Efficacy and Safety by BMI Category and Gender 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 multidrug-resistant Gram-positive pathogens. Contezolid acefosamil (CZA; formerly MRX-4) is an intravenous (IV) prodrug 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 to 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. Body weight and gender can affect drug pharmacokinetics (PK) and potentially efficacy and safety outcomes, though in CZA and CZD Phase 1 (Ph1) pharmacokinetics (PK) studies, variations between male and female healthy subjects were not considered to be significant. Efficacy and safety outcomes for male and female patients, and for subjects of different body mass index (BMI) were evaluated in completed Ph2 and Ph3 CZD and CZA studies.

BMI Categories (FDA Guidance for Industry Developing Products for Weight Management)

Classification	BMI
Underweight	< 18.5 kg/m2
Normal weight	18.5 kg/m2 – 24.9 kg/m2
Overweight	25 kg/m2 – 29.9 kg/m2
Obesity (class 1)	30 kg/m2 – 34.9 kg/m2
Obesity (class 2)	35 kg/m2 – 39.9 kg/m2
Extreme obesity (class 3)	≥ 40 kg/m2

Methods

In 4 CZD and CZA Ph2 and Ph3 skin infection trials, men and women were enrolled with no weight restrictions, and no dose adjustments were made for gender or BMI Primary efficacy outcomes and occurrence of TEAEs were evaluated for CZD and CZA subjects in 3 BMI categories consistent with FDA guidance for weight management products.

Due to the relatively small proportion of subjects with BMI in the highest categories, data from subjects with BMI ≥30 kg/m^2 were combined. Primary efficacy outcomes and TEAEs were also assessed in male and female subjects.

Table 1

Study	Primary Efficacy Outcome	Dose Regimens	Subjects	
			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 and incidence of TEAEs were comparable for CZD and CZA subjects in 3 different BMI categories in 4 skin infection clinical trials. Outcomes for primary efficacy and occurrence of TEAEs also were comparable between male and female subjects. Figure 2

Results (continued)

Table 2

Study	Primary Efficacy Outcome by BMI Category (CZD or CZA subjects; % (n/N))			Primary Efficacy Outcome by Gender (CZD or CZA subjects: % (n/N))	
	BMI <25 kg/m^2	BMI 25 to <30 kg/m^2	BMI ≥30 kg/m^2	Male	Female
CZD Ph2 ABSSSI (MRX-I-03)	93.8% (30/32)	86.2% (25/29)	89.5% (17/19)	90.6% (48/53)	88.9% (24/27)
CZD Ph2 cSSTI (MRX-I-04)	94.6% (70/74)	93.9% (31/33)	87.5% (7/8)	92.0% (80/87)	100 % (28/28)
CZD Ph3 cSSTI (MRX-I-06)	95.4% (145/152)	87.2% (82/94)	95.7% (44/46)	92.1% (174/189)	94.2% (97/103)
CZA Ph2 ABSSSI (MRX4-201)	73.8% (45/61)	80.0% (32/40)	83.3% (25/30)	78.5% (62/79)	76.9% (40/52)

Table 3

Study	TEAEs by BMI Category (CZD or CZA subjects with at least 1 TEAE; % (n/N))			TEAEs by Gender (CZD or CZA subjects with at least 1 TEAE; % (n/N))	
	BMI <25 kg/m^2	BMI 25 to <30 kg/m^2	BMI ≥30 kg/m^2	Male	Female
CZD Ph2 ABSSSI (MRX-I-03)	56.3% (18/32)	62.1% (18/29)	57.9% (11/19)	60.4% (32/53)	55.6% (15/27)
CZD Ph2 cSSTI (MRX-I-04)	42.7% (41/96)	44.7% (21/47)	36.4% (4/11)	36.9% (41/111)	58.1% (25/43)
CZD Ph3 cSSTI (MRX-I-06)	44.9% (83/185)	49.1% (56/114)	52.7% (29/55)	45.6% (104/228)	50.8% (64/126)
CZA Ph2 ABSSSI (MRX4-201)	12.1% (7/58)	15.8% (6/38)	25.9% (7/27)	16.0% (12/75)	16.7% (8/48)

Conclusions

In four completed Ph2 and Ph3 skin infection clinical trials, primary efficacy and safety outcomes were comparable between male and female subjects, and also for subjects of varying BMI. These findings support the current Ph3 global DFI and ABSSSI studies which will enroll men and women with no body weight restrictions, and administer a fixed dose regimen of CZA IV and CZD PO.