Food and Drug Administration

Antimicrobial Drugs Advisory Committee

Errata for the FDA Briefing Document

Applicant: Shionogi, Inc.
NDA 209445

October 16, 2019

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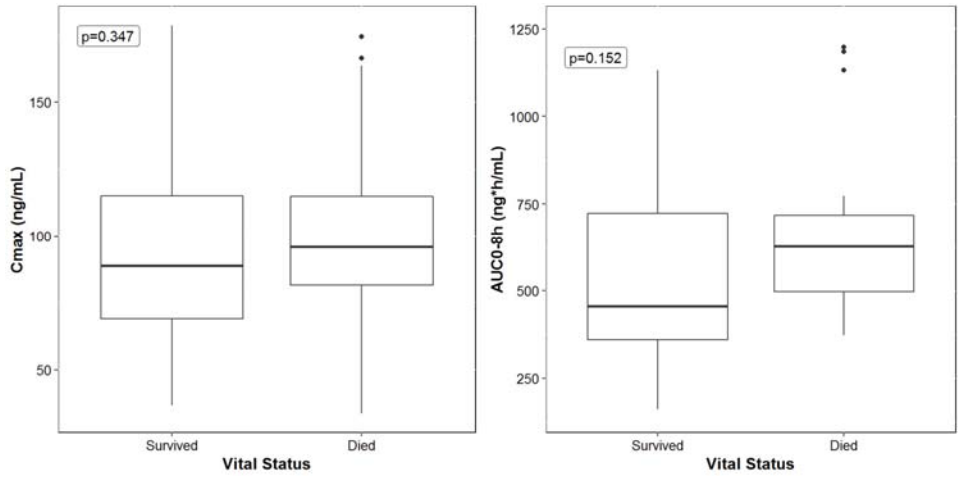
1) Page 18 states that "In this Micro-ITT Population used for the primary efficacy analysis, there were 290 subjects in the cefiderocol group and 147 subjects in the IMP group." This sentence should say that there were 252 subjects in the cefiderocol group and 119 subjects in the IMP group.
2) Page 34 states that "The vitamin K antagonists (acenocoumarol, warfarin, warfarin potassium, and warfarin sodium) were reported as concomitant medications in more patients in the cefiderocol group, 5.7% (17/300) than in the IMP group, 2% (23/148)." This sentence should be changed to "The vitamin K antagonists (acenocoumarol, warfarin, warfarin potassium, and warfarin sodium) were reported as concomitant medications in more patients in the cefiderocol group, 5.7% (17/300) than in the IMP group, 2% (3/148).
3) Page 38 correctly states regarding the CREDIBLE-CR trial that "The Agency recommended that an independent DSMB monitor patient safety" after the Applicant notified the Agency of mortality rates on September 1, 2017. However, we would like to clarify that the Applicant independently began organizing a Medical Review Committee in August 2017 based on its observation of mortality rates and planned to convert this committee to an independent DSMB.
4) Pages 44-45 state that "Day 49 mortality was assessed because it almost completely coincided with mortality through the EOS visit, with the difference being that it additionally included one patient in the BAT group who died on Day 43 with unknown cause of death. The Day 49 all-cause mortality was analyzed because it included more events and because there were numerical trends with higher cefiderocol mortality at later times. However, Day 49 mortality results were limited by missing data." We would like to clarify that missing data at Day 49 did not represent protocol violations because with limited exceptions mortality was only to be captured through the End of Study (EOS) visit 28 days after the end of treatment. The Day 49 all-cause mortality results were displayed because this was a post-randomization timepoint considered reasonable given numerical trends, and because results closely aligned with mortality results through the EOS visit.
5) On Page 49, the subsection "Comparison of Cefiderocol Exposures by Survival Status" which reads as follows:

"In CREDIBLE-CR study, the steady-state cefiderocol Cmax and $AUC_{0\text{-}8h}$ (post-hoc estimates) in patients who survived (N=57) were comparable with those in patients who died (N=22) (Figure Error**! No text of specified style in document.**.1), indicating that there was no apparent association between cefiderocol exposure and death.

Figure Error! No text of specified style in document.**.1: Comparisons of the Cmax and $AUC_{0\text{-}8h}$ between patients who survived (N=57) *versus* patients who died (N=22).**



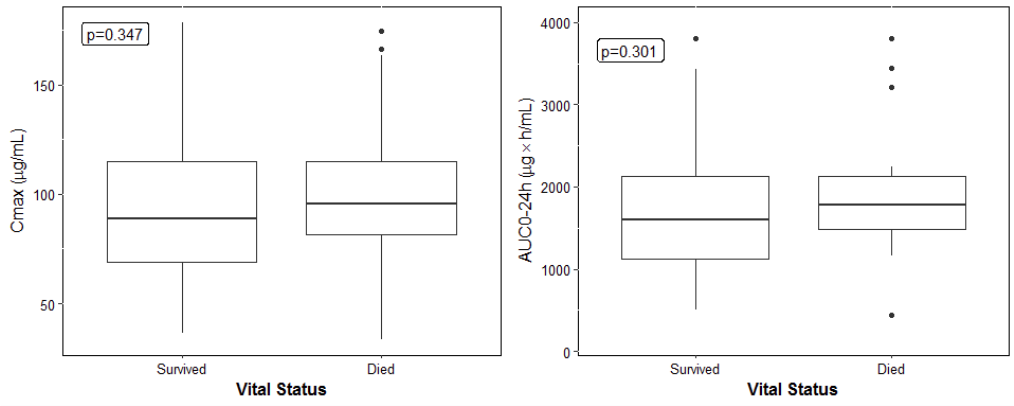
Cmax was measured at the end of drug infusion at steady state. $AUC_{0\text{-}8h}$ values were post-hoc estimates of AUC during a dosing interval at steady state.

Source: Clinical Pharmacology reviewer "

Should be changed to the following:

"In CREDIBLE-CR study, the steady-state cefiderocol Cmax and $AUC_{0\text{-}24h}$ (post-hoc estimates) in patients who survived (N=57) were comparable with those in patients who died (N=20) (Figure 9.3), indicating that there was no apparent association between cefiderocol exposure and death.

Figure 9.3: Comparisons of the Cmax and $AUC_{0\text{-}24h}$ in patients who survived (N=57) *versus* patients who died (N=20).



Cmax was measured at the end of drug infusion at steady state. $AUC_{0\text{-}24h}$ values were post-hoc estimates of daily AUC at steady state. 77 out of a total of 101 patients who received cefiderocol treatment provided evaluable cefiderocol concentration data.
Source: Clinical Pharmacology reviewer ”

6) Page 59 states that “Patient #20 had a new pathogen (*C. meningosepticum*) in sputum culture…” This sentence should be changed to Patient #20 had a new pathogen (*E. meningoseptica*) in sputum culture…”
7) Page 67 states that meropenem was dosed at 1 gram in the APEKS-NP study. However, it was a 2 gram dose.
8) Table 9-9 on page 47, the total count in the cefiderocol group should be changed to “3 (3.0)” not “2 (2.0)” in the general and administration primary SOC. Also, the total count in the BAT group should be changed to “1 (2.0)” not “(0).”
9) Table 9-17 on page 58, the footnote should be changed from “elevated liver tests include AST, ALT, transaminases increased, liver function test abnormal, hepatic function abnormal” to “elevated liver tests include AST, ALT, transaminases increased, liver function test abnormal, hepatic function abnormal, and hepatic enzyme increased.”
10) Table 9-18, on page 61, there are two rows for PT “hepatic cirrhosis” and it should only be one row.
11) Page 62 states “The patient had no prior history of liver disease…”should be changed to “The patient had no history of chronic liver disease...”.