An Analysis of Pooled Efficacy Data from Two Phase 3 Trials of Iclaprim Compared to Vancomycin for the Treatment of Acute Bacterial Skin and Skin Structure Infections

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ABSTRACT

Background: The objective of this evaluation was to provide an analysis of pooled efficacy data from two parallel Phase 3 trials of iclaprim, a diaminopyrimidine, compared to vancomycin for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI).

Methods: Two parallel Phase 3, double-blind, randomized (1:1), active-controlled, multinational, multicenter trials (REVIVE-1 and REVIVE-2) including a total of 1,198 patients with ABSSSI, were analyzed separately and then pooled to determine the efficacy of iclaprim 80 mg fixed dose compared with vancomycin 15 mg/kg. Both drugs were administered intravenously every 12 hours for 5 to 14 days with the length of treatment dependent on investigator assessment of clinical response. The primary endpoint of these studies was to determine whether iclaprim was non-inferior (NI; 10% margin) to vancomycin in achieving a ≥20% reduction in lesion size (early clinical response [ECR] at 48 to 72 hours after initiation of the study drug (early time point [ETP]), compared to baseline, in the intent-to-treat (ITT) population.

Results: Iclaprim achieved NI compared to vancomycin for ECR at the ETP in two Phase 3 studies of ABSSSI compared to vancomycin (Table). The median treatment duration for both iclaprim and vancomycin was 7 days (minimum 5 days, maximum 14 days).

Conclusion: Iclaprim was efficacious in two Phase 3 trials for the treatment of ABSSSI. Iclaprim met its primary endpoint of NI to vancomycin in both studies, based on ECR at ETP, separately and pooled in two Phase 3 trials, compared to vancomycin. These results suggest that iclaprim is a valuable treatment option for patients with ABSSSI caused by suspected or confirmed to be due to Gram-positive pathogens.

BACKGROUND

- Iclaprim is a novel diaminopyrimidine antibiotic, which inhibits bacterial dihydrofolate reductase, a critical enzyme in the bacterial folate synthesis pathway.
- Iclaprim is active against MRSA resistant or nonsusceptible to vancomycin, linezolid and daptomycin [1].
- In two Phase 3 clinical trials, iclaprim has shown clinical response comparable to vancomycin among patients treated for skin and skin structure infections [2,3].
- This evaluation provides an analysis of efficacy data from two parallel Phase 3 trials.

METHODS

- Two parallel Phase 3, double-blind, randomized (1:1), active-controlled, multinational, multicenter trials (REVIVE-1 and REVIVE-2) including a total of 1,198 patients with ABSSSI, were analyzed separately and then pooled to determine the efficacy of iclaprim 80 mg q12h fixed dose compared with vancomycin 15 mg/kg.
- Both drugs were administered intravenously every 12 hours for 5 to 14 days with the length of treatment dependent on investigator assessment of clinical response.
- The primary endpoint of these studies was to determine whether iclaprim was non-inferior (NI; 10% margin) to vancomycin in achieving a ≥20% reduction in lesion size (early clinical response [ECR] at 48 to 72 hours after initiation of the study drug (early time point [ETP]), compared to baseline, in the intent-to-treat (ITT) population.

RESULTS

- Baseline demographics are shown in Table 1.
- Iclaprim achieved NI compared to vancomycin for ECR at the ETP, separately and pooled, in two Phase 3 trials of ABSSSI compared to vancomycin (Table 2).
- The median treatment duration for both iclaprim and vancomycin was 7 days (minimum 5 days, maximum 14 days).

RESULTS

Table 1: Baseline and demographic characteristics among ITT population be treatment in REVIVE trials

	REVIVE-1		REVIVE-2		Pooled REVIVE	
Characteristics	Iclaprim (n=298)	Vancomycin (n=300)	Iclaprim (n=295)	Vancomycin (n=305)	Iclaprim (n=593)	Vancomycin (n=605)
Age, year *	46.4 (13.3)	48.2 (14.8)	50.0 (15.7)	50.8 (15.0)	48.2 (14.6)	49.5 (15.0)
Female, n (%)	109 (36.6)	129 (43.0)	103 (34.9)	108 (35.4)	212 (35.8)	237 (39.2)
Race, n (%)						
White	266 (89.3)	269 (89.7)	267 (90.5)	276 (90.5)	533 (89.9)	545 (90.1)
Black	4 (1.3)	7 (2.3)	12 (4.1)	11 (3.6)	16 (2.7)	18 (3.0)
Other	28 (9.4)	24 (8.0)	16 (5.4)	18 (5.9)	44 (7.4)	42 (6.9)
Weight, kg *	80.5 (20.0)	80.3 (18.2)	84.2 (20.8)	85.5 (22.2)	82.3 (20.5)	82.9 (20.4)
Lesion Type, n (%)						
Major Cutaneous Abscess	40 (13.4)	55 (18.3)	53 (18.0)	45 (14.8)	93 (15.7)	100 (16.5)
Cellulitis / Erysipelas	76 (25.5)	87 (29.0)	115 (39.0)	125 (41.0)	191 (32.2)	212 (35.0)
Wound Infection	182 (61.1)	158 (52.7)	127 (43.1)	135 (44.3)	309 (52.1)	293 (48.4)
Mean lesion Size, cm^2 *	333 (317.1)	337 (317.5)	372.3 (305.8)	357.0 (271.1)	352.6 (311.8)	347.2 (295.0)
Comorbidities, n (%)						
Diabetes	20 (6.7)	35 (11.7)	36 (12.2)	36 (11.8)	56 (9.4)	71 (11.7)
CrCL <90 ml/min, n (%)	36 (12.1)	56 (18.7)	54 (18.5)	68 (23.0)	90 (15.5)	124 (21.2)
Illicit drug use, n (%)	189 (63.4)	149 (49.7)	137 (46.4)	152 (49.8)	326 (55.0)	301 (49.8)
Only Gram-positive pathogens, n (%)	211 (70.8)	200 (66.3)	170 (57.6)	167 (54.8)	381 (64.2)	366 (60.5)
Mixed Gram-positive and Gram-negative, n (%)	23 (7.7)	21 (7.3)	20 (6.8)	27 (8.9)	43 (7.3)	49 (8.1)

Table 2: Early clinical response at the early time point among ITT population by treatment in REVIVE trials

	REVIVE-1		REVIVE-2		Combined REVIVE-1/2	
	Iclaprim (N=298)	Vancomycin (N=300)	Iclaprim (N=295)	Vancomycin (N=305)	Iclaprim (N=593)	Vancomycin (N=605)
Early Clinical Response, n (%)	241 (80.9)	243 (81.0)	231 (78.3)	234 (76.7)	472 (79.6)	477 (78.8)
% Difference (iclaprim-vancomycin)	-0.13		1.58		0.75	
95% CI	-6.42, 6.17		-5.10, 8.26		-3.84, 5.35	

CONCLUSIONS

- Iclaprim was efficacious in two Phase 3 trials for the treatment of ABSSSI.
- Iclaprim met its primary endpoint of NI to vancomycin, based on ECR at ETP, separately and pooled in two Phase 3 trials, compared to vancomycin.
- These results suggest that iclaprim is a valuable treatment option for patients with ABSSSI suspected or confirmed to be due to Gram-positive pathogens.

REFERENCES

1. Huang DB, et al. Can J Infect Dis Med Microbiol. 2017.
2. Huang DB, et al. Clin Infect Dis. 2017.
3. Holland T, et al. AAC. 2018.

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