CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-572

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA:	21-572
NAME OF DRUG:	CIDECIN® (Daptomycin for Injection)
APPLICANT:	Cubist Pharmaceuticals Inc.
SUBMISSION DATE:	December 19, 2002
INDICATION(S):	Complicated Skin and Skin Structure Infections (CSSSI)
NUMBER AND TYPE OF CLINICAL:	Two completed phase III studies
STATISTICAL REVIEWER:	Joel Jiang, Ph.D.
CLINICAL REVIEWER:	Susan Thompson, M.D.
PROJECT MANAGER:	LTJG Raquel Peat, M.S., M.P.H, HFD-520
45 DAY MEETING DATE:	February 13, 2003
USER FEE DATE:	June 20, 2003

I. ORGANIZATION AND DATA PRESENTATION		**YES**	**NO**	**N/A**
A.	Is there a comprehensive table of contents with adequate indexing and pagination?	✔		
B.	Are the original protocols, protocol amendments and proposed label provided?	✔		
C.	Adverse event listings by center and time of occurrence relative to enrollment date.	✔		
1.	Are adverse events from cited sources (foreign and domestic) provided?	✔		
D.	Is a CANDAR or an electronic submission of the data necessary?	✔		

		YES	NO	N/A
E.	If the data have been submitted electronically, has adequate documentation of the data sets been provided?		✔	
		—	—	—

Reviewer's comment: Format files are not found in sponsor's SAS data set package, which may have difficulty to reference formats or identify codes of variables in using SAS.

F.	Are inclusion/exclusion (evaluability) criteria adequately coded and described:	✔		
		—	—	—
G.	Are there discrepancies between CRF information and CANDAR/Jacket data?			✔
		—	—	—
H.	If the data have been submitted electronically, can laboratory data be easily merged across studies and indications?			✔
		—	—	—
I.	If not, can you estimate the time required to correct problems?			✔
		—	—	—

II. STATISTICAL METHODOLOGY

A.	Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	✔		
		—	—	—
B.	For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)?	✔		
		—	—	—
	If subset analyses were not done, was an acceptable explanation of why given?			✔
		—	—	—

		YES	NO	N/A
C.	Based on the summary analyses of each study, do you believe:			
1.	The analyses are appropriate for the type data collected, the study design, and the study objectives (based on protocol and proposed label claims)?	✔		
2.	If there are multiple endpoints, has this been adequately addressed?			✔
3.	Intent-to-treat (ITT and MITT) analyses are properly performed?	✔		
4.	Sufficient and appropriate references were included for novel statistical approaches?			✔
D.	If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?			✔
E.	Are there studies which are incomplete or ongoing?		✔	
F.	Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline?	✔		
1.	Is there anything significant yet regarding safety or AE evaluations?		✔	

III. FILEABILITY CONCLUSIONS

From a statistical perspective is this submission, or indications therein, reviewable with only minor further input from the sponsor?

This submission is fileable. However the sponsor needs to clarify some issues in electronic submitted data files.

APPENDIX

Table of the Studies:

Protocol	Daptomycin Regimen	N	Comparator Regimen	N	Type of Study
COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS (cSSSI)					
CSR-DAP-9801 3/15/99 – 8/2/01	Daptomycin: 4 mg/kg administered I.V. q.d. for 7 to 14 days	272# 265^ 256♣ 209♦ 223♥ 187♠	Vancomycin: 1 g administered I.V. BIDx7 to 14 days Or selected semi-synthetic penicillins: Nafcillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days Cloxacillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days Oxacillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days.	275# 265^ 261♣ 212♦ 222♥ 189♠	Phase III, active-controlled, randomized (1:1 ratio), investigator-blinded, Multicenter (69)
Duration of treatment: Maximum study duration from Pre-therapy to Post-Study was to be 44 days. Study drug was to be administered for 7 to 14 days, followed by TOC and Post-Study visits conducted 7 to 12 and 21 to 28 days, respectively, after the last dose of study drug. Therapy could be extended beyond 14 days with the approval of the Medical Monitor.					
Primary efficacy: The primary outcome variable was the Sponsor-Defined Clinical Outcome, which was based on the Investigator's evaluation of Clinical Response at the TOC visit, with adjustment for specific events (e.g., removal surgery) and evaluability criteria.					
Objective: The primary objectives of this study were to compare the safety and to demonstrate the equivalent efficacy of I.V. Daptomycin to that of I.V. Vancomycin or selected I.V. semi-synthetic penicillins in the treatment of cSSSI due to Gram-positive bacteria.					
CSR-DAP-9901 3/17/00 – 12/28/00	Daptomycin: 4 mg/kg administered I.V. q.d. for 7 to 14 days	276# 269^ 270♣ 213♦ 245♥ 196♠	Vancomycin: 1 g administered I.V. BIDx7 to 14 days Or selected semi-synthetic penicillins: Oxacillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days Cloxacillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days Flucloxacillin 4 to 12 g I.V. q.d. in equally divided doses for 7 to 14 days.	295# 293^ 292♣ 255♦ 262♥ 231♠	Phase III, active-controlled, randomized (1:1 ratio), investigator-blinded, Multicenter (67)
Duration of treatment: see Study CSR-DAP-9801.					
Primary efficacy: see Study CSR-DAP-9801.					
Objective: see Study CSR-DAP-9801.					
# Number of all enrolled and randomized; ^ Number of safety (as treated); ♣ Number of ITT; ♦ Number of MITT; ♥ Number of clinically evaluable; ♠ Number of microbiologically evaluable					

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