

A2-033

AN EVALUATION OF THE ABSORPTION, METABOLISM, AND EXCRETION OF ORALLY ADMINISTERED [¹⁴C]-TR-701 FA IN HEALTHY SUBJECTS

Howard Dreskin, MS
Trius Therapeutics
6310 Nancy Ridge Drive, Suite 105
San Diego, CA 92121
(858) 452-0370 x286
hdreskin@triusrx.com

H. DRESKIN, T. BOYEA, J. BARKER, E. FANG, and P. PROKOCIMER
Trius Therapeutics, Inc., San Diego, CA 92009



INTRODUCTION

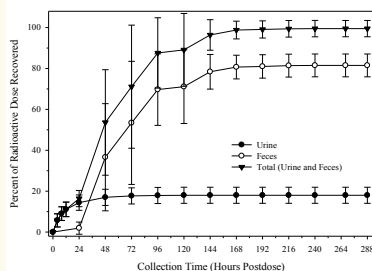
TR-701 free acid (FA) (tedizolid phosphate, formally known as torezolid phosphate) is a novel oxazolidinone prodrug antibiotic currently in Phase 3 clinical trials for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI). Preclinical, PK/PD, and Phase 2 clinical data generated with the oral formulation suggested that 200 mg QD is the lowest effective dose and therefore has been selected for the Phase 3 pivotal trials in ABSSSI. The aim of the present study was to characterize the absorption, metabolism, and excretion of a single 200-mg dose of [¹⁴C]-TR-701 FA in healthy male subjects to determine its metabolic fate and the design, and/or timing of other special population studies.

STUDY DESIGN

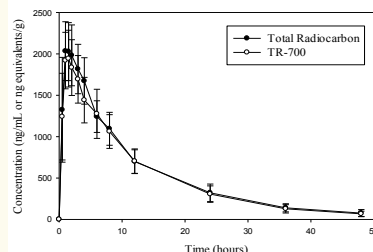
This was an open-label, single-dose study of the absorption, metabolism, and excretion of TR-701 FA administered orally in 6 healthy male volunteers. Subjects received a single dose of [¹⁴C]-TR-701 FA administered as an oral solution (the actual dose was adjusted to 100 μCi resulting in 204 mg TR-701 FA). Blood, urine, and fecal samples were collected at protocol defined time points from pre-dose through 312 hours post dose or until clinic discharge criteria were met, for profiling excretion, pharmacokinetic parameter determination and metabolite profiling. Assays included scintillation counting of blood, plasma and excreta, a validated LC-MS-MS assay for quantitation of TR-700 in plasma, and LC-MS and HPLC with radiochemical detection for metabolite profiling.

DATA

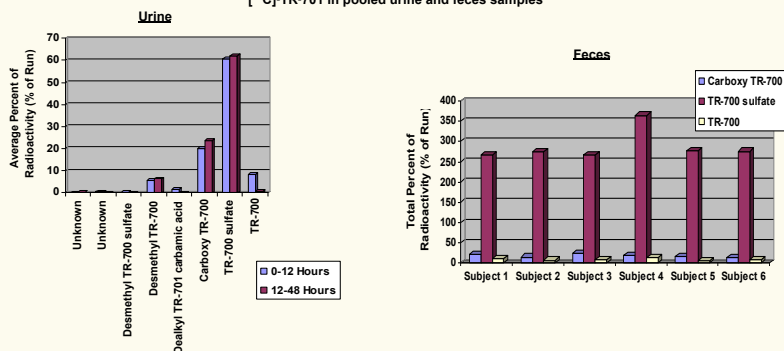
Mean Cumulative Percent of Radioactive Dose Recovered in Urine and Feces at Specified Intervals After a Single 204-mg (100-μCi) Oral Dose of [¹⁴C]-TR-701 FA to Healthy Male Subjects



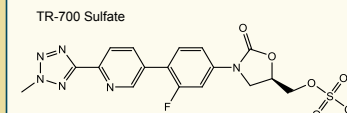
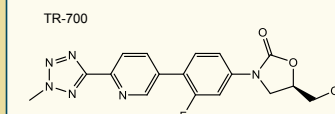
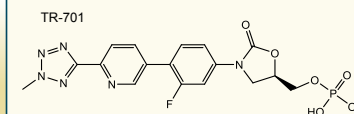
Mean (± SD) Concentration-Time Profiles for TR-700 in Plasma and Total Radioactivity in Plasma and Whole Blood



Plots of the percent of sample radioactivity as [¹⁴C]-TR-701 or metabolites of [¹⁴C]-TR-701 in pooled urine and feces samples



MOLECULAR STRUCTURES



RESULTS

The majority (87.6%) of the radioactivity was recovered by 96 hours post dose, and total recovery in urine and feces combined was approximately 99.5% by 288 hours post dose. Mean recovery of total radioactivity in urine was 18.0%, with 81.5% of the radioactive dose recovered in feces. Eight metabolites were identified in plasma, urine, and feces. The only significant circulating metabolite found in plasma was the hydrolyzed alcohol product, TR-700, which constituted approximately 94.54% - 98.23% of sample radioactivity. Mean plasma concentration versus time curves were similar for TR-700 and total radiocarbon with TR-700 accounting for approximately 95% of the total radiocarbon AUC.

The sulfate analog of TR-700 was a minor metabolite detected in the plasma of 1 subject only, at less than 1%. The main metabolite found in feces and urine was the sulfate analog of TR-700. No TR-701 was identified in plasma.

CONCLUSIONS

TR-701 underwent rapid and extensive hydrolysis of the phosphate moiety and converted into TR-700, the microbiologically active moiety.

Feces was the major elimination pathway for total radioactivity, and urine was a minor pathway of elimination. The mean recovery of the radioactive dose in urine and feces was approximately 99.5% by 288 hours post dose, with 81.5% recovered in feces and 18.0% recovered in urine.

TR-700 was the only appreciable circulating metabolite following oral administration.