An Analysis of Pooled Safety 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 safety data from two 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 Phase 3, double-blind, randomized (1:1), active-controlled, multinational, multicenter trials (REVIVE-1 and REVIVE-2) treating a total of 1,191 patients with ABSSSI, were analyzed separately and pooled to determine the safety of iclaprim 80 mg compared with vancomycin 15mg/kg. All patients who received any study drug were included in this analysis for safety.

Results: Iclaprim was well tolerated in two Phase 3 studies of ABSSSI compared to vancomycin. TEAEs reported in >2% of patients in any treatment group are summarized (Table). In most patients the events were mild to moderate in severity, events of severity were reported in <5% of all patients. The median treatment duration for both iclaprim and vancomycin was 7 days (minimum 5 days, maximum 14 days).

No deaths occurred among patients treated with iclaprim. The causes of the three deaths occurring among patients treated with vancomycin were heroin overdose, cardiac arrest, and sudden death. AST (2.0% and 2.0%) and ALT (1.9% and 2.0%) increases were similar between iclaprim and vancomycin. Three and one patients had a QTc prolongation (>60 msec compared to baseline) among patients treated with iclaprim and vancomycin, respectively.

Conclusion: Iclaprim was well tolerated compared to vancomycin in two Phase 3 trials for the treatment of ABSSSI. Iclaprim was well tolerated with a low rate of drug related adverse events.

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 pooled safety data from two Phase 3 trials.

METHODS

- Two Phase 3, double-blind, randomized (1:1), active-controlled, multinational, multicenter trials (REVIVE-1 and REVIVE-2) treating a total of 1,191 patients with ABSSSI, were analyzed separately and pooled to determine the safety of iclaprim 80 mg q12h compared with vancomycin 15mg/kg.
- All patients who received any study drug were included in this analysis for safety.

RESULTS

- Iclaprim was well tolerated in two Phase 3 studies of ABSSSI compared to vancomycin. TEAEs reported in >2% of patients in any treatment group are summarized in Table 1.
- In most patients the events were mild to moderate in severity, events of severity were reported in <5% of all patients.
- The median treatment duration for both iclaprim and vancomycin was 7 days (minimum 5 days, maximum 14 days).
- No deaths occurred among patients treated with iclaprim. The causes of the three deaths occurring among patients treated with vancomycin were heroin overdose, cardiac arrest, and sudden death.
- AST (2.0% and 2.0%) and ALT (1.9% and 2.0%) increases were similar between iclaprim and vancomycin. Three and one patients had a QTc prolongation (>60 msec compared to baseline) among patients treated with iclaprim and vancomycin, respectively.
- Acute kidney injury or elevated serum creatinine occurred in 7 patients treated with vancomycin and in 0 patients treated with iclaprim.

RESULTS

Table 1: Adverse events, n(%), reported in the REVIVE trials by treatment

	REVIVE-1		REVIVE-2		Combined REVIVE-1/2	
	Iclaprim (N=293)	Vancomycin (N=297)	Iclaprim (N=299)	Vancomycin (N=302)	Iclaprim (N=592)	Vancomycin (N=599)
Patients with:						
Any TEAE	151 (51.5)	128 (43.1)	140 (46.8)	133 (44.0)	291 (49.2)	261 (43.6)
Study Drug Related TEAEs	57 (19.5)	53 (17.8)	42 (14.0)	39 (12.9)	99 (16.7)	92 (15.4)
TEAE with Discontinuation of Study Drug	8 (2.7)	13 (4.4)	16 (5.4)	17 (5.6)	24 (4.1)	30 (5.0)
SAEs	9 (3.1)	14 (4.7)	16 (5.4)	14 (4.6)	25 (4.2)	28 (4.7)
Deaths	0	2 (0.7)[4]	0	1 (0.3)	0	3 (0.5)
MedDRA Preferred Terms:						
Nausea	29 (9.9)	17 (5.7)	17 (5.7)	17 (5.6)	46 (7.8)	34 (5.7)
Headache	30 (10.2)	23 (7.7)	7 (2.3)	13 (4.3)	37 (6.3)	36 (6.0)
Cellulitis	9 (3.1)	5 (1.7)	18 (6.0)	9 (3.0)	27 (4.6)	14 (2.3)
Infusion site extravasation	14 (4.8)	12 (4.0)	13 (4.3)	12 (4.0)	27 (4.6)	24 (4.0)
Skin bacterial infection	15 (5.1)	9 (3.0)	8 (2.7)	2 (0.7)	23 (3.9)	11 (1.8)
Vomiting	14 (4.8)	15 (5.1)	7 (2.3)	7 (2.3)	21 (3.5)	22 (3.7)
Pyrexia	12 (4.1)	12 (4.0)	7 (2.3)	5 (1.7)	19 (3.2)	17 (2.8)
Fatigue	18 (6.1)	9 (3.0)	0	4 (1.3)	18 (3.0)	13 (2.2)
Diarrhea	5 (1.7)	14 (4.7)	8 (2.7)	11 (3.6)	13 (2.2)	25 (4.2)
AST increased	6 (2.0)	7 (2.4)	6 (2.0)	5 (1.7)	12 (2.0)	12 (2.0)
Peripheral edema	8 (2.7)	9 (3.0)	4 (1.3)	3 (1.0)	12 (2.0)	12 (2.0)
Alanine aminotransferase increased	6 (2.0)	5 (1.7)	5 (1.7)	7 (2.3)	11 (1.9)	12 (2.0)
Anaemia	5 (1.7)	2 (0.7)	6 (2.0)	6 (2.0)	11 (1.9)	8 (1.3)
Pain in extremity	6 (2.0)	3 (1.0)	5 (1.7)	2 (0.7)	11 (1.9)	5 (0.8)
Hypertension	3 (1.0)	2 (0.7)	7 (2.3)	5 (1.7)	10 (1.7)	7 (1.2)
Hypokalaemia	1 (0.3)	2 (0.7)	6 (2.0)	11 (3.6)	7 (1.2)	13 (2.2)

CONCLUSIONS

- Iclaprim was well tolerated compared to vancomycin in two Phase 3 trials for the treatment of ABSSSI.
- Iclaprim showed a low rate of drug related adverse events.
- There were no adverse events of acute kidney injury or increased creatinine with iclaprim compared to 7 AEs with vancomycin

REFERENCES

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