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THE SAFETY OF SINGLE ASCENDING ORAL DOSES OF TR-701, A NOVEL OXAZOLIDINONE PRODRUG ANTIBIOTIC

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INTRODUCTION

The prodrug TR-701 is a novel oxazolidinone prodrug antibiotic that is rapidly converted in vivo by blood and tissue phosphatases, to the microbiologically-active molecule torezolid (TR-700). TR-700 is active against Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE). TR-701 is currently being investigated in a Phase 2 study of complicated skin and skin structure infections.

METHODS

Clinical trial TR701-101 (Part A) was a randomized, double-blind, placebo-controlled, single-ascending oral dose study performed to assess the safety, tolerability, and pharmacokinetic profile of TR-701 in healthy adult subjects. A total of 40 healthy male and female subjects were enrolled. Cohorts of 8 subjects (6 active and 2 placebo) received a single oral dose of 200, 400, 600, 800, or 1200 mg TR-701 after a 10-hr fast. Safety was assessed via adverse events, physical examination, ECG and laboratory evaluations. Adverse Events (AEs) were solicited proactively by asking multiple "how do you feel?" questions.

DEMOGRAPHICS

Demographic Variable	Single Ascending Dose N = 40
Mean age in years (range)	25 (18 to 41)
Mean weight in kg (range)	73.1 (52.2 to 92.9)
Mean height in cm (range)	173.7 (158.2 to 189.1)
BMI in kg/m^2 (range)	24.2 (20.1 to 30.0)
Gender (n[%])	
Male	23 (57.5%)
Female	17 (42.5%)
Ethnicity (n[%])	
Hispanic or Latino	6 (15.0%)
Not Hispanic or Latino	34 (85.0%)
Race (n[%])	
White	36 (90.0%)
Black	3 (7.5%)
Other: Filipino	1 (2.5%)

INCIDENCE OF ADVERSE EVENTS

	Incidences (Number of Distinct Subjects)						
	Overall Placebo (N = 10)	TR-701 200 mg (N = 6)	TR-701 400 mg (N = 6)	TR-701 600 mg (N = 6)	TR-701 800 mg (N = 6)	TR-701 1200 mg (N = 6)	TR-701 Overall (N = 30)
Any Adverse Event (AE)	-	10 (n=4)	4 (n=2)	7 (n=3)	2 (n=1)	5 (n=3)	28 (n=13)
Mild	-	10 (n=4)	4 (n=2)	7 (n=3)	2 (n=1)	5 (n=3)	28 (n=13)
Moderate	-	-	-	-	-	-	-
Severe	-	-	-	-	-	-	-
Related AE	-	7 (n=3)	-	6 (n=3)	2 (n=1)	4 (n=3)	19 (n=10)
AE leading to Study Discontinuation	-	-	-	-	-	-	-
Serious AE	-	-	-	-	-	-	-

ADVERSE EVENTS REPORTED BY AT LEAST 2 SUBJECTS IN TR-701 OVERALL

	Number of Distinct Subjects (%)						
System Organ Class Preferred Term	Overall Placebo (N = 10)	TR-701 200 mg (N = 6)	TR-701 400 mg (N = 6)	TR-701 600 mg (N = 6)	TR-701 800 mg (N = 6)	TR-701 1200 mg (N = 6)	TR-701 Overall (N = 30)
All System Organ Classes	-	4 (66.7%)	2 (33.3%)	3 (50.0%)	1 (16.7%)	3 (50.0%)	13 (43.3%)
Gastrointestinal Disorders	-	1 (16.7%)	1 (16.7%)	2 (33.3%)	-	3 (50.0%)	7 (23.3%)
Nausea	-	1 (16.7%)	1 (16.7%)	-	-	1 (16.7%)	3 (10.0%)
Diarrhea	-	-	-	2 (33.3%)	-	-	2 (6.7%)
Nervous System Disorders	-	2 (33.3%)	1 (16.7%)	-	-	-	3 (10.0%)
Dizziness	-	1 (16.7%)	1 (16.7%)	-	-	-	2 (6.7%)
Respiratory, Thoracic and Mediastinal Disorders	-	1 (16.7%)	1 (16.7%)	-	-	-	2 (6.7%)
Nasal Congestion	-	1 (16.7%)	1 (16.7%)	-	-	-	2 (6.7%)
General Disorders	-	1 (16.7%)	-	1 (16.7%)	-	-	2 (6.7%)

RESULTS

- 28 treatment-emergent AEs were reported by 13 subjects receiving TR-701 and no AEs were reported by subjects receiving placebo.
- 19 AEs were considered treatment-related. All AEs were considered "mild" in severity.
- Similar numbers of AEs were reported in each cohort with the greatest number occurring following administration of 200 mg TR-701.
- AEs reported in at least 2 subjects receiving TR-701 were: nausea (3 subjects [10.0%]), dizziness, diarrhea, and nasal congestion (2 subjects each [6.7%]).
- There were no deaths, Serious AEs, or discontinuations due to Aes.
- No clinically significant changes or findings were noted in clinical laboratory evaluations, vital sign measurements, 12-lead ECGs, and physical examinations.
- There was no dose-response relationship to the number of AEs and, overall, changes in safety evaluations were unremarkable.

CONCLUSIONS

- TR-701 administered orally is safe and well tolerated in healthy volunteers at single doses up to 1200 mg.