

FDA Briefing Document Addendum
Iclaprim for the Treatment of Complicated Skin and Skin Structure Infections

Modified FDA Analysis

Since preparation of the FDA briefing document, the FDA reviewers have revised their efficacy analyses of the ASSIST-1 and ASSIST-2 trials. In the briefing document, 17 patients who were considered cured in the sponsor’s analyses were assigned indeterminate outcomes by FDA reviewers because they received systemic antimicrobials after the start of study drug.

For this analysis, the medical officer reviewed the case report forms for this group of patients, without knowledge of the specific treatment given (iclaprim or linezolid). The reviewer assigned each of the 17 patients an outcome of cured, failed or indeterminate, based on the information in the case report form and central microbiology lab data in submitted files.

The following tables show the FDA reviewers’ revised analyses. The table numbers here are the same as the related tables in the FDA briefing document. The figures that have been changed from the original briefing document are shown in italics.

Table 6.3: Clinical Cure at TOC – Primary Efficacy Populations

	ASSIST-1		ASSIST-2	
	Iclaprim	Linezolid	Iclaprim	Linezolid
ITT	N = 249	N = 248	N = 251	N = 243
Clinical cure, n (%)	<i>204 (81.9%)</i>	220 (88.7%)	<i>201 (80.1%)</i>	<i>198 (81.5%)</i>
Treatment difference (iclaprim – linezolid) and [95% CI]	<i>-6.8% [-13.0%, -0.5%]</i>		<i>-1.4% [-8.3%, 5.6%]</i>	
PP	N = 206	N = 213	N = 209	N = 195
Clinical cure, n (%)	<i>192 (93.2%)</i>	211 (99.1%)	<i>185 (88.5%)</i>	<i>187 (95.9%)</i>
Treatment difference (iclaprim – linezolid) and [95% CI]	<i>-5.9% [-10.2%, -2.2%]</i>		<i>-7.4% [-12.8%, -2.1%]</i>	

FDA Analyses

Table 6.4: Clinical Cure at TOC Visit in ASSIST-1– All Primary Efficacy Populations by Geographic Region

	North America		Eastern Europe	
	Iclaprim	Linezolid	Iclaprim	Linezolid
ITT	N = 52	N = 53	N = 197	N = 195
Clinical cure, n (%)	34 (65.4%)	41 (77.4%)	170 (86.3%)	179 (91.8%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-12.0% [-28.4%, 5.3%]		-5.5% [-11.8%, 0.7%]	
PP	N = 36	N = 38	N = 170	N = 175
Clinical cure, n (%)	29 (80.6%)	36 (94.7%)	163 (95.9%)	175 (100%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-14.2% [-30.2%, 1.3%]		-4.1% [-8.3%, -1.1%]	

Table 6.5: Clinical Cure at TOC Visit in ASSIST-2– All Primary Efficacy Populations by Geographic Region

	North America		Rest of the World	
	Iclaprim	Linezolid	Iclaprim	Linezolid
ITT	N = 148	N = 142	N = 103	N = 101
Clinical cure, n (%)	115 (77.7%)	106 (74.6%)	86 (83.5%)	92 (91.1%)
Treatment difference (iclaprim – linezolid) and [95% CI]	3.1% [-6.7%, 12.8%]		-7.6% [-16.9%, 1.7%]	
PP	N = 123	N = 108	N = 86	N = 87
Clinical cure, n (%)	107 (87.0%)	101 (93.5%)	78 (90.7%)	86 (98.9%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-6.5% [-14.3%, 1.4%]		-8.1% [-16.2%, -1.4%]	

Table 6.6: Clinical Cure at TOC Visit– ITT Population by Type of Infection⁴

	ASSIST-1						ASSIST-2					
	Iclaprim			Linezolid			Iclaprim			Linezolid		
	Cured	Total	Rate	Cured	Total	Rate	Cured	Total	Rate	Cured	Total	Rate
Infected ulcers, First or second degree burns	34	37	91.9	33	36	91.7	17	22	77.3	14	18	77.8
Major abscess	27	34	79.4	25	31	80.7	12	15	80.0	19	22	86.4
Deep or extensive cellulitis	40	53	75.5	47	53	88.7	60	76	79.0	55	71	77.5
Wound infections	96	121	79.3	104	117	88.9	52	71	73.2	55	69	79.7
	20	29	69.0	36	43	83.7	94	112	83.9	92	111	82.9

Table 6.7: Clinical Cure at TOC – MITT and MEPP Populations

	ASSIST-1		ASSIST-2	
	Iclaprim	Linezolid	Iclaprim	Linezolid
MITT	N = 183	N = 191	N = 192	N = 184
Clinical cure, n (%)	149 (81.4%)	170 (89%)	153 (79.7%)	149 (81.0%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-7.6% [-14.9%, -0.3%]		-1.3% [-9.3%, 6.8%]	
MEPP	N = 150	N = 167	N = 165	N = 149
Clinical cure, n (%)	139 (92.7%)	165 (98.8%)	143 (86.7%)	142 (95.3%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-6.1% [-11.5%, -1.7%]		-8.6% [-15.1%, -2.2%]	

Table 6.8: Clinical Cure at TOC visit by Pathogen - MITT Population

Baseline Gram-positive Pathogen	ASSIST-1						ASSIST-2					
	Iclaprim (N = 183)			Linezolid (N = 191)			Iclaprim (N = 192)			Linezolid (N = 184)		
	Cure	Tot	Rate	Cure	Tot	Rate	Cure	Tot	Rate	Cure	Tot	Rate
<i>Staphylococcus aureus, total</i>	115	138	83.3	131	144	91.0	117	149	78.5	130	160	81.3
<i>S. aureus, MRSA</i>	36	45	80.0	34	36	94.4	56	74	75.7	62	80	77.5
<i>S. aureus, MSSA</i>	79	93	84.9	97	108	89.8	61	73	83.6	67	78	85.9
<i>Streptococcus pyogenes</i>	24	30	80.0	30	34	88.2	21	28	75.0	19	22	86.4
<i>Enterococcus faecalis</i>	11	14	78.6	11	13	84.6	13	15	86.7	14	15	93.3
<i>Streptococcus agalactiae</i>	1	3	33.3	4	7	57.1	3	5	60.0	4	4	100

Errata:

Please note the following corrections for the FDA briefing document for iclaprim

Page 4, Table 2.1: For ASSIST-1, there were 59 centers in this study, not 9.

Page 13: The definition of indeterminate outcomes should read as follows:

Indeterminate: conditions for “Cure” and conditions for “Failure” were not met and for EOT: patients who had <4 days or <7 doses of treatment but did fulfill all other criteria for “Cure;” For TOC: patients who had <4 days or <7 doses of treatment but did fulfill all other criteria for “Cure” or patients with “Cure” at EOT but no TOC visit;

Page 17: The first paragraph on this page states “Thirty-four patients from the ITT population have been excluded from the analysis by the sponsor due to co-medication with prohibited antibiotics and/or steroids...” This should be corrected to state that

“Thirty-four patients from the ITT population were considered to have indeterminate or failure outcomes due to co-medication with prohibited antibiotics and/or steroids...”

Page 22, Table of Combined Phase 3 Data: For any TEAE causing discontinuation, there were 12 (2.4%) iclaprim patients, not 11(2.2%). Also, there were 12 (2.4%) linezolid patients with any TEAE causing discontinuation, not 6 (1.2%). For deaths, there were 2 (0.4%) linezolid patients, not 1 (0.2%).