CLINICAL REVIEW

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Application Number(s)	21572
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Division / Office	DAIP/OAP
Reviewer Name(s)	Amol Purandare, MD
Review Completion Date	March 23, 2017
Established Name	Daptomycin
(Proposed) Trade Name	Cubicin
Therapeutic Class	Cyclic Lipopeptide
Applicant	Cubist Pharmaceuticals
Formulation(s)	Injection
Dosing Regimen	5 mg/kg (12-<18 years), 7 mg/kg (7-11 years), 9 mg/kg (2-6 years), and 10 mg/kg (1-< 2 years)
Indication(s)	Complicated Skin and Skin Structure Infections

Intended Population(s) Ages 1 year to <18 years

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant has submitted a response to a pediatric postmarketing requirement issued in 2005, and reissued February, 2015, to provide information on the use of daptomycin in pediatric patients with complicated skin and skin structure infections (cSSSI). Daptomycin is currently approved in adults for treatment of cSSSI at a dose of 4mg/kg every 24 hours. The overall efficacy and safety profile for daptomycin in pediatric patients with cSSSI was similar to the profile described in the current daptomycin product labeling for adults. The reviewer recommends approval of daptomycin for treatment of cSSSI in pediatric patients 1 year and older. This study fulfills the postmarketing requirement of PREA study 2864-1.

1.2 Risk Benefit Assessment

The current antibiotic armamentarium for treatment of Gram positive, in particular methicillin-resistant *Staphylococcus aureus* (MRSA), infections in the pediatric population is limited. The results of the postmarketing study DAP-PEDS-07-03 in pediatric patients 1 year of age and older demonstrated similar benefit in efficacy of IV daptomycin to current standard of care comparators for the treatment of complicated skin and skin structure infections.

Daptomycin was dosed by weight and age to provide similar exposure as the 4 mg/kg dose in adults, with 5 mg/kg in 12-17 year olds, 7 mg/kg in 7-11 year olds, 9 mg/kg in 2-6 year olds, and 10 mg/kg in 1-<2year olds. The study was not powered to demonstrate efficacy, though the efficacy data are consistent with the observations in adults. The safety profile in pediatric patients is similar to what has been seen in the adult clinical trials and in postmarketing reports. The most frequently reported adverse reactions in pediatric patients receiving daptomycin were gastrointestinal conditions as diarrhea and vomiting. Pyrexia and pruritus were also common adverse reactions. Daptomycin-associated changes in laboratory parameters from adult trials and postmarket data have focused on CPK and hepatic function. Likewise, shifts from baseline to high occurred in slightly more patients in the daptomycin arm at end of therapy (EOT) for AST, CPK, and total bilirubin. Evaluation of mean changes of laboratory parameters indicated comparable values per parameter for daptomycin and comparator arms. Changes in CPK levels deemed clinically significant (>500 U/L and 3 × Baseline level) were observed in approximately 2% of patients in each arm.

With clinical response rates and safety of daptomycin in pediatric cSSSI comparable to adults, and similarity of daptomycin to current comparators approved for cSSSI in pediatric patients, the risk-benefit assessment for use of daptomycin in pediatric patients with cSSSI can be considered favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommended postmarket risk management strategies other than monitoring and reporting of adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended additional postmarketing requirements or commitments. This study fulfills the postmarketing requirement of PREA study 2864-1.

2 Introduction and Regulatory Background

2.1 Product Information

Daptomycin is a cyclic lipopeptide class antibiotic available for intravenous use as single-use vials containing 500 mg daptomycin as a sterile, lyophilized powder.

Daptomycin is currently indicated for the treatment of adults at least 18 years of age with complicated skin and skin structure infections (cSSSI) caused by susceptible strains of Gram-positive organisms. Daptomycin is also indicated in adults at least 18 years of age for treatment of *Staphylococcus aureus* bacteremia and right-sided infective endocarditis.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: FDA Treatment for cSSSI caused by Gram positive pathogens

Drug	Route	Pediatric approval
amoxicillin and clavulanate potassium	Oral	Yes
cefazolin sodium	Intravenous	Yes
ceftaroline fosamil	Intravenous	Yes
ceftriaxone	Intramuscular or Intravenous	Yes >28 days
cephalexin	Oral	Yes
clindamycin	Oral or Intravenous	Yes- >0
dalbavancin hydrochloride	Intravenous	no
daptomycin	Intravenous	No
demeclocycline	Oral	If no alternative ≥8 years
linezolid	Oral or Intravenous	Yes
minocycline	Oral	If no alternative ≥8 years
oritavancin diphosphate	Intravenous	no
piperacillin/tazobactam	Intravenous	Yes >8 months
tigecycline	Intravenous	If no alternative ≥8 years
tedizolid	Oral or intravenous	no
telavancin	Intravenous	No
tetracycline	Oral	Yes

Drug	Route	Pediatric approval
		≥8 years
vancomycin	Intravenous	yes

Other medications approved for treatment of Gram positive SSI prior to separation of skin infections into complicated and uncomplicated categories will include ampicillin/sulbactam cefotaxime, ceftazidime, nafcillin, dicloxacillin, and oxacillin. All of which are with pediatric indication.

2.3 Availability of Proposed Active Ingredient in the United States

Daptomycin is currently available in the US marketed as a brand name Cubicin for intravenous use.

2.4 Important Safety Issues With Consideration to Related Drugs

Daptomycin is associated with number of serious adverse reactions described in the boxed warning and warnings and precautions section of the approved product labeling:

- Anaphylaxis/Hypersensitivity
- Myopathy and Rhabdomyolysis
- Eosinophilic pneumonia
- Peripheral neuropathy
- Increased International Normalized Ratio (INR)/prolonged prothrombin time

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Cubicin (daptomycin for injection) was approved for adult use on September 12, 2003. On December 3, 2003 PREA was enacted. The FDA issued a post-marketing study commitment for Cubicin on August 18, 2005, which was subsequently re-issued, on February 11, 2015, as PMR 2864-1. In addition, in response to the Sponsor's Proposed Pediatric Study Request (PPSR) from July 22, 2011 (amended February 26, 2013) to NDA 21572, the Food and Drug Administration (FDA) issued a formal Written Request (PWR) on May 24, 2013. The PWR was amended on August 27, 2013, and December 19, 2014. The final study report for PMR 2864-1 was submitted June 30, 2016.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well organized. There were no meaningful concerns noted by this reviewer regarding the quality and integrity of the datasets. This reviewer reviewed the datasets and the applicant's analyses were verified. There was no evidence that the studies reviewed were not conducted in accordance with acceptable clinical ethical standards.

3.2 Compliance with Good Clinical Practices

The studies submitted were stated to be compliant with Good Clinical Practices.

3.3 Financial Disclosures

The applicant submitted financial disclosure form 3454 and debarment certification for all investigators involved in the studies conducted. The form states that the applicant had not entered into any financial arrangement with the listed clinical investigators in which compensation to the investigator could be affected by the outcome of the study. See Appendix.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC information was submitted in this supplement.

4.2 Clinical Microbiology

The clinical microbiology review by Dr. Avery Goodwin discussed daptomycin for CSSSI in regards to indicated Gram positive organisms. As analysis of data indicates, daptomycin continues to demonstrate in vitro activity against indicated organisms. Based on FDA break points, all gram positive isolates obtained from surveillance and clinical studies were deemed susceptible to daptomycin. There were similar causative organisms in the clinical studies as compared to isolates from adult data; though there is a greater predominance of MRSA in pediatric population compared to MSSA in adult population. Bacteriological eradication rates and clinical success rates in the microbiological ITT population were similar as pathogen eradication was presumed in cases with clinical success. Per microbiology team review, the Phase 4 clinical microbiology data suggests daptomycin is non-inferior to the SOC (IV vancomycin, IV clindamycin or IV semi-synthetic penicillins [nafcillin, oxacillin, or cloxacillin]). The clinical microbiology team concluded that the sNDA was approvable.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology-toxicology information was submitted for review.

4.4 Clinical Pharmacology

The clinical pharmacology/pharmacology team consisting of Drs. Sonia Pahwa and Seong Jang reviewed pharmacokinetic data and the applicant's population pharmacokinetic analyses from pediatric studies. Details are can be obtained from their full review.

4.4.1 Mechanism of Action

Daptomycin is a cyclic lipopeptide bactericidal against Gram-positive bacteria with activity against growing and stationary-phase bacteria. Daptomycin binds to bacterial cell membranes and causes a rapid depolarization of membrane potential. This loss of membrane potential causes inhibition of DNA, RNA, and protein synthesis, which results in bacterial cell death.

4.4.2 Pharmacodynamics

Dose-selection for the pediatric efficacy and safety study (Study DAP-PEDS-07-03) was not based on efficacy or on efficacy-related pharmacodynamic (PD) markers, but based on the exposures achieved in the prior Phase 1 studies.

4.4.3 Pharmacokinetics

Dosing strategy evaluated in pediatric patients in the Phase 4 CSSSI study were selected based on matching projected exposures (AUC) in pediatric patients with the observed exposures in adults dosed at 4mg/kg once daily whereby efficacy and safety were established previously. In addition the three dedicated Phase 1 pediatric studies demonstrated daptomycin exposure was generally lower in pediatric patients compared with adults at the same dose. Regimen for dosing was then set as 5 mg/kg once daily in 12 to 17 years of aged children, 7 mg/kg once daily in 7 to 11 years of aged children, 9 mg/kg once daily in 2 to 6 years of aged children, and 10 mg/kg once daily in 1 to less than 2 years of aged children. At the evaluated dosing regimens, the exposures in pediatric patients with cSSSI are comparable to the exposures in adult patients with cSSSI, with similar efficacy and safety profiles in pediatric and adult patients. Clinical Pharmacology review team concluded that the pharmacokinetic information of daptomycin was shown to be efficacious in the treatment of cSSSI caused by Gram-positive pathogens and the safety of daptomycin at administered doses was acceptable.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 : Studies

Study Type	Study Identifier	Study Objective(s)	Study Design and Control	Test Product(s); Dose Administration	Number of Subjects	Patient Characteristics	Region

Study Type	Study Identifier	Study Objective(s)	Study Design and Control	Test Product(s); Dose Administration	Number of Subjects	Patient Characteristics	Region
PK	DAP-PEDS-05-01	Evaluation of pharmacokinetics of a single dose of daptomycin in patients aged 2 to 17 years for proven or suspected Gram-positive infection	Multi-center, open label, non-comparative,, single dose pharmacokinetics (Phase 1)	Daptomycin (MK-3009) 4mg/kg, single dose given intravenously over 30 minutes	25	Males/females Ages 2 to 17 years	USA, 3 sites initiated and enrolled
PK, Safety	DAP-PEDS-07-02	Evaluation of pharmacokinetics of a single dose of daptomycin in patients aged 2 to 6 years for proven or suspected Gram-positive infection	Multi-center, open label, non-comparative,, single dose pharmacokinetics (Phase 1)	Daptomycin (MK-3009), 8mg/kg single dose given intravenously over 1 or 2 hours 10mg/kg, single dose given intravenously over 1 or 2 hours	12	Males/females Ages 2 to 6 years	USA, 6 sites initiated, 4 sites enrolled
PK, Safety	DAP-PEDS-09-01	Evaluation of pharmacokinetics and safety of a single dose of daptomycin in patients aged 3 months to 24 months concurrently receiving standard antibiotic therapy for proven or suspected bacterial infection	Multi-center, open label, non-comparative, single dose pharmacokinetics (Phase 1)	Daptomycin (MK-3009) 4mg/kg, single dose given intravenously over 30 minutes 6mg/kg, single dose given intravenously over 30 minutes	24	Males/females Ages 3 months to 24 months	USA, 8 sites initiated, 7 sites enrolled

Study Type	Study Identifier	Study Objective(s)	Study Design and Control	Test Product(s); Dose Administration	Number of Subjects	Patient Characteristics	Region
PK, Safety, Efficacy	DAP-PEDS-07-03	Evaluation of safety, efficacy, and pharmacokinetics of daptomycin in pediatric subjects aged 1-17 years with complicated skin and skin structure in	Multicenter, evaluator blinded, randomized study of pharmacokinetics, safety, efficacy (Phase 3)	Daptomycin (MK-3009) 5, 7, 9, or 10 mg/kg intravenously Q24 hours over 30 minutes to 1 hour respectively in in ages 12-17 years, 7-11 years, 2-6 years, 1-<2 years Up to 14 days	389	Males/females ages 1 year to 17 years	USA, India 37 sites initiated, with 30 enrolled

5.2 Review Strategy

The focus of efficacy and safety reviews was on study DAP-07-03, a multi-center, randomized, evaluator-blinded, comparative study in pediatric patients ages 1 to 17 years, with cSSSI caused by Gram-positive pathogens, evaluating safety, efficacy, and PK of daptomycin compared with current standard therapies for Gram positive infections.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

There are a growing number of infections in the pediatric population with resistant Gram positive organisms. Of primary concern are methicillin-resistant *Staphylococcus aureus* (MRSA) infections. There are limited therapeutic options, particularly in pediatric patients, which have been evaluated for safety and efficacy for treating MRSA and other serious Gram positive infections.

6.1.1 Methods

A multi-center, randomized, evaluator-blinded, comparative study in pediatric patients ages 1 to 17 years, with cSSSI caused by Gram-positive pathogens, evaluating safety, efficacy, and PK of daptomycin to current standard therapies for Gram positive infections. Comparators used included vancomycin, clindamycin, or penicillinase resistant semi-synthetic penicillins (nafcillin, oxacillin, cloxacillin.) Study population was assigned to treatment groups by means of computer-generated randomization stratified by age group, providing a 2:1 ratio of subjects in daptomycin vs comparator groups. Study investigators were not blinded to treatments, design therefore included evaluators who did not enroll subjects, and were blinded for study entirety to reduce bias and assess safety and efficacy endpoints. Patients were switched to oral therapy fitting standard of care at the discretion of investigator. A single dose of IV therapy was the minimum required for study inclusion.

There was a minimum of 3 days of therapy needed of IV and oral medication combined to be included in the clinically evaluable population as compared to the intent to treat population.

6.1.2 Demographics

6.1.2 Demographics

396 children were enrolled from 30 study centers between the United States and India, randomized and stratified by age group, to receive either daptomycin or a standard of care comparator. Of the 396 children, randomization occurred in a ratio of 2:1, with 263 children receiving daptomycin and 133 receiving a comparator. Enrollment into each decreasing age group followed a step-wise approach. Of those randomized, 273 subjects were from sites in the United States, and 123 were from sites in India. The patients enrolled in India were limited due to local regulations to ages 7 and older.
Table 5 below depicts demographic characteristics of patients treated with study drugs

Table 3: Demographic Characteristics of Safety Analysis Set

Parameter	Age Group 1		Age Group 2		Age Group 3		Age Group 4		Total	
	DAP 5 mg/kg (N=73)	SOC (N=37)	DAP 7 mg/kg (N=73)	SOC (N=38)	DAP 9 mg/kg (N=81)	SOC (N=42)	DAP 10 mg/kg (N=30)	SOC (N=15)	DAP (N=257)	SOC (N=132)
Age (yrs) [a]										
N	73	37	73	38	81	42	30	15	257	132
Mean (SD)	15.02 (1.584)	14.84 (1.735)	9.05 (1.443)	8.98 (1.305)	3.92 (1.556)	3.86 (1.555)	1.46 (0.231)	1.43 (0.299)	8.25 (5.162)	8.14 (5.098)
Median (Range)	15.2 (12.1-17.9)	14.8 (12.1-17.7)	9.2 (7.1-11.8)	9 (7.1-11.8)	3.3 (2.1-6.9)	3.45 (2.0-7.0)	1.45 (1.1-1.9)	1.3 (1.1-1.9)	7.6 (1.1-17.9)	7.65 (1.1-17.7)
Sex n (%)										
Male	44 (60.3)	22 (59.5)	45 (61.6)	23 (60.5)	33 (40.7)	22 (52.4)	9 (30.0)	3 (20.0)	131 (51.0)	70 (53.0)
Female	29 (39.7)	15 (40.5)	28 (38.4)	15 (39.5)	48 (59.3)	20 (47.6)	21 (70.0)	12 (80.0)	126 (49.0)	62 (47.0)
Race n (%)										
Asian	33 (45.2)	16 (43.2)	49 (67.1)	25 (65.8)	1 (1.2)	0	0	1 (6.7)	83 (32.3)	42 (31.8)
Black or African American	12 (16.4)	6 (16.2)	8 (11.0)	5 (13.2)	33 (40.7)	10 (23.8)	12 (40.0)	4 (26.7)	65 (25.3)	25 (18.9)
White	28 (38.4)	14 (37.8)	15 (20.5)	7 (18.4)	43 (53.1)	31 (73.8)	18 (60.0)	9 (60.0)	104 (40.5)	61 (46.2)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (2.6)	0	1 (2.4)	0	0	0	2 (1.5)
Other	0	1 (2.7)	1 (1.4)	0	4 (4.9)	0	0	1 (6.7)	5 (1.9)	2 (1.5)
Height (in percentile)										
N	71	37	73	37	80	42	30	15	254	131
Mean (SD)	33.345 (31.6927)	39.704 (35.8688)	30.235 (33.8936)	28.939 (35.7407)	64.045 (32.6191)	52.314 (29.5215)	65.556 (33.9225)	58.747 (32.5784)	45.925 (36.5230)	42.887 (34.8594)
Median (Range)	23.8 (0.01-99.40)	38.2 (0.01-99.99)	16.3 (0.01-96.40)	8.6 (0.01-96.80)	77.6 (0.01-99.80)	51.05 (0.10-99.80)	81.4 (0.60-99.99)	68.1 (1.40-97.70)	45.5 (0.01-99.99)	40.3 (0.01-99.99)
Weight (in percentile)										
N	73	37	73	38	81	42	30	15	257	132
Mean (SD)	45.194 (35.2030)	49.152 (38.9630)	31.465 (37.9523)	27.863 (33.4671)	64.89 (29.9537)	59.471 (30.4983)	50.46 (28.1091)	54.42 (28.0544)	48.117 (35.9820)	46.906 (35.6716)
Median (Range)	47.5 (0.01-99.99)	48.9 (0.01-99.70)	9.7 (0.01-99.60)	11.6 (0.01-99.10)	67.3 (1.50-99.80)	56.45 (0.30-99.70)	52.3 (3.50-97.70)	62.2 (9.10-99.90)	51.7 (0.01-99.99)	50 (0.01-99.90)
BMI										
N	71	37	73	37	80	42	30	15	254	131
Mean (SD)	21.7 (6.031)	22.29 (5.583)	16.65 (4.934)	16.01 (4.201)	16.85 (2.597)	17.03 (2.753)	16.49 (1.637)	17.5 (2.571)	18.11 (4.944)	18.28 (4.82)
Median (Range)	20.5 (13.3-53.3)	21.5 (13.7-36.3)	15.3 (8.7-30.0)	15 (10.3-28.4)	16.5 (12.5-29.7)	16.6 (13.0-27.5)	16.5 (13.8-20.8)	16.9 (14.2-24.5)	17 (8.7-53.3)	16.9 (10.3-36.3)
Any Gram Negative Pathogen	5 (6.8)	3 (8.1)	4 (5.5)	0	1 (1.2)	0	0	0	10 (3.9)	3 (2.3)
Gram Positive Baseline Infecting Pathogen[b,c]	66 (90.4)	31 (83.8)	58 (79.5)	31 (81.6)	59 (72.8)	32 (76.2)	27 (90.0)	11 (73.3)	210 (81.7)	105 (79.5)
MRSA	22 (30.1)	10 (27.0)	13 (17.8)	6 (15.8)	41 (50.6)	20 (47.6)	18 (60.0)	8 (53.3)	94 (36.6)	44 (33.3)
MSSA	34 (46.6)	16 (43.2)	28 (38.4)	16 (42.1)	8 (9.9)	8 (19.0)	8 (26.7)	1 (6.7)	78 (30.4)	41 (31.1)
S. pyogenes	4 (5.5)	1 (2.7)	13 (17.8)	5 (13.2)	2 (2.5)	1 (2.4)	0	0	19 (7.4)	7 (5.3)

Excerpted from pgs. 64-65 of 21572 study report

MO comment: *The study groups were well balanced according to demographic characteristics. It is notable that overall there were fewer children in the youngest age group (45/396). Also notable is that the study population was primarily Caucasian and Asian given study locations, with 94/396 being Black or other race. Incidence of causative bacterial pathogenic agent was similar in daptomycin and comparator arms. Of note younger subjects (Groups 3 and 4) had greater incidence with MRSA infection.*

The presence and severity of clinical signs and symptoms at pre-treatment were typical for patients with cSSSI. No differences were apparent between the treatment arms.

Table 4: Baseline Disease Characteristics of Pediatric Patients

Type of cSSSI	***Daptomycin N = 257 (%)***	***Comparator N = 132 (%)***
Major Abscess	136 (52.9)	72 (54.5)
Wound Infection	21 (8.2)	9 (6.8)
Complicated Cellulitis	95 (37.0)	49 (37.1)
Diabetic Ulcer Infection	0 (0)	0 (0)
Infected Ulcer Non-Diabetic	3 (1.2)	0 (0)
Other	2 (0.8)	2(1.5)

Adapted from study report table 11-3

Table 5: Baseline Disease Characteristics in Adults

Primary Diagnosis	Daptomycin N = 256	Comparator N = 261	p-value
Wound Infection	97 (37.9%)	114 (43.7%)	0.421
Major Abscess	55 (21.5%)	43 (16.5%)	
Infected Diabetic Ulcer	33 (12.9%)	38 (14.6%)	
Infected Ulcer (non-diabetic)	32 (12.5%)	34 (13.0%)	
Other Infection	39 (15.2%)	32 (12.3%)	

* Excerpted from Cubicin MO review by Sumathi Nambiar, MD and Susan Thompson, MD

MO comment: *The overall incidence of wound infection and diabetic ulcers in adult patients in cSSSI trials was higher than that of pediatric patient. Incidence of types of cSSSI was relatively equal in adult population, whereas majority of pediatric disease was due to major abscess or complicated cellulitis. Diabetic and other ulcers are rare in the general pediatric population.*

6.1.3 Subject Disposition

Subject disposition is displayed in the Table 11 below.

Table 6: Study Patient Disposition of ITT population

Patient Status	**Daptomycin N=257(%)**	**SOC Comparator N=132 (%)**
Completed study	**236 (91.8)**	**114 (86.4)**
Discontinued study	**21 (8.2)**	**18 (13.6)**
Adverse event	1 (0.4)	1 (0.8)
Microbiological failure	0 (0)	2(1.5)
Investigator decision	0 (0)	3(2.3)
Subject decision	0 (0)	2(1.5)
Lost to follow up	17 (6.6)	9(6.8)
Other	3 (1.2)	1(0.8)
Completed IV Study Medication	247 (96.1)	121 (91.7)
Early discontinuation of IV therapy	10 (3.9)	11 (8.3)

Adverse event	2 (0.8)	4 (3.0)
Microbiological failure	0 (0)	1 (0.8)
Clinical response unsatisfactory	2(0.8)	0 (0)
Major protocol violation	2 (0.8)	0(0)
Investigator's decision	0 (0)	2 (1.5)
Subject's decision	0 (0)	1 (0.8)
Other	4 (1.6)	3 (2.3)
Converted to oral study medication	**248 (96.5)**	**124 (93.9)**
Completed oral therapy	**225 (87.5)**	**116 (87.9)**
Did not complete oral therapy	**23 (8.9)**	**8(6.1)**
Adverse event	4 (1.6)	2 (1.5)
Investigator's decision	0 (0)	1 (0.8)
Subject decision	1 (0.4)	1 (0.8)
Lost to follow up	8 (3.1)	2 (1.5)
Other	10 (3.9)	2 (1.5)

Adapted from the study report p.56-58, and using ADSL.xpt dataset

MO comment: *More patients on the daptomycin arm completed the study treatment and the study relative to subjects on comparator arm. Majority of patients in both arms were converted to and completed oral therapy. The primary reason for discontinuation at each stage was loss to follow up; adverse effects were a factor similarly in both arms with oral therapy.*

The ITT population was one which patients received any study drug, while the mITT population included patients who grew Gram positive organism at baseline. CE population is subset of ITT population which met criteria to indicate confirmed cSSSI, received correct treatment, received at least 3 days of study drug or marked a failure, had necessary TOC evaluations, and did not have confounders such as non-study medication or surgical removal of infection.

Table 7: Analysis Populations

	Daptomycin N = 263 (%)	***SOC Comparator N = 133 (%)***
ITT population	257 (97.7)	132 (99.2)
CE population	207 (78.7)	99 (74.4)

MO comment: *There is a similar proportion of patients in the daptomycin arm and the SOC comparator arm with microbiological confirmation of cSSSI.*

6.1.4 Analysis of Primary Endpoint(s)

Assessment of daptomycin safety was the primary objective of this study. Please refer to the safety section 7.1 of this review.

6.1.5 Analysis of Secondary Endpoints(s)

Although the primary objective of the study was to assess the safety of daptomycin in pediatric patients, secondary endpoints evaluated efficacy: clinical outcome with study treatment at TOC as defined by blinded medical director. The test of cure visit 7-14 days after the last dose of study medication was the time point chosen for assessment of efficacy in patients with cSSSI. Patients were classified as Successes of Failures by combining clinical and microbiological efficacy responses. Table 13 below presents clinical responses to treatment at the TOC visit. Per blinded evaluator assessment, there was a difference in clinical success rate of

4.0% (ITT) and 4.2% (mITT) at TOC visit in patients receiving daptomycin as compared to those treated with standard of care therapy. This differs from the sponsor defined clinical percentages in ITT and mITT populations, with differences of 2.0% and 0.9% respectively in patients treated with daptomycin vs. standard of care therapy.

Table 8: Clinical Efficacy at TOC

	Daptomycin n (%)	***SOC Comparator n (%)***	***Difference* (95% CI)***
ITT Population	**N=256**	**N=132**	
Cure/Improvement	227 (88.7)	114 (86.4)	**2.0 (-5.1,9.1)**
Failure	3 (1.2)	1 (0.8)	
Non-Evaluable	26 (10.2)	17 (12.9)	
mITT Population	**N=210**	**N = 106**	
Cure/Improvement	186 (88.6)	92 (86.8)	**0.9 (-6.7,8.6)**
Failure	2 (1.0)	1 (1.0)	
Non-Evaluable	22 (10.5)	13 (12.2)	

*Difference in clinical cure rates (daptomycin-comparator) and 95% confidence intervals, presented as percentages.
Source: Created using dataset ADSL.xpt

MO comment: *Efficacy findings at TOC in two analyses population show similarity of daptomycin to comparator in the treatment of cSSSI in pediatric patients. Data sets listed results as Cure, Improvement, Failure, Non-Evaluable; in the clinical report Clinical success is defined as patients with either Cure or Success. There is a data set discrepancy between those listed as Clinical Response at TOC and Sponsor response at TOC. There is one fewer patient included in the Clinical Response at TOC population with 387 patients, while Sponsor response at TOC consisted of 388 patients. Patient profiles were examined, and study report values were verified. Differences between Cure, Fail, and Non-evaluable patients primarily resulted from loss to follow up from EOT to TOC visits in particular if Cure listed at EOT.*

Table 9 Daptomycin Clinical Efficacy at TOC per Days of IV Therapy

	<=7 Days							**> 7 Days**			**Subjects (filtered)**
Sponsor Clinical Response at TOC N, n (%)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Success	32 (69.6)	67 (90.5)	33 (86.8)	18 (94.7)	19 95.0)	10 (90.9)	30 (100.0)	11 (100.0)	4 (100.0)	3 (100.0)	227 (88.7)
Failure	2 (4.3)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)
Non-evaluable	12 (26.1)	7 (9.5)	4 (10.5)	1 (5.3)	1 (5.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	26 (10.2)
Subjects (filtered)	46 (18.0)	74 (28.9)	38 (14.8)	19 (7.4)	20 (7.8)	11 (4.3)	30 (11.7)	11 (4.3)	4 (1.6)	3 (1.2)	256 (100.0)

Created using ADSL.xpt dataset

MO comment: *Majority of the patients receiving daptomycin treatment (61.7%) were treated with the study medication for ≤ 3 days. Of the safety population patients treated with daptomycin, 12 were only given IV therapy with no conversion to oral therapy. From these 12 patients 5 (4.7) were marked clinical success at*

TOC. Given the small population, and transition as early as 1 day of therapy, measuring efficacy is difficult. Efficacy can be extrapolated as the course of cSSSI and response to therapy are sufficiently similar in comparing pediatric patients and adults.

Study drug clinical cure rates against individual cSSSI pathogens are presented in the table below. A deep wound specimen was obtained if possible at Screening/Baseline, and follow up cultures were performed if clinically indicated while on the therapy, at EOT, TOC visits or at time of early discontinuation. Similarly, blood cultures were to be obtained at investigator discretion at Screening, while on therapy, at EOT,TOC visits, and at early drug discontinuation if indicated.
Efficacy rates between daptomycin and standard of care therapy ranged in a percent difference in microbiological success rates of 5% for MRSA and MSSA, whereas for subjects with *Streptococcus pyogenes*, there was a 30 percent greater success rate in daptomycin patients.

Table 10: Clinical Success per Sponsor-Defined Outcome at TOC by Causative Organism (mITT population)

Causative Organism	***Daptomycin n/N (%)***	***SOC Comparator n/N (%)***
Staphylococcus aureus(MRSA)	89/106 (84.0)	44/48 (91.6)
Staphylococcus aureus(MSSA)	81 /87 (93.1)	43/49 (87.8)
Streptococcus pyogenes	23/24 (95.8)	7/10 (70.0)
Enterococcus faecalis (VSE)	3/4 (75.0)	2/2 (100.0)

Created using ADMB.xpt and ADSL.xpt datasets

Table 11 Clinical Success Rates by Infecting Pathogen in cSSSI Adult Trials

Pathogen	***Daptomycin N = 382 (%)***	***Comparator N = 424 (%)***
Methicillin-susceptible S. Aureus	170/198 (86.0)	180/207 (87.0)
Methicillin-resistant S. aureus	21/28 (75.0)	25/36 (69.0)
Streptococcus pyogenes	84 (94.0)	80/88 (91.0)
Streptococcus agalactiae	27 (85.0)	22/29 (76.0)
Streptococcus dysgalactiae	8/8 (100.0)	9/11 (82.0)
Enterococcus faecalis	27/37 (73.0)	40/53 (76.0)

Adapted from Cubicin product label

MO comment: *The review indicates similar pathogenic source of infection and clinical successes in both daptomycin and comparator arms. These findings are similar to those found in adult trials. Older patients in the pediatric trial (Group1) are similar in causative bacterial pathogen of MSSA over MRSA, and indicate similar success rates as well.*

MO comment: In review of study DAP-PEDS-07-03, a discrepancy in the safety and efficacy findings from sites in India compared to USA was noticed. Study data indicated higher efficacy and lower AE rates in sites from India as compared to the USA study population. No definitive cause for differences discerned by reviewer after a comparison of baseline demographic, pathogens, lesions characteristics, or duration of therapy. An IR from company indicated no definitive cause as well. Given the discrepancy efficacy and safety data was analyzed with and without sites from India. Assessment performed by OSI deemed data from India sites to be acceptable, and able to be incorporated in this clinical review. The applicant's submissions related to this issue resulted in a major amendment and an extension of the user fee goal date to March 30, 2017.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

There were no specific subpopulations focus in the study; all patients were with cSSSI and placed in daptomycin or standard of care therapy. There were no pertinent differences in clinical outcomes with gender. Overall outcomes per race were similar, with exception of observed differences between countries as discussed in 6.1.5, which may play a role in Asian race clinical results.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In the pediatric population, with decreasing age there was higher volume of distribution and clearance of daptomycin as compared to adults. Dosing was varied by age group to produce exposures comparable to those in adults. Dosage adjustment for pediatric patients with renal impairment has not been established.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

6.2 Efficacy Summary and Conclusion

The trial was not powered to demonstrate efficacy, which is extrapolated from adult trials. The study indicated pediatric patients 1 year of age and older demonstrated similar efficacy of intravenous daptomycin to intravenous standard of care therapy (clindamycin, vancomycin, semi-synthetic penicillin) [difference 2.0% (-5.1, 9.1)] for the treatment of cSSSI. Other than the power of the study, an additional limitation was study drug

duration. The majority of patients received daptomycin therapy for ≤ 3 days before being switched to alternate oral therapy to complete treatment.

7 Review of Safety

Safety Summary

Overall, daptomycin dosed at 5,7,9, or 10 mg/kg for ages 12-17, 7-11, 2-6, and 1-<2 years respectively for up to 14 days has a similar safety profile in the pediatric population as in adults. In comparing overall clinical trial safety between daptomycin and standard of care comparators, the incidence of adverse events was similar. The incidence of drug related adverse events was 13.7% in daptomycin arm compared to 16.5% in comparator arm. Study design and safety findings are similar to data in adult trials. There were no deaths reported in this cSSSI trial. In adult clinical trials deaths which occurred, primarily were due to adverse events secondary to infection or infestations.

The majority of AEs were ranked as either mild or moderate with no indication of persistence. There was similar proportion of study patients reporting at least one AE between the daptomycin group (38.3%) and comparator (36.1%). The most common adverse events noted to occur in the daptomycin arm were gastrointestinal conditions as diarrhea and vomiting. Pyrexia and pruritus were also common adverse events. The severe TEAEs occurred in equal incidence of 2.3% in both in the daptomycin and comparator group. There were 9 subjects with serious adverse events: 6 subjects were in the group treated with daptomycin and 3 subjects in the group treated with comparator. An increase of blood CPK in a patient in daptomycin arm was listed as possibly related to study. No other serious adverse events indicated causality to study drug.

In the clinical trial of the 389 subjects, 21 prematurely discontinued IV study treatment. Of those who discontinued, 10 subjects (3.9%) were treated with daptomycin and 11 (8.3%) with a comparator. Only 2 (0.8%) subjects in daptomycin group discontinued due to adverse events of rashes. Clinical failure counted for 2 (0.8%) discontinuations as well, and was similar to comparator. Once patients had transitioned from IV therapy, subsequent discontinuations from the daptomycin study arm were predominantly due to patient loss to follow up and incorrect usage of oral therapy.

There is a greater incidence of adverse events in the 1-<2 year and 2-6 year old age group as compared to older children in the daptomycin arm. The 2-6 year age group did have a higher incidence of adverse events in daptomycin arm compared to comparator arm. There was a significant increase in adverse events in the 1-<2 year age group in comparator vs. daptomycin groups.

Daptomycin-associated changes in laboratory parameters from adult trials and postmarket data have focus on CPK and hepatic function. The number of patients with shifts from baseline to high was noted slightly more in daptomycin arm at EOT for AST, CPK, and total bilirubin. Comparing mean changes of laboratory parameters indicated comparable values per parameter for daptomycin and comparator arms. Investigation of CPK levels, post-baseline changes deemed clinically significant (>500 U/L and 3 × Baseline level) had similar percent of study population of 2% in each arm. In the pediatric study population there were no clinically significant changes in hematology or urinalysis. There was no notable variation of changes in laboratory parameters across age groups.

There were no apparent significant changes in vital signs, neurological examinations, or physical examination findings between daptomycin group vs. comparator, or among age groups. There were 4.0% of subjects in daptomycin arm with pyrexia, however only 2 (0.8%) cases were listed as serious. These 2 cases were indicated as being unlikely due to study drug.

There were no additional significant adverse reactions to daptomycin or new safety concerns from those described in the current product label evident in this pediatric clinical trial.

7.1 Methods

Sources of safety data
The pediatric development program for daptomycin included 4 studies: two single-dose and one repeated-dose clinical trials, as well as a safety, efficacy, and pharmacokinetic (PK) clinical trial. The latter was the focus of safety and efficacy data.

The primary study was a multicenter, randomized, evaluator-blinded, comparative pediatric study with safety of daptomycin as a primary focus. Pediatric patients aged 1 to 17 years with cSSSI caused by Gram- positive pathogens were randomized 2:1 to daptomycin vs. a standard of care comparator and treated with age-dependent doses over a period of up to 14 days. Safety was evaluated by clinical assessment including changes in physical and neurological findings, vital signs, and lab markers like serum creatine phosphokinase (CPK) levels, in addition to tracking reports of adverse events (AEs) and serious adverse events (SAEs). Safety was assessed from entirety of administration of study medication first dose through the last follow-up visit.
A blinded medical monitor reviewed safety parameters to ensure any indication of AE was documented and classified per severity and causality.

The safety data were collected across 30 clinical locations in either the United States or India. Overall, the safety database included 396 treated pediatric patients who received at least one dose of study medication. Incidence of adverse events, changes in vital signs, clinical findings, and laboratory parameters were compared between the study groups.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study DAP-PEDS-07-03 enrolled pediatric patients 1 months to 17 years of age with complicated skin and skin structure infections (cSSSI) caused by gram positive organism, groups by age-descending order: Group 1 (12-17years),Group 2 (7-11 years), Group 3 (2-6 years), and Group 4 (1-<2 years). Dosing was guided through PK studies with target steady state exposure levels (AUC) in children that were comparable to the AUC in adults treated with 4 mg/kg. Using these metrics, dosing was designated as 5 mg/kg in Group 1 (12-17 year olds), 7 mg/kg in Group 2 (7-11 year olds), 9 mg/kg in Group 3 (2-6 year olds), and 10 mg/kg in Group 4 (1- less than 2 year olds). Groups 3 and 4 also had infusions run over extended time of 60 minutes as compared to 30 minutes of Groups 1 and 2, given the potential for an elevated maximum plasma concentration (C_{max}).

7.1.2 Categorization of Adverse Events

The adverse events (AE) in this study were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 11.0. The AEs were categorized by preferred term and system organ class. Safety data in

subjects valid for safety were analyzed for the incidence of treatment emergent AEs (TEAEs), TESAEs, relation to study drug, deaths, and treatment related discontinuations of treatment or study.

Table 12 Adverse Event Characterization

Subjects with AEs	*Daptomycin N= 256 (%)*	*SOC Comparator N = 133 (%)*	*Total N = 389 (%)*
At least one TEAE	98 (38.3%)	48 (36.1%)	146 (37.5%)
At least one drug related TEAE	35 (13.7%)	22(16.5%)	57 (14.7%)
At least one TESAE	6 (2.3%)	3 (2.3%)	9 (2.3%)
Relation of TEAE to study drug			
Not related	40 (15.6%)	21 (15.8%)	61 (15.7%)
Unlikely	23 (9.0%)	5 (3.8%)	28 (7.2%)
Possibly Related	30 (11.7%)	16 (12.0%)	46 (11.8%)
Related	5 (2.0%)	6 (4.5%)	11 (2.8%)
TEAE severity			
Mild	71 (27.7%)	30 (22.6%)	101 (26.0%)
Moderate	21 (8.2%)	15 (11.3%)	36 (9.3%)
Severe	6 (2.3%)	3 (2.3%)	9 (2.3%)
AE with outcome death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discontinuation of treatment due to TEAE	7 (2.7%)	7 (5.3%)	14 (3.6%)
Discontinuation of study due to TEAE	1 (0.4%)	1 (0.8%)	2 (0.5%)

Adapted from sponsor table 12-2 and AECB.xpt dataset

MO Comment: *Any new adverse events which occurred after study drug was initiated were listed as treatment emergent. Hence, no non-treatment-emergent adverse events were listed. Causality was labeled to degree of which treatment emergent adverse events were considered related to study drug. There was a single life threatening event in the study, noted as toxic shock syndrome in a patient in comparator arm. Patient recovered and completed study. Of the seven discontinuations of treatment due to TEAE, one subject was listed as having drug related symptoms of diarrhea. Four of the discontinuations were listed as possibly related with adverse effects listed as rash, dysphagia, and diarrhea. The other discontinuations were considered unlikely or not related.*

Table 13 Occurrences of Treatment Emergent Adverse Events Across Age Groups

Age Group	***Daptomycin***	***SOC Comparator***
1 (12-17 years)	26/72 (36.1%)	14/38 (36.8%)
2 (7-11 years)	17/73 (23.3%)	17/38 (18.4%)
3 (2-6 years)	41/81 (50.6%)	16/42 (38.1%)
4 (1-<2 years)	14/30 (46.7%)	11/15 (73.3%)
Subjects	98/256 (38.3%)	48/133 (36.1)

Created using AECB.xpt dataset

MO Comment: *There is a relatively similar incidence of adverse events with daptomycin and comparator overall. There was a greater incidence of adverse events in age group 3 in the daptomycin group, and overall greater incidence of adverse events in groups 3 and 4 in both daptomycin and comparator groups.*

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable; data from a single large multi-dose safety trial in pediatric patients with cSSSI, protocol DAP-PEDS-07-03, were analyzed for safety.

7.2 Adequacy of Safety Assessments

The study was divided into two arms: daptomycin and a standard of care comparator. Dosing was based on age and weight, guided by the pharmacokinetic parameters determined from prior single dose data as well as extrapolation from adult data. Patients were evaluated for entry into study, within 48 hours prior to dosing. Adverse events were reported throughout the treatment phase, including an EOT visit within 3 days of drug completion and a TOC/Safety visit 7-14 days post treatment for all safety assessments. Adverse events were categorized by organ system or investigation, and labeled as treatment emergent, serious, or those resulted in premature termination per investigator's assessment. Laboratory safety monitoring included routine hematology, chemistry, and urinalysis.

MO comment: *Overall safety assessments performed are adequate given the safety profile of daptomycin.*

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Per study protocol, the treatment duration was specified to last up to 14 days. Patients were switched to oral medication at investigator discretion; with single dose of study being minim criteria for study inclusion. Table below summarizes the actual length of study treatment per arm.

Table 14 Summary of IV Medication Exposure in Days for Safety Population

Treatment N (n%)	1	2	3	4	5	6	7	8	9	10	14
SOC (N = 133)	11 (8.3)	36 (27.1)	26 (19.5)	10 (7.5)	9 (6.8)	13 (9.8)	14 (10.5)	8 (6.0)	4 (3.0)	1 (0.8)	1 (0.8)
DAP 5MG/KG Q24H (N = 72)	5 (6.9)	20 (27.8)	9 (12.5)	4 (5.6)	8 (11.1)	4 (5.6)	13 (18.1)	6 (8.3)	2 (2.8)	1 (1.4)	0 (0.0)
DAP 7MG/KG Q24H (N= 73)	9 (12.3)	7 (9.6)	6 (8.2)	8 (11.0)	11 (15.1)	6 (8.2)	17 (23.3)	5 (6.8)	2 (2.7)	2 (2.7)	0 (0.0)
DAP 9MG/KG Q24H (N = 81)	21 (25.9)	40 (49.4)	14 (17.3)	4 (4.9)	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DAP 10MG/KG Q24H (N = 30)	11 (36.7)	7 (23.3)	9 (30.0)	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Total (N=389)	57 (14.6)	110 (28.2)	64 (16.5)	29 (7.5)	29 (7.5%)	24 (6.7)	44 (11.3)	19 (4.9)	8 (2.0)	4 (1.0)	1 (0.3)

Created using ADSL.xpt Dataset

MO Comment: *Greater than 85% of subjects completed both arms, with 90% of those in daptomycin group completed therapy. For daptomycin as previously indicated dosing correlates with treatment age groups.*

Table 15 Study Drug Completion

Study Medication completed	***Daptomycin N = 257(%)***	***SOC Comparator N = 132 (%)***
Not Completed	21 (8.2%)	18 (13.6%)
Complete	236 (91.8%)	114 (86.4%)

Adapted from study report table 10-3

MO Comment: *Daptomycin arm had slightly greater percentage of patients complete study medication. Those who did not complete were mostly listed as being lost to follow up. There were 244(95.3%) of daptomycin arm patients and 125 (94.0%) of comparator arm patients converted to oral therapy. Oral therapy was not specified in protocol and was chosen at investigator discretion. The most common oral antibiotic chosen was clindamycin, with 39% of daptomycin arm and 35% of comparator arm using the medication once converted.*

7.2.2 Explorations for Dose Response

The study did not evaluate dose-response. Doses selected for this study were the result of exposure data analysis generated in single dose safety and PK study in pediatric patients designed to target daptomycin exposures similar to AUC in adults treated with 4mg/kg.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing while on study treatment included evaluation of the parameters potentially affected by daptomycin, such as: complete blood count, comprehensive metabolic panel including liver function tests, creatine phosphokinase, and urinalysis.

7.2.5 Metabolic, Clearance, and Interaction Workup

PK modeling was performed to guide dosing in pediatric population, to provide similar exposure as 4mg/kg in adults. Modeled data from adult exposure indicated targets of 494 mcg*h/L for AUC0-24 and 57.8 mcg/mL for C_{max}. Projections in the single dose PK study showed AUC below lower target thresholds. The C_{max} for all groups exceeded adult values with means of 62.4 mcg/mL in Group 1, 64.9-74.4 mcg/mL in Group 2, 81.9 mcg/mL in Group 3, and 79.2 mcg/mL in Group 4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in this clinical study.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events were defined in the protocol as those resulting in death, were life-threatening, required hospitalization or prolonged current hospitalization, resulted in persistent/significant disability, congenital anomaly, or were deemed medically important by the investigator. As noted, all adverse events listed in the study were labeled as treatment emergent.

Table 16 Serious Adverse Events

Body System or Organ Class Term	Dictionary Derived Term	Daptomycin N = 256 (%)	SOC Comparator N = 133 (%)
Infections and infestations	Abscess	1 (0.4%)	0 (0.0%)
	Bacteremia	0 (0.0%)	1 (0.8%)
	Osteomyelitis	0 (0.0%)	1 (0.8%)
	Subcutaneous Abscess	1 (0.4%)	0 (0.0%)
	Toxic Shock Syndrome	0 (0.0%)	1 (0.8%)
General disorders and administration site conditions	Chest Pain	1 (0.4%)	0 (0.0%)
	Pyrexia	2 (0.8%)	0 (0.0%)
Investigations	Blood creatine phosphokinase increased	1 (0.4%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Myopathy	1 (0.4%)	0 (0.0%)
Respiratory, thoracic, and mediastinal disorders	Status asthmaticus	1 (0.4%)	0 (0.0%)
Surgical and medical procedures	Wound drainage	1 (0.4 %)	0 (0.0%)
Total Subjects(filtered)		6 (2.3%)	3 (2.3%)

Created using AECB.xpt dataset

MO comment: *There were 6 (2.3%) patient in the daptomycin arm and 3 (2.3%) in comparator treatment group reported experiencing serious adverse events. The events are not correlated with daptomycin dose; 3 (1.2%) patients were in the 5mg/kg group, 1 (0.4%) in 7mg/kg group, and 2 (0.8%) in 9mg/kg group. Of the patients listed there was 1 (0.4%) patient in daptomycin arm and 1 (0.8%) patient in comparator arm who discontinued study drug due to the SAE. The increase in blood creatine phosphokinase is labeled as possibly related to study drug, but was not a cause of drug withdrawal.*

7.3.3 Dropouts and/or Discontinuations

Twenty-one of 395 subjects (5.3%) discontinued the study during primary IV therapy. Of these 21 subjects, 10 were part of daptomycin treatment arm and 11 were part of comparator treatment. Drug discontinuation of daptomycin did not indicate a primary cause or correlation.

Table 17 Study Drug Discontinuations

Primary reason for IV study drug discontinuation	Daptomycin N = 256 (%)	SOC Comparator N = 133 (%)
Adverse Event	2 (0.8%)	4 (3.0%)
Microbiological failure	0 (0.0%)	1 (0.8%)
Unsatisfactory clinical response	2 (0.8%)	0 (0.0%)
Major protocol violation	2 (0.8%)	0 (0.0%)
Investigators decision	0 (0.0%)	2 (1.5%)
Subject's decision	0 (0.0%)	1 (0.8%)
Other	4 (1.6%)	3 (2.3%)
Subjects(filtered)	10 (3.9%)	11 (8.3%)

Created using ADSL.xpt dataset

MO comment: *There was a lesser incidence of discontinuations in the daptomycin arm. There were fewer adverse events resulting in study drug discontinuation on the daptomycin arm (0.8%) as compared to the comparator arm (3.0%). Adverse events leading to discontinuation during IV phase were secondary to rashes listed as possibly related to study drug. Considering microbiological failure and unsatisfactory clinical response as failures, discontinuation due to efficacy was equal in both arms at (0.8%). There were increased protocol violations in the daptomycin arm (0.8%). 1 of the subjects was given a prohibited drug due to medical error resulting in disqualification from study. The other subject required further imaging, and there was suspicion of osteomyelitis, beyond the scope of study indications. Discontinuations labeled as "Other," are with indications not related to study drug including medical order for medication not being continued on floor transfer, elevated baseline CPK, family choosing to leave for non-medical reason, or incorrect medication was administered. There were a greater number of patients discontinued from the study after IV therapy was already completed due to loss to follow up and incorrect usage of oral therapy.*

7.3.4 Significant Adverse Events

Significant adverse events coinciding with IV drug treatment were described in section 7.3.2 and 7.3.3 as SAEs or cause for discontinuation. In addition to the 2 subjects in the daptomycin arm discontinued due to adverse effects during IV therapy, there were 5 additional subjects treated with daptomycin who discontinued due to adverse events once on oral therapy. Dysphagia, pyrexia, subcutaneous abscess, diarrhea, and vomiting were the adverse events with led to oral drug discontinuation.

7.3.5 Submission Specific Primary Safety Concerns

Rhabdomyolysis/Myopathy
Safety data from adults indicated skeletal muscle a potential target of daptomycin toxicity. Elevation of CPK with muscle related symptoms were investigation and adverse event focus points. The study pursued a broad

and narrow relationship Standardized MedDRA Query (SMQ) of rhabdomyolysis and myopathy.

Table 18 ITT Population Adverse Events Meeting SMQ Terms Rhabdomyolysis/Myopathy

SYSTEM ORGAN CLASS TERM	PREFERRED TERM	Daptomycin N = 256 (%)	SOC Comparator N = 133 (%)
Subjects with one or more TEAE	--	15 (5.9)	8 (6.0)
Investigations	Blood creatine phosphokinase increased	14 (5.5)	7 (5.3)
Metabolism and nutritional disorders	Hypocalcemia	0 (0.0)	1 (0.8)
Musculoskeletal and connective tissue disorders	Myalgia	2 (0.8)	0 (0.0)
	Myopathy	1 (0.4)	0 (0.0)

Adapted from sponsor table 12-6, and AECB.xpt dataset

***MO comment**: There was a similar incidence of adverse events in both daptomycin and comparator arms in regards to relation to rhabdomyolysis or myopathy. Blood creatine phosphokinase was elevated in similar proportion of each study arm. Daptomycin arm did have more patients indicating myalgia/myopathy. In the daptomycin arm, the 14 subjects with increased CPK were all treated with less than 7 days of IV therapy, with 12 treated at ≤3 days of IV therapy. None of the adverse events were reason for transition or considered early discontinuation of therapy. The events occurred primarily in subjects in Age Groups 1 or 3. Increased blood creatine phosphokinase was noted in 5 (6.9%) patients of daptomycin arm and 2 (5.3%) comparator arm in Age Group 1, and 8 (9.9%) daptomycin treated patients and 2 (4.8%) comparator treated subjects in Age Group 3. This does not, however, seem to indicate an age-related trend. There were 2 patients in daptomycin arm with TESAE with skeletal muscle events; 1 patient with increased blood creatine phosphokinase, and 1 patient with myopathy.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Over 1/3 of patients, 146/389 (37.5%), in the clinical study experienced at least one adverse event. The percentage of patients who experienced an adverse event was similar between the two randomized groups, with 98/256 (38.3%) patients in the daptomycin group and 48/133 (36.1%) patients in the comparator group.

Table 19 Common Adverse Events

Body System or Organ Class	Dictionary Term	Daptomycin N = 256 (%)	SOC Comparator N = 133 (%)
Blood and lymphatic system disorders	**Lymphadenopathy**	0 (0.0%)	1 (0.8%)
	Thrombocythaemia	1 (0.4%)	0 (0.0%)
Ear and labyrinth disorders	**Ear pain**	0 (0.0%)	1 (0.8%)
Eye disorders	**Eye swelling**	1 (0.4%)	0 (0.0%)
	Eyelid bleeding	1 (0.4%)	0 (0.0%)

Body System or Organ Class	Dictionary Term	Daptomycin N = 256 (%)	SOC Comparator N = 133 (%)
	Vision blurred	1 (0.4%)	0 (0.0%)
Gastrointestinal disorders	**Abdominal pain**	5 (1.9%)	0 (0.0%)
	Abdominal pain upper	2 (0.8%)	0 (0.0%)
	Abnormal faeces	1 (0.4%)	0 (0.0%)
	Cheilitis	0 (0.0%)	2 (1.5%)
	Constipation	0 (0.0%)	1 (0.8%)
	Diarrhoea	18 (7.0%)	7 (5.3%)
	Dysphagia	1 (0.4%)	0 (0.0%)
	Glossitis	0 (0.0%)	1 (0.8%)
	Haematochezia	0 (0.0%)	1 (0.8%)
	Lip pain	0 (0.0%)	1 (0.8%)
	Lip swelling	0 (0.0%)	2 (1.5%)
	Nausea	3 (1.2%)	1 (0.8%)
	Stomatitis	1 (0.4%)	0 (0.0%)
	Vomiting	7 (2.7%)	1 (0.8%)
General disorders and administration site conditions	**Chest pain**	2 (0.8%)	0 (0.0%)
	Fatigue	0 (0.0%)	1 (0.8%)
	Induration	1 (0.4%)	0 (0.0%)
	Infusion site extravasation	1 (0.4%)	2 (1.5%)
	Infusion site pain	3 (1.2%)	2 (1.5%)
	Infusion site phlebitis	1 (0.4%)	0 (0.0%)
	Nodule	1 (0.4%)	0 (0.0%)
	Pain	1 (0.4%)	0 (0.0%)
	Pyrexia	10 (4.0%)	4 (3.0%)
	Swelling	1 (0.4%)	0 (0.0%)
Immune system disorders	**Drug hypersensitivity**	0 (0.0%)	1 (0.8%)
	Hypersensitivity	0 (0.0%)	1 (0.8%)
Infections and infestations	**Abscess**	1 (0.4%)	0 (0.0%)
	Abscess limb	1 (0.4%)	1 (0.8%)
	Abscess neck	0 (0.0%)	1 (0.8%)
	Bacteraemia	0 (0.0%)	1 (0.8%)
	Body tinea	1 (0.4%)	0 (0.0%)
	Bronchitis	1 (0.4%)	0 (0.0%)
	Candida nappy rash	1 (0.4%)	1 (0.8%)
	Cellulitis	4 (1.6%)	0 (0.0%)
	Folliculitis	0 (0.0%)	1 (0.8%)
	Fungal infection	1 (0.4%)	1 (0.8%)
	Genital candidiasis	0 (0.0%)	1 (0.8%)
	Hand-foot-and-mouth disease	0 (0.0%)	1 (0.8%)
	Infection	0 (0.0%)	1 (0.8%)
	Malaria	1 (0.4%)	0 (0.0%)
	Nasopharyngitis	1 (0.4%)	0 (0.0%)
	Osteomyelitis	0 (0.0%)	1 (0.8%)
	Rhinitis	0 (0.0%)	1 (0.8%)
	Subcutaneous abscess	1 (0.4%)	0 (0.0%)
	Tinea capitis	1 (0.4%)	0 (0.0%)
	Tinea infection	0 (0.0%)	1 (0.8%)
	Toxic shock syndrome	0 (0.0%)	1 (0.8%)
	Upper respiratory tract infection	0 (0.0%)	3 (2.3%)

Body System or Organ Class	Dictionary Term	Daptomycin N = 256 (%)	SOC Comparator N = 133 (%)
	Viral upper respiratory tract infection	1 (0.4%)	0 (0.0%)
Injury, poisoning and procedural complications	**Arthropod bite**	3 (1.2%)	0 (0.0%)
	Contusion	1 (0.4%)	0 (0.0%)
	Excoriation	3 (1.2%)	0 (0.0%)
	Mouth injury	1 (0.4%)	2 (1.5%)
	Procedural pain	0 (0.0%)	1 (0.8%)
	Thermal burn	1 (0.4%)	0 (0.0%)
Investigations	**Arterial bruit**	0 (0.0%)	1 (0.8%)
	Aspartate aminotransferase increased	2 (0.8%)	0 (0.0%)
	Blood albumin increased	1 (0.4%)	0 (0.0%)
	Blood creatine phosphokinase increased	14 (5.5%)	7 (5.3%)
	Blood phosphorus increased	2 (0.8%)	1 (0.8%)
	Blood urine present	0 (0.0%)	1 (0.8%)
	Body temperature increased	1 (0.4%)	0 (0.0%)
	Cardiac murmur	1 (0.4%)	0 (0.0%)
	Hepatic enzyme increased	1 (0.4%))	1 (0.8%)
	Liver function test abnormal	1 (0.4%)	0 (0.0%)
	Lymphocyte percentage increased	0 (0.0%)	1 (0.8%)
	Monocyte count increased	1 (0.4%)	0 (0.0%)
	Neutrophil count decreased	0 (0.0%)	1 (0.8%)
	Platelet count decreased	1 (0.4%)	0 (0.0%)
	Platelet count increased	0 (0.0%)	1 (0.8%)
	Protein total increased	1 (0.4%)	0 (0.0%)
	Red blood cells urine	0 (0.0%)	1 (0.8%)
	Urine analysis abnormal	0 (0.0%)	1 (0.8%)
	Urine output decreased	0 (0.0%)	1 (0.8%)
Metabolism and nutrition disorders	**Decreased appetite**	1 (0.4%)	1 (0.8%)
	Dehydration	0 (0.0%)	1 (0.8%)
	Hyperalbuminaemia	1 (0.4%)	0 (0.0%)
	Hyperphosphataemia	3 (1.2%)	0 (0.0%)
	Hyperproteinaemia	1 (0.4%)	0 (0.0%)
	Hypocalcaemia	0 (0.0%)	1 (0.8%)
Musculoskeletal and connective tissue disorders	**Arthralgia**	2 (0.8%)	0 (0.0%)
	Muscle spasms	1 (0.4%)	0 (0.0%)
	Musculoskeletal stiffness	1 (0.4%)	0 (0.0%)
	Myalgia	2 (0.8%)	0 (0.0%)
	Myopathy	1 (0.4%)	0 (0.0%)
	Pain in extremity	1 (0.4%)	1 (0.8%)
Nervous system disorders	**Dizziness**	2 (0.8%)	0 (0.0%)
	Headache	7 (2.7%)	3 (2.3%)
	Syncope	0 (0.0%)	1 (0.8%)
Renal and urinary disorders	**Proteinuria**	1 (0.4%)	0 (0.0%)
	Urinary retention	1 (0.4%)	0 (0.0%)
Reproductive system and breast disorders	**Dysmenorrhoea**	1 (0.4%)	0 (0.0%)
	Genital lesion	2 (0.8%)	0 (0.0%)

Body System or Organ Class	Dictionary Term	Daptomycin N = 256 (%)	SOC Comparator N = 133 (%)
Respiratory, thoracic and mediastinal disorders	**Atelectasis**	1 (0.4%)	0 (0.0%)
	Bronchial hyperreactivity	1 (0.4%)	0 (0.0%)
	Cough	1 (0.4%)	1 (0.8%)
	Dyspnoea	0 (0.0%)	1 (0.8%)
	Epistaxis	1 (0.4%)	1 (0.8%)
	Nasal congestion	1 (0.4%)	1 (0.8%)
	Pharyngeal lesion	0 (0.0%)	1 (0.8%)
	Pharyngolaryngeal pain	1 (0.3%)	1 (0.8%)
	Respiratory disorder	1 (0.3%)	0 (0.0%)
	Rhinorrhoea	4 (1.6%)	1 (0.8%)
	Status asthmaticus	1 (0.4%)	0 (0.0%)
	Wheezing	1 (0.4%)	0 (0.0%)
Skin and subcutaneous tissue disorders	**Alopecia**	1 (0.4%)	0 (0.0%)
	Blister	2 (0.8%)	0 (0.0%)
	Dermatitis contact	1 (0.4%)	0 (0.0%)
	Dermatitis diaper	2 (0.8%)	3 (2.3%)
	Erythema	2 (0.8%)	3 (2.3%)
	Pruritus	8 (3.1%)	2 (1.5%)
	Rash	1 (0.4%)	4 (3.0%)
	Rash erythematous	0 (0.0%)	1 (0.8%)
	Rash generalized	1 (0.4%)	0 (0.0%)
	Rash macular	0 (0.0%)	1 (0.8%)
	Rash maculo-papular	1 (0.4%)	0 (0.0%)
	Rash popular	3 (1.2%)	1 (0.8%)
	Rash pruritic	1 (0.4%)	0 (0.0%)
	Scab	1 (0.4%)	0 (0.0%)
	Skin lesion	1 (0.4%)	0 (0.0%)
	Swelling face	1 (0.4%)	0 (0.0%)
	Urticaria	0 (0.0%)	2 (1.5%)
Surgical and medical procedures	**Wound drainage**	1 (0.4%)	0 (0.0%)
Vascular disorders	**Flushing**	1 (0.4%)	0 (0.0%)
	Haemorrhage	0 (0.0%)	1 (0.8%)
	Thrombophlebitis	1 (0.4%)	0 (0.0%)
	Subjects(filtered)	98 (38.3%)	48 (36.1%)

Created using AECB.xpt dataset

MO comment: *There is a wide range of adverse events experienced by the patients in the study. However, the majority of these AEs are in less than 1% of the study population for the study drug or comparator. There were similar proportions of adverse events in both daptomycin and comparator groups. The spectrum of adverse events listed is similar to those occurring in adults per current daptomycin package insert. Gastrointestinal disorders were the predominant adverse events, notably diarrhea and vomiting. Pyrexia and pruritus were also common, and in greater incidence in daptomycin arm over comparator. Rashes when taken cumulatively also occurred in 2.7% of the daptomycin arm. Of study specific investigations established from adult trials, increased blood creatinine phosphokinase was noted in 5.5% of daptomycin arm patients. Only one patient was listed as having a severe rated increase in blood CPK. This did not result in study discontinuation.*

7.4.2 Laboratory Findings

All patients on the study underwent hematology, blood chemistry, CPK, myoglobin, and urinalysis checks at baseline, during treatment, and end of treatment. Data collected were analyzed for treatment-emergent abnormalities and change from pre-therapy baseline.

Table 20 Lab Specific Adverse Events During IV Therapy

Dictionary Term	Daptomycin N = 256 (%)	SOC Comparator N = 133 (%)
Aspartate aminotransferase increased	2 (0.8%)	0 (0.0%)
Blood albumin increased	1 (0.4%)	0 (0.0%)
Blood creatine phosphokinase increased	14 (5.5%)	7 (5.3%)
Blood phosphorus increased	2 (0.8%)	1 (0.8%)
Blood urine present	0 (0.0%)	1 (0.8%)
Hepatic enzyme increased	1 (0.4%)	1 (0.8%)
Hyperalbuminaemia	1 (0.4%)	0 (0.0%)
Hyperphosphataemia	3 (1.2%)	0 (0.0%)
Hyperproteinaemia	1 (0.4%)	0 (0.0%)
Hypocalcaemia	0 (0.0%)	1 (0.8%)
Liver function test abnormal	1 (0.4%)	0 (0.0%)
Lymphocyte percentage increased	0 (0.0%)	1 (0.8%)
Monocyte count increased	1 (0.4%)	0 (0.0%)
Neutrophil count decreased	0 (0.0%)	1 (0.8%)
Platelet count decreased	1 (0.4%)	0 (0.0%)
Platelet count increased	0 (0.0%)	1 (0.8%)
Protein total increased	1 (0.4%)	0 (0.0%)
Red blood cells urine	0 (0.0%)	1 (0.8%)
Thrombocytopenia	1 (0.4%)	0 (0.0%)
Urine analysis abnormal	0 (0.0%)	1 (0.8%)
Urine output decreased	0 (0.0%)	1 (0.8%)

MO comment: *In both arms the most common adverse event related to abnormal laboratory value was increased blood creatine phosphokinase. Rates were similar in both arms (5.5% in daptomycin arm vs 5.3 in comparator arm). Hyperphosphatemia was demonstrated in daptomycin arm at 1.2%, with no cases in comparator. All episodes were listed as single events, possibly related to the study drug, but not causative or associated with discontinuations.*

Table 21 Creatine Phosphokinase Shifts Post Baseline

CPK Post Baseline	DAPTOMYCIN (N= 256)	COMPARATOR (N = 133)	Subjects(filtered)
CPK >1xULN - <=3xULN	37 (14.5%)	22 (16.5%)	59 (14.9%)
CPK>3xULN - <=5xULN	3 (1.2%)	0 (0.0%)	3 (0.8%)
CPK>5xULN - <=10xULN	0 (0.0%)	2 (1.5%)	2 (0.5%)
CPK>10xULN	2 (0.8%)	1 (0.8%)	3 (0.8%)
Subjects(filtered)	42 (16.4%)	25 (18.8%)	396 (100.0%)

Created using ADSL.xpt and LBCB.xpt

MO comment: *Analysis of blood creatine phosphokinase indicates similar post base line CPK changes in both arms. Baseline value for daptomycin arm was 103.0 U/L and was 100.0 for comparator arm. Values indicated in table above include arms through completion of study, consisting of IV and oral therapy. Most subjects with elevated CPK, had an increase between 1 to 3 times the upper limit of normal. Of the 5 cases above 3 times the upper limit than normal in the daptomycin arm, most were listed as unlikely to be related to study drug. Group 1 consisting of ages 12 to <18 had most occurrences. The increased CPK levels were not sustained, and were not cause of drug discontinuation.*

Table 22 Lab Value Shifts to High from Baseline

LAB TEST NAME	VISIT NAME	DAPTOMYCIN (N= 256)	COMPARATOR (N = 133)	Subjects(filtered)
ALANINE AMINOTRANSFERASE (SGPT)	**EOT/ET**	13 (5.1%)	6 (4.5%)	19 (4.8%)
	TOC/SAFETY	1 (0.4%)	2 (1.5%)	3 (0.8%)
ASPARTATE AMINOTRANSFERASE (SGOT)	**EOT/ET**	24 (9.4%)	9 (6.8%)	33 (8.3%)
	TOC/SAFETY	1 (0.4%)	3 (2.3%)	4 (1.0%)
BILIRUBIN, TOTAL	**EOT/ET**	2 (0.8%)	0 (0.0%)	2 (0.5%)
CREATININE, SERUM	**EOT/ET**	5 (2.0%)	2 (1.5%)	7 (1.8%)
	Subjects(filtered)	36 (14.1%)	14 (10.5%)	396 (100.0%)

Created using ADSL.xpt and LBCB.xpt

MO comment: *The table contains data for shifts from low or normal to high in regards to lab tests of interest as referenced in adult data review. Shifts include both IV and oral phase. Given range in use of daptomycin, shifts may not be fully representative of study drug solely, with oral transition potentially being causative.*

7.4.3 Vital Signs

Table 23 Changes in Vital Signs from Baseline to EOT and TOC Visit

	Daptomycin		*SOC Comparator*	
	N	**Mean ± SD**	**N**	**Mean ± SD**
Systolic blood pressure (mmHg)	EOT 238	-2.5 ± 12.3	EOT 120	-2.7 ± 10.9
	TOC 230	-1.7 ± 12.8	TOC 117	-1.5 ± 10.4
Diastolic blood pressure (mmHg)	EOT 238	-0.1 ± 11.4	EOT 120	0.2 ± 10.5
	TOC 230	0.3 ± 12.4	TOC 117	0.7 ± 9.7
Heart rate (BPM)	EOT 243	-7.0 ± 15.4	EOT 122	-8.8 ± 18.4
	TOC 236	-7.3 ± 16.4	TOC 119	-8.9 ± 18.4
Temperature (°C)	EOT 243	-0.5 ± 0.7	EOT 121	-0.5 ± 0.7
	TOC 235	-0.5 ± 0.7	TOC 119	-0.5 ± 0.7

Created with VSCB dataset and adapting sponsor table 14.3.6.1

MO comment: *Study data indicate mean vital sign changes from baseline to EOT and TOC visits to be unremarkable. Pyrexia was only vital sign change which became evident for concern in relation to daptomycin or comparators. There were 4% of daptomycin treated subjects and 3% of comparator treated subjects with pyrexia. 2 of the 10 subjects in the daptomycin arm with pyrexia were deemed to be serious, but not related to study drug. There were no additional clinically relevant abnormalities in vital signs.*

7.4.4 Electrocardiograms (ECGs)

Not applicable.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

Not applicable.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

Not applicable

9.2 Labeling Recommendations

Label changes with pediatric update include updates to dosing in regards to cSSSI including daptomycin dosed at 5,7,9, or 10 mg/kg for ages 12-17, 7-11, 2-6, and 1-<2 years respectively for up to 14 days. Duration of infusion is specifically labeled to highlight differences between adult and pediatric infusion times. Safety highlights, specifying common adverse events in pediatrics were specified. Updates have been made to include new data clarifying pregnancy and lactation sections of label. Pediatric use updated to establish indication in regards to safety and efficacy of use between ages 1 year to 17 years of age in pediatric patients.

9.3 Advisory Committee Meeting

Not applicable.

9.4 Clinical Investigator Financial Disclosure Review

Application Number: 21572

Submission Date(s):

Applicant: Cubist Pharmaceuticals

Product: Cubicin (Daptomycin)

Reviewer: Amol Purandare, MD

Date of Review: March 23, 2017

Covered Clinical Study: A multi-center, randomized, evaluator-blinded, comparative study in pediatric patients ages 1 to 17 years, with complicated skin and skin structure infections caused by Gram-positive pathogens, evaluating safety, efficacy, and PK of daptomycin to current standard therapies for Gram positive infections, Protocol # DAP-PED-07-03

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 34 primary investigators who enrolled subjects		
Number of investigators who are sponsor employees (including both full-time and part-time		

employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] There were no interests/arrangements between the sponsor and its investigators that affected the study outcome; none of the clinical investigators on the study were sponsor employees.

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/s/

AMOL PURANDARE
03/27/2017

THOMAS D SMITH
03/27/2017