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EFFICACY AND SAFETY OF TOREZOLID PHOSPHATE (TR-701) IN A DOSE-RANGING PHASE 2 RANDOMIZED, DOUBLE-BLIND STUDY IN PATIENTS WITH SEVERE COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS (cSSSI)

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INTRODUCTION

The objective of this Phase 2 study was to compare efficacy, safety and tolerability of 3 doses of oral torezolid phosphate, a second generation oxazolidinone, in patients with severe cSSSI. Community-acquired MRSA has become an epidemic in the United States and has become a major public health issue requiring new treatment options.[1,2] Torezolid (TR-700) is the active moiety of the prodrug torezolid phosphate (TR-701), an oxazolidinone with 4-16 fold greater activity than linezolid against gram-positive species including MRSA, and has a favorable PK profile allowing once-daily dosing, while retaining activity against linezolid-resistant strains.[3]

STUDY DESIGN

This was a Phase 2 dose-ranging, randomized, double-blind study of oral torezolid phosphate in adult patients diagnosed with severe cSSSI (≥ 5 cm and/or systemic signs of infection). The study was conducted at 12 sites in the United States. Patients were randomized 1:1:1 to 200 mg, 300 mg or 400 mg oral torezolid phosphate once-a-day for 5-7 days. Patients were evaluated at Screening/Day 1, Day 2, Day 3, and 5 (if applicable), and at End of Therapy (EOT), Test of Cure (TOC; 7-14 days post treatment) and Late Follow-Up (LFU; 21-28 days post treatment). The primary efficacy parameter was the clinical response at the TOC visit in the Clinically Evaluable (CE) and clinical Modified Intent-to-Treat (cMITT) patient populations. Secondary objectives included clinical outcome in the Microbiologically Evaluable (ME) population, per pathogen eradication rate, and per pathogen clinical outcome. Safety was monitored in the Modified Intent-to-Treat (MITT) population comprising all patients who took at least one dose of study drug.

Key inclusion criteria

Males or females ≥ 18 to 75 years old; diagnosed with cSSSI requiring oral antimicrobial therapy that had at least one of the following: Abscess with ≥ 2 cm induration or required incision and drainage, Surgical Wound or Post-Traumatic Wound, Deep Cellulitis; presence of 2 or more local symptoms including: erythema, heat/warmth, pain/ tenderness, swelling and/or induration, fluctuance, requirement for drainage of discharge PLUS at least 1 systemic sign of infection: Oral temperature >38°C within previous 24 hours, WBC count >10,000 mm^3, >10% immature neutrophils, OR lesion size ≥5 cm in its longest dimension; suspected or confirmed infection due to a gram-positive organism.

Key exclusion criteria

Uncomplicated SSSI; cSSSI infections requiring gram-negative coverage; more than 24 hours of antibiotic administration within 96 hours prior to randomization for the treatment of the current infection, unless patient is considered a failure of at least 48 hours of previous treatment that was not linezolid; immunocompromised patients.

DEMOGRAPHICS

A total of 192 patients were randomized with 188 receiving at least one dose of study drug of which 64.9% were male and 35.1% were female. The mean age was 36.4 years. The three treatment groups were well balanced across all parameters at Baseline (Table 1).

TABLE 1. Baseline Demographics (MITT Population)

Parameter	200 mg N=63	300 mg N=63	400 mg N=62	All N=188
Age				
Mean (SD)	37.3 (12.1)	36.0 (12.4)	35.8 (12.0)	36.4 (12.1)
Min, Max	18, 62	18, 68	19, 58	18, 68
Gender				
Female	20 (31.7%)	24 (38.1%)	22 (35.5%)	66 (35.1%)
Male	43 (68.3%)	39 (61.9%)	40 (64.5%)	122 (64.9%)
Race				
White	48 (76.2%)	50 (79.4%)	42 (67.7%)	140 (74.5%)
Black	15 (23.8%)	13 (20.6%)	17 (27.4%)	45 (23.9%)
Asian	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Pacific Islander	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Other	0 (0.0%	0 (0.0%)	1 (1.6%)	1 (0.5%)
cSSSI Diagnosis				
Infected Wound	1 (1.6%)	4 (6.3%)	6 (9.7%)	11 (5.9%)
Cellulitis	13 (20.6%)	13 (20.6%)	7 (11.3%)	33 (17.6%)
Severe Abscess	49 (77.8%)	46 (73.0%)	49 (79.0%)	144 (76.6%)
Systemic Signs of Infection	40 (63.5%)	35 (55.6%)	36 (58.1%)	111 (59.0%)
Longest Dimension				
Mean (SD)	14.1 (8.3)	13.9 (7.7)	13.4 (8.0)	13.8 (8.0)
Min, Max	5.2, 46.0	2.8, 42.0	5.0, 42.0	2.8, 46.0
< 5 cm	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
5-10 cm	24 (38.1%)	20 (31.7%)	21 (33.9%)	65 (34.6%)
10-20 cm	24 (38.1%)	30 (47.6%)	31 (50.0%)	85 (45.2%)
≥ 20 cm	15 (23.8%)	12 (19.0%)	10 (16.1%)	37 (19.7%)

CLINICAL OUTCOMES

All 188 patients that received study drug were included in the cMITT population at TOC, 56 (87.5%) patients in the 200 mg cohort, 54 (84.4%) patients in the 300 mg cohort, and 54 (84.4%) patients in the 400 mg cohort were included in the CE population for an overall clinical evaluability of 85.4%. The overall clinical cure rate was 87.8% in the cMITT population and 95.7% in the CE population (Table 2). Mean duration of therapy was 6.4 days.

TABLE 2. Clinical Outcomes at TOC in cMITT, CE and ME Populations

Population	200 mg	300 mg	400 mg	All
cMITT	N=63	N=63	N=62	N=188
Clinical Cure	56 (88.9%)	56 (88.9%)	53 (85.5%)	165 (87.8%)
Clinical Failure*	7 (11.1%)	7 (11.1%)	9 (14.5%)	23 (12.2%)
CE	N=56	N=54	N=54	N=164
Clinical Cure	55 (98.2%)	51 (94.4%)	51 (94.4%)	157 (95.7%)
Clinical Failure	1 (1.8%)	3 (5.6%)	3 (5.6%)	7 (4.3%)
ME	N=43	N=44	N=46	N=133
Clinical Cure	43 (100%)	41 (93.2%)	44 (95.7%)	128 (96.2%)
Clinical Failure	0 (0.0%)	3 (6.8%)	2 (4.3%)	5 (3.8%)

*Failure in cMITT includes patients with an indeterminate outcome (i.e. lost to follow-up)

CLINICAL OUTCOMES Continued

Clinical outcomes were similar for all dosage groups based on lesion type, size of the lesion, and presence of systemic signs of infection (Tables 3, 4, and 5). At TOC, clinical cure rates in microbiologically evaluable (ME) patients with methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA infections were 95.7% and 96.9%, respectively (Table 6).

TABLE 3. Clinical Cure at TOC in the CE Population by Lesion Type

Dosage	Abscess	Wound	Cellulitis
200 mg	43/43 (100%)	1/1 (100%)	11/12 (91.7%)
300 mg	36/38 (94.7%)	3/4 (75%)	12/12 (100%)
400 mg	39/42 (92.9%)	5/5 (100%)	7/7 (100%)

TABLE 4. Clinical Cure at TOC in the CE Population by Lesion Size

Dosage	5 to <10 cm	10 - <20 cm	≥20 cm
200 mg	21/21 (100%)	21/21 (100%)	13/14 (92.9%)
300 mg	14/15 (93.3%)	26/28 (92.9%)	11/11 (100%)
400 mg	15/17 (88.2%)	28/28 (100%)	8/9 (88.9%)

TABLE 5. Clinical Cure at TOC in the CE Population by Presence of Systemic Signs of Infection at Baseline

Dosage	Presence of Systemic Signs of Infection at Baseline
200 mg	35/36 (97.2%)
300 mg	27/29 (93.1%)
400 mg	31/32 (96.9%)

TABLE 6. Clinical Outcome of *Staphylococcus aureus* in the ME Population

	200 mg		300 mg		400 mg		All	
	Cure	Failure	Cure	Failure	Cure	Failure	Cure	Failure
MRSA	32 (100%)	0 (0.0%)	25 (92.6%)	2 (7.4%)	36 (97.3%)	1 (2.7%)	93 (96.9%)	3 (3.1%)
MSSA	7 (100%)	0 (0.0%)	8 (88.9%)	1 (11.1%)	7 (100%)	0 (0.0%)	22 (95.7%)	1 (4.3%)

MICROBIOLOGICAL OUTCOMES

Microbiological eradication rates were similar in all treatment groups (Table 7). The most common pathogen isolated was *Staphylococcus aureus* in 119 patients (89.5% of pts in the ME population), of which 81% were MRSA. MICs shown in Table 8.

TABLE 7. Eradication Response at TOC in the ME Population

Microbiological Response*	200 mg	300 mg	400 mg	All
Overall	N=43	N=44	N=46	N=133
Eradication	43 (100%)	41 (93.2%)	46 (100%)	130 (97.7%)
Persistence	0 (0.0%)	3 (6.8%)	0 (0.0%)	3 (2.3%)
MRSA	N=32	N=27	N=37	N=96
Eradication	32 (100%)	25 (92.6%)	37 (100%)	94 (97.9%)
Persistence	0 (0.0%)	2 (7.4%)	0 (0.0%)	2 (2.1%)
MSSA	N=7	N=9	N=7	N=23
Eradication	7 (100%)	8 (88.9%)	7 (100%)	22 (95.7%)
Persistence	0 (0.0%)	1 (11.1%)	0 (0.0%)	1 (4.3%)

*Includes proven or presumed eradication or persistence

MICROBIOLOGICAL OUTCOMES Continued

TABLE 8. MICs to TR-700 of Key Baseline Pathogens (mMITT Population)

Baseline Pathogen	0.12	0.25	0.5	1	≥2
Staphylococcus aureus	2	124	9	0	0
MRSA	2	100	6	0	0
MSSA	0	24	3	0	0
Streptococcus agalactiae	0	2	0	0	0
Streptococcus pyogenes	1	0	0	0	0

SAFETY

The most common Treatment-Emergent Adverse Events (TEAEs) reported by patients are listed in Table 9. No patients discontinued study medication due to an adverse event. TEAEs were reported to be mostly mild (72.3%) or moderate (24.6%) with a limited number reported as severe (3.1%). Significant abnormal lab values are shown in Table 10.

TABLE 9. Most Common TEAEs (>10%) Overall

Adverse Event	200 mg N=63	300 mg N=63	400 mg N=62	All N=188
Nausea	10 (15.9%)	12 (19.0%)	13 (21.0%)	35 (18.6%)
Vomiting	7 (11.1%)	6 (9.5%)	6 (9.7%)	19 (10.1%)
Headache	5 (7.9%)	10 (15.9%)	6 (9.7%)	21 (11.2%)
Secondary abscess	6 (9.5%)	8 (12.7%)	8 (12.9%)	22 (11.7%)

TABLE 10. Percentage of Patients with Significant* Abnormal Lab Values

Laboratory Value	200 mg N=63	300 mg N=63	400 mg N=62	All N=188
Absolute Neutrophil Count (ANC)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Platelets	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Alanine aminotransferase (ALT)	1 (1.6%)	3 (4.8%)	1 (1.6%)	5 (2.7%)
Asparatate aminotransferase (AST)	0 (0.0%)	1 (1.6%)	2 (3.2%)	3 (1.6%)
Alkaline phosphatase	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
Total Bilirubin	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood Urea Nitrogen (BUN)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Creatinine	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)

*Hematology: <75% of LLN (<50% for neutrophils) for values normal at baseline; <75% of LLN (<50% for neutrophils) of baseline for values abnormal at baseline. Serum Chemistry: >2 X ULN for values normal at baseline; > 2x ULN and > 2x baseline for values abnormal at baseline.

SAFETY Continued

There were 5 patients who experienced a serious adverse event (SAE), of which one was considered possibly drug-related (acute cholecystitis in an obese 57 year old female 2 days after end of therapy).

Hepatitis B was tested in 75.5% (142) of patients in which 1.4% (2) patients had a positive serology. Hepatitis C was tested in 75.0% (141) patients in which 18.4% (26) patients presented with a positive serology.

ECG data over-read by a cardiologist confirmed no clinically significant changes in QTc.

CONCLUSIONS

- **All doses investigated proved to be equally effective.**
- **Oral torezolid phosphate administered over 5 to 7 days is safe and well tolerated at all dose levels tested.**
- **These results in conjunction with PK-PD simulations support 200 mg once daily to be the lowest effective dose for selection in the Phase 3 pivotal cSSSI studies.[4,5]**

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