U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ADDENDUM

NDA/BLA #:	021572
Supplement #:	55
Drug Name:	Cubicin® (Daptomycin for injection)
Indication(s):	Complicated skin and skin structure infections (cSSSI)
Applicant:	Cubist Pharmaceuticals, Inc.
Date(s):	Stamp Date: 06/30/2016 Filing Date: 09/12/2016 PDUFA Goal Date: 3/28/2017 with a 3-month extension
Review Priority:	Priority
Biometrics Division:	DB4/OB/OTS/CDER
Statistical Reviewer:	Xianbin Li
Concurring Reviewers:	Karen Higgins, Statistical team leader
Medical Division:	DAIP/OAP/OND/CDER
Clinical Team:	Maria Allende, Amol Purandare
Project Manager:	Christopher Davi

During our review of this supplemental NDA, we found higher clinical success proportions in India and lower proportions of subjects with at least one treatment-emergent adverse event than in the USA. This led to a possible concern regarding the study conduct at sites in India. The following three tables are the summaries from the primary statistical review dated 11/21/16.

Sponsor-Defined Clinical Outcome at TOC by Geographic Region (ITT Population)

	India		USA	
	DAP N=81 n (%)	**SOC N=41 n (%)**	**DAP N=176 n (%)**	**SOC N=91 n (%)**
Clinical Success	81 (100)	39 (95.1)	146 (83.0)	75 (82.4)
Clinical Failure	0	0	3 (1.7)	1 (1.1)
Unable to Evaluate	0	2 (4.9)	27 (15.3)	15 (15.6)

Summary of Subjects with at least One Treatment-Emergent Adverse Event (Safety Population)

	India		USA	
	DAP	**SOC**	**DAP**	**SOC**
Age Group 1	6.3% (2/32)	12.5% (2/16)	60.0% (24/40)	54.5% (12/22)
Age Group 2	6.1% (3/49)	8.0% (2/25)	58.3% (14/24)	38.5% (5/13)
Age Group 3	-	-	50.6% (41/81)	38.1% (16/42)
Age Group 4	-	-	46.7% (14/30)	73.3% (11/15)
All	6.2% (5/81)	9.8% (4/41)	53.1% (93/175)	47.8% (44/92)

Summary of Sponsor-Defined Clinical Success (ITT Population) and Subjects with at least One Treatment-Emergent Adverse Event (Safety Population) by India Study Site

	Efficacy n/N(%)		**Safety n/N (%)**	
Site	**DAP**	**SOC**	**DAP**	**SOC**
200	48/48 (100)	26/26 (100)	4/48 (8.3)	0/26 (0)
201	2/2 (100)	0/1	0/2	1/1 (100)
202	2/2 (100)	5/6 (83.3)	1/2 (50)	3/6 (50)
203	25/25 (100)	8/8 (100)	0/25	0/8
204	2/2 (100)	-	0/2	-
205	1/1 (100)	-	0/1	-
207	1/1 (100)	-	0/1	-

The two largest study sites in India contained the majority of the data from India; however, the pattern of very high efficacy and very low rates of adverse events are seen in the remaining small sites as well. Due to our concerns for these differences between the two countries, we requested the sponsor provide additional information, including any findings from site monitoring that could possibly help explain these differences.

The sponsor provided a response on 11/29/16 (SDN 691) that contained additional analysis results for baseline characteristics, efficacy, and safety by country and age group. However, the sponsor did not provide any information on site monitoring. There were no convincing explanations for these differences. Given the possible concerns regarding the conduct in the Indian sites and the lack any information of site monitoring, the FDA conducted an inspection at the two largest sites in India and two sites in the USA. This led to a 3-month extension. Conclusions from the FDA's inspection were that the data from all four sites were reliable. Therefore, the review team considered the inclusion of the Indian site acceptable. The conclusions and recommendations from the statistical review dated 11/21/16 remain.

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/s/

XIANBIN LI
03/27/2017

KAREN M HIGGINS
03/27/2017
I concur.