WCK 771 - IntraVenous Multiple Dose Phase-I Study.

R. JHA, N. MAHARAJ, S. DESHMUKH, Y. CHUGH, V. PATTIL, S. LATAD, R. YEOLE, V. KULKARNI, M. PATEL, H. KHORAKIWALA, M. NAIDU, P. USHA, T. RAO, Y. RAJU,

WOCKHARD RESEARCH CENTRE, AURANGABAD, INDIA. NIZAM’S INSTITUTE OF MEDICAL SCIENCES, HYDERABAD, INDIA.

ABSTRACT

Background: WCK 771 is a broad spectrum anti-MRSA (Methicillin Resistant Staphylococcus aureus) agent in phase II development. WCK 771 has bactericidal activity against quinolone resistant MRSA, vancomycin- glycylglycophosphate intermediate and vancomycin resistant Staphylococcus aureus (VISA/VIRSA) respectively.

Methods: We examined safety, tolerability and pharmacokinetics of intravenous (IV) infusion of WCK 771 on multiple dose administration in three healthy adult male subjects in a double blinded, placebo (P) controlled study. In first part of the study, WCK 771 (500 mg or 600 mg) or P was administered to 10 subjects twice daily (BID) for one day and in second part, WCK 771 (800 mg) or P was administered to 12 subjects BID for five days. Safety was monitored for 30 days after the last dose. Safety was evaluated by vital signs measurement and clinical examination, clinical laboratory tests, electrocardiogram (ECG) and electroencephalogram (EEG). Blood samples were collected to measure the serum concentrations of WCK 771 using LC-MS-MS method. Pharmacokinetic parameters were calculated using non-linear least square regression.

Results: WCK 771 was well tolerated without any serious AEs. Observed non-serious AEs included injection site pain, headache, palpitations, sinus tachycardia, elevated liver enzymes and borderline EEG abnormalities. All non-serious AEs were mild in severity and resolved within 24 hours. No increase in liver enzymes was observed in placebo group. The highest incidence of EEG abnormality was seen with elevated theta activity. No clinically significant adverse events were observed in any subjects.

Conclusions: WCK 771 is a novel, broad-spectrum, parenteral, anti-MRSA fluoroquinolone with a coverage of even vancomycin/teicoplanin resistant S. aureus (VISA/VIRSA). WCK 771 has PK-PD breakpoint of 2 mcg/ml for Gram-negative pathogens including anaerobes.

INTRODUCTION

WCK 771 is a novel, broad-spectrum, parenteral, anti-MRSA fluoroquinolone with a coverage of even vancomycin/teicoplanin resistant S. aureus (VISA/VIRSA). WCK 771 has PK-PD breakpoint of 2 mcg/ml for Gram-negative pathogens including anaerobes. WCK 771 was excreted primarily by kidneys as sulphate metabolite and showed terminal elimination half-life of around 8.8 hours. Conclusions: Multiple dose administration of WCK 771 IV infusion is safe. The steady state PK indicates potential for therapeutic use as these doses.

RESULTS

This study was conducted at the Department of Clinical Pharmacology and Therapeutics, Nanatz Institute of Medical Sciences, Hyderabad, India. The study protocol was approved by the Institutional Ethics Committee and the Regulatory Authority of India. All participating subjects signed informed consent form.

Safety study: The study was conducted as an inpatient care facility. The subjects were housed at least 24 hours before administration of the first dose and continued to remain in the clinical facility for at least 48 hours after receiving the last dose of WCK 771 or placebo. Subjects were followed up every day up to seven days after the last dose.

Safety and tolerability were assessed based on vital signs and adverse events recorded in the CRF. Safety and tolerability were calculated as reported cases/subject/day. These were followed up till resolution. There was no serious AE and no subject was dropped out of the study due to non-study drug related adverse event (AE).

Safety results: A total of 30 subjects were recruited in the study out of which 29 subjects completed the study. One subject was dropped out of the study due to non-study drug related adverse event (AE).

CONCLUSIONS

WCK 771 is well tolerated on multiple dose administration.

steady state PK at 600 mg b.i.d. does indicate the potential for therapeutic use at this dose.

Based on results of this study, proof-of-concept phase-II clinical studies are initiated.

REFERENCES