330, the Applicant submitted URRA and justification for not submitting HF validation study results to support their marketing application.

On December 07, 2022, we reviewed the aforementioned URRA and justification and determined that the Applicant did not need to submit human factors validation study data with their marketing application for Sulbactam-durlobactam 1 g / 1 g per vial, injection, to be used by healthcare professionals, to treat infections due to Acinetobacter baumannii-calcoaceticus complex (ABC), including multidrug and carbapenem-resistant strains. We also stated that if the Applicant modified the product user interface additional human factors considerations may apply.[a]

On September 29, 2022, the Applicant submitted a marketing application under NDA 216974 for Sulbactam-durlobactam 1 g / 1 g per vial, injection. The submission included use-related risk analysis (URRA) and justification for not submitting further human factors (HF) data to support their marketing application. However, the Applicant did not indicate whether the commercial product user interface had been modified since their August 27, 2021, submission. As such, we issued an information request (IR) on October 13,2022 asking the Applicant to clarifying the following:

- *if the product user interface of your proposed sulbactam-durlobactam injection in your August 27, 2021, submission is identical to the product user interface of the sulbactam-durlobactam injection proposed in your September 29, 2022, submission*
- *if the URRA submitted on August 27, 2021, is the same as the URRA submitted in your September 29, 2022, submission*

Subsequently, on October 14, 2022, the Applicant provided the following response to the IR:

> *Entasis confirms that the product user interface of the sulbactam-durlobactam injection in the August 27, 2021, submission [Type C/Written Response Only (WRO) (IND 131330, SN-0109)] is identical to the product user interface of sulbactam-durlobactam injection proposed in the September 29, 2022, submission [NDA 216974].*

[a] Oguntimein M. Use-Related Risk Analysis Review for Sulbactam-durlobactam 1 g / 1 g per vial injection (IND 131330). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);07 DEC 2021. RCM No.: 2021-1771.

Entasis confirms that the URRA submitted on August 27, 2021 [Type C/Written Response Only (WRO) (IND 131330, SN-0109)] is the same as the URRA submitted in the September 29, 2022, submission [NDA 216974].

Based on the aforementioned information, we maintain that the Applicant does not need to submit human factors validation study results with their new drug application under NDA 216974 for Sulbactam-durlobactam 1 g / 1 g per vial, injection. We have no Human Factors recommendations for this marketing application.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. Comparative Threshold Analysis

Use Related Risk Analysis are accessible in EDR via:
\\CDSESUB1\EVSPROD\nda216974\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acinetobacterbaumanniiinfection\5354-other-stud-rep\urra\use-related-risk-analysis.pdf

APPENDIX B. INFORMATION REQUEST ISSUED DURING THIS REVIEW

On October 13, 2022, we issued an information request asking the Applicant to clarifying the following:

- if the product user interface of your proposed sulbactam-durlobactam injection in your August 27, 2021, submission is identical to the product user interface of the sulbactam-durlobactam injection proposed in your September 29, 2022, submission
- if the URRA submitted on August 27, 2021, is the same as the URRA submitted in your September 29, 2022, submission

The Applicant provided an acceptable response on October 14, 2022, that can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda216974\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acinetobacterbaumanniiinfection\5354-other-stud-rep\urra\urra-report-response-to-fda-hf-information-request.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

OLUWAMUREWA OGUNTIMEIN
11/09/2022 11:09:17 AM

JASON A FLINT
11/09/2022 02:38:00 PM