Efficacy and Safety in Subjects with Renal Impairment in Contezolid and Contezolid Acefosamil Phase 2 and Phase 3 Skin Infection Clinical Trials

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Background

Contezolid (CZD; formerly MRX-I) is a novel oral (PO) oxazolidinone with potent activity against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enteroccocus* (VRE). Contezolid acefosamil (CZA; formerly MRX-4) is a double prodrug intravenous (IV) formulation of CZD. Nonclinical and initial clinical data indicate CZA and CZD cause less myelosuppression, particularly with longer duration therapy, and with reduced risk of monoamine oxidase inhibition compared with linezolid (LZD).

In three CZD Phase 2 (Ph2) and Phase 3 (Ph3) skin infection trials and a CZA Ph2 acute bacterial skin and skin structure infection (ABSSSI) study, primary efficacy and overall safety outcomes were comparable to LZD. The most common treatment emergent adverse events (TEAEs) were gastrointestinal; however, hematologic laboratory abnormalities and TEAEs were less common with CZD and CZA. In June 2021, CZD was approved in China for complicated skin and soft tissue infections (cSSTI).

Sequential therapy with CZA IV followed by CZD PO is being evaluated in global Ph3 diabetic foot infection (DFI) and ABSSSI clinical trials. Because patients with diabetes commonly have diminished kidney function, efficacy and safety outcomes in subjects with renal impairment were evaluated in completed Ph2 and Ph3 CZD and CZA studies

Methods

In 4 CZD and CZA Ph2 and Ph3 skin infection trials, subjects were included with estimated creatinine clearance (CLcr) of 60 to <90 mL/min (mild impairment) and 30 to <60 mL/min (moderate impairment). no dose adjustments were made for renal function status.

Primary efficacy outcomes and occurrence of TEAEs were evaluated for CZD and CZA subjects with no renal impairment (CLcr ≥90 mL/min), and those with mild and moderate renal impairment

Table 1

Study	Primary Efficacy Outcome	Dose Regimens	Subjects Enrolled	
			CZD or CZA	LZD
CZD Ph2 ABSSSI (MRX-I-03)	Lesion size reduction ≥20% at Early Assessment (48-72 hours after first dose)	CZD 800 mg PO q12h x10 days vs LZD 600 mg PO q12h x10 days	80	40
CZD Ph2 cSSTI (MRX-I-04)	Clinical cure at Test of Cure (7-14 days after last dose)	CZD 600 or 800 mg PO q12h x7-14 days vs LZD 600 mg PO q12h x7-14 days	143	73
CZD Ph3 cSSTI (MRX-I-06)	Clinical cure at Test of Cure (7-14 days after last dose)	CZD 800 mg PO q12h x7-14 days vs LZD 600 mg PO q12h x7-14 days	360	359
CZA Ph2 ABSSSI (MRX4-201)	Lesion size reduction ≥20% at Early Assessment (48-72 hours after first dose)	CZA 1500 mg IV loading dose, then 1000 mg IV or 1300 mg PO q12h x10-14 days vs LZD 600 mg IV/PO q12h x10-14 days	131	65

Results

Primary efficacy outcomes for CZD and CZA subjects with mild or moderate renal impairment were similar to that of subjects with no impairment in 4 skin infection trials. Occurrence of TEAEs was also similar between subjects with no renal impairment and subjects with mild or moderate impairment.

Results (continued)

Table 2

Study	Primary Efficacy Outcome by Renal Impairment Category (CZD or CZA subjects; % (n/N))		
	No	Mild	Moderate
CZD Ph2 ABSSSI (MRX-I-03)	89.6% (69/77)	100% (3/3)	-
CZD Ph2 cSSTI (MRX-I-04)	93.1% (81/87)	91.7% (22/24)	100% (5/5)
CZD Ph3 cSSTI (MRX-I-06)	93.1% (202/217)	92.5% (62/67)	87.5% (7/8)
CZA Ph2 ABSSSI (MRX4-201)	83.5% (86/103)	83.3% (15/18)	50.0% (1/2)

Table 3

Study	TEAEs by Renal Impairment Category (CZD or CZA subjects with at least 1 TEAE; % (n/N))		
	No	Mild	Moderate
CZD Ph2 ABSSSI (MRX-I-03)	58.4% (45/77)	66.7% (2/3)	-
CZD Ph2 cSSTI (MRX-I-04)	44.4% (52/117)	37.9% (11/29)	37.5% (3/8)
CZD Ph3 cSSTI (MRX-I-06)	48.6% (125/257)	43.7% (38/87)	50.0% (5/10)
CZA Ph2 ABSSSI (MRX4-201)	16.5% (17/103)	16.7% (3/18)	0% (0/2)

Conclusions

In four completed Ph2 and Ph3 skin infection clinical trials, subjects who received CZD or CZA with mild and moderate renal impairment had comparable primary efficacy and safety outcomes to subjects with no impairment. This data supports current Ph3 global DFI and ABSSSI studies which will enroll subjects with reduced kidney function, and administer the same doses of CZA IV and CZD PO to all subjects.