

SAFETY PROFILE OF ORAL TOREZOLID PHOSPHATE 200, 300, OR 400 MG ONCE DAILY IN AN ACUTE COMPLICATED SKIN AND SKIN STRUCTURE INFECTION PHASE 2 STUDY

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INTRODUCTION

Torezolid (TR-700) is the active moiety of the prodrug torezolid phosphate (TR-701), a second generation oxazolidinone with 4- to 16-fold greater activity than linezolid against gram-positive species.

Our objective was to investigate and compare the safety profiles of oral TR-701 200, 300 and 400 mg once daily for 5 to 7 days in patients with complicated skin and skin structure infections (cSSSI) enrolled in the Phase 2 dose-ranging study.

STUDY DESIGN

This was a Phase 2 dose-ranging, randomized, double-blind study of oral TR-701 in adult patients diagnosed with cSSSI. 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 TR-701 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).

Adverse events were collected from signing of informed consent through the LFU visit. Laboratory evaluations including hematology, chemistry, and urinalysis were collected at Screening/Day 1, 3, 5 (if applicable), EOT, and TOC and were sent to the central laboratory. Coagulation parameters were collected at Screening/Day 1 and EOT and also were sent to the central laboratory.

RESULTS

There were 188 patients that received at least one dose of study drug, of which 69% experienced at least one Treatment Emergent Adverse Event (TEAE). TEAEs were overwhelmingly mild (72%) to moderate (25%). The most common TEAEs overall are listed in Table 1. The most common study drug-related TEAEs (> 5%) reported were nausea, diarrhoea, vomiting, and headache. No patients discontinued study drug due to an adverse event.

Table 1. Most Common TEAEs 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%)

Five patients reported a serious adverse event (SAE) during the study. All SAEs were considered non-related and all resolved by the end of the reporting period. Table 2 lists the details of these events.

TABLE 2. SAE Details

SAE	Onset Study Day	Study Drug Relation	Severity	Outcome
Acute Cholecystitis	9	Not related	Severe	Recovered
Suicidal Ideation	28	Not related	Moderate	Recovered
Secondary Abscess	22	Not related	Severe	Recovered
Worsening Cellulitis	3	Not related	Severe	Recovered
Secondary Abscess	2	Not related	Severe	Recovered

RESULTS

Five patients had substantially abnormal laboratory values (defined using standard regulatory criteria) in ALT, 3 in AST, 1 in alkaline phosphatase, and 1 in serum creatinine (see Table 3). Of the 8 patients with substantially abnormal ALT or AST, none had elevated levels of both, 3 were Hepatitis C positive (3 were negative and 2 were not tested), and 5 have an admitted history of IV drug or alcohol abuse. No patients had substantially abnormal values in platelet count, absolute neutrophil count, or hemoglobin levels.

Table 3. Abnormal Laboratory 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%)
Aspartate 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) and of baseline for values abnormal at baseline. Serum Chemistry: > 2x ULN for values normal at baseline; > 2x ULN and > 2x baseline for values abnormal at baseline.

Results from the centrally analyzed ECG data identified no patients with a QTc > 500 msec and only 1 patient with a QTc increase > 60 msec from baseline to EOT (374 msec at baseline and 444 msec at EOT). There were no cardiac adverse events associated with ECG findings.

CONCLUSIONS

TR-701 proved to be well tolerated in all dosage levels with no significant difference in TEAE occurrences among the doses over a 5-7 day period of administration.

There was no dose-related increase in incidence of TEAEs.