Platelet Counts in Contezolid Complicated Skin and Soft Tissue Infection Phase 2 and Phase 3 Clinical Trials

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Background

Contezolid (CZD; formerly MRX-I) is a novel oral (PO) oxazolidinone antibacterial with potent activity against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococccus* (VRE). Nonclinical and Phase 1 (Ph1) clinical data indicate CZD causes less myelosuppression, particularly with longer duration therapy, and with reduced risk of monoamine oxidase inhibition compared with linezolid (LZD).

In Phase 2 (Ph2) and Phase 3 (Ph3) complicated skin and soft tissue infections (cSSTI) clinical trials, CZD was compared with LZD with dosing for 7-14 days, and efficacy noninferiority was demonstrated in the Ph3 study. Overall safety profile was comparable to LZD, and the most common treatment emergent adverse events (TEAEs) in both the CZD and LZD groups were gastrointestinal; however, hematologic laboratory abnormalities and TEAEs were less common with CZD. In June 2021, CZD was approved in China for cSSTI.

Sequential therapy with intravenous contezolid acefosamil (CZA; prodrug of CZD; formerly MRX-4) followed by CZD PO is being evaluated in global Ph3 diabetic foot infection (DFI) and acute bacterial skin and skin structure infection (ABSSSI) clinical trials. Because DFI requires longer treatment (14-28 days), changes in platelet counts were evaluated in completed Ph2 and Ph3 CZD cSSTI studies, including subsets of subjects who received therapy for ≥11 days.

Methods

In Ph2 and Ph3 cSSTI studies, subjects received CZD or LZD for 7-14 days. Mean percent changes in platelet counts from baseline (BSL) to the end of therapy (EOT) visit were compared for all subjects in the safety analysis sets (SS) who received CZD 800 mg and LZD.

Some subjects in the SS received therapy for ≥11 days, and changes from BSL to EOT were also compared between CZD 800 mg and LZD subjects in these subsets.

Table 1

Study	Dose Regimens	Subjects Enrolled	
		CZD	LZD
Ph2 cSSTI (MRX-I-04)	CZD 600 or 800 mg PO q12h x7-14 days vs LZD 600 mg PO q12h x7-14 days	143	73
Ph3 cSSTI (MRX-I-06)	CZD 800 mg PO q12h x7-14 days vs LZD 600 mg PO q12h x7-14 days	360	359

Results

In the Ph2 and Ph3 cSSTI studies, subjects in the SS who received 7-14 days of study drug had a greater percentage decrease in platelet count from BSL to EOT in the LZD groups compared with the CZD groups, and with a large difference in the proportion of subjects that were observed to have a greater than 30% decrease in platelet counts from BSL to EOT.

In these cSSTI studies, the differences in platelet count decreases between the CZD and LZD groups was even greater among subjects that received ≥11 days of study drug, with both percentage decrease from BSL to EOT, and in the proportion of subjects with >30% decrease.

Results (continued)

Table 2

Ph2 MRX-I-04		CZD 800 mg	LZD	P-value
All SS subjects	Number of subjects	70	71	-
	% change in platelet count from BSL to EOT (mean (SD))	9.52% (25.7%)	-2.61% (28.0%)	0.0081
	% subjects with greater than 30% decrease in platelet count from BSL to EOT	1.4%	16.9%	0.0022
SS subjects who received study drug ≥11 days	Number of subjects	30	32	-
	% change in platelet count from BSL to EOT (mean (SD))	13.9% (28.0%)	-8.35% (34.0%)	0.007
	% subjects with greater than 30% decrease in platelet count from BSL to EOT	0	31.3%	0.0009

Table 3

Ph3 MRX-I-06		CZD	LZD	P-value
All SS subjects	Number of subjects	333	336	-
	% change in platelet count from BSL to EOT (mean (SD))	15.62% (28.4%)	-2.72% (29.2%)	<0.001
	% subjects with greater than 30% decrease in platelet count from BSL to EOT	1.8%	16.4%	<0.001
SS subjects who received study drug ≥11 days	Number of subjects	204	201	-
	% change in platelet count from BSL to EOT (mean (SD))	13.5% (29.8%)	-11.11% (28.2%)	<0.001
	% subjects with greater than 30% decrease in platelet count from BSL to EOT	2.5%	25.4%	<0.001

Conclusions

In the Ph2 and Ph3 cSSTI clinical trials with treatment durations of 7-14 days, mean platelet counts did not decrease for CZD subjects while mean values for LZD subjects did decline, consistent with nonclinical and Ph1 clinical data. Differences were more significant in subjects who received ≥11 days of therapy. In the current Ph3 global DFI study which compares 14-28 days of CZA/CZD to LZD, evaluation of hematological safety is an important outcome measure.