[NIH Clinical Research Studies]

Protocol Number: 01-C-0084

[Active Accrual, Protocols Recruiting New Patients]

Title: A Multicenter, Open, Non-Comparative, Sequential Dose-Escalation Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Two Separate Doses of MK-0991 in Children with New Onset Fever and Neutropenia

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Summary: The objective of this study is to evaluate the safety, tolerance, and pharmacokinetics of MK-0991, a novel echinocandin (cell wall-active antifungal lipopeptide), as early empirical therapy for prevention of fungal infections in immunocompromised children. The study is designed as a multicenter open label, sequential dose escalation study of intravenous MK-0991. Intravenous MK-0991 will be administered daily as a one hour infusion to patients with new onset of fever and neutropenia (absolute neutrophil count less than or equal to 500 milliammeter (3)) who will be initiated onto broad spectrum empirical antibacterial therapy. The patient population consist of children ages 2 to 17 years of age; two age cohorts will be studied (2-11, 12-17). Dosage levels will be 1.0 milligrams/kilograms/day day (not to exceed 50 milligrams/day) and 1.5 milligrams/kilograms/day (not to exceed 70 milligrams/day). The planned sample size is 32 patients (a maximum of 64 patients may participate in the study allowing for one replacement patient of each age enrolled). At each dosage level, a total of 8 patients will be enrolled into each age cohort (2-11, 12-17); a total of 16 patients will be enrolled at each dosage level. The first group of patients will receive MK-0991 at 1.0 milligrams/kilograms/day (not to exceed 50 milligrams/day). Study drug will continue until recovery from neutropenia (ANC post nadir greater than or equal to 250 millimeters (3)) or until the initiation of conventional deoxidate amphotericin B or a lipid formulation of amphotericin B for either empirical antifungal therapy or for proven fungal infection. Patients may receive MK-0991 for a maximum duration of 28 days. For any patient who meets criteria to start standard empirical antifungal therapy with conventional deoxycholate amphotericin B or a lipid formulation of amphotericin B (fever greater than 38.0 Celsius despite greater than or

equal to 96 hours of neutropenia and broad spectrum antibacterial therapy) or who has a proven breakthrough fungal infection, MK-0991 will be discontinued and conventional deoxycholate amphotericin B or a lipid formulation of amphotericin will be initiated.

Sponsoring Institute:
National Cancer Institute (NCI)

Recruitment Detail
Type: Active Accrual Of New Subjects
Gender: Male & Female

Referral Letter Required: Yes

Population Exclusion(s): None

Eligibility Criteria:
Children ages 2-17 with one or more of the following conditions: Leukemia, Lymphoma or other cancers; bone marrow or peripheral stem cell transplantation; aplastic anemia.

Chemotherapy anticipated to incur more than 10 days of neutropenia.

Patient has an absolute neutrophil count less than or equal to 500 millimeters (3) and at lease one recorded fever greater than 38 degrees Celsius within 24 hours or screening.

Patient has or will receive parenteral systemic antibacterial therapy for fever and neutropenia within 48 hours of screening.

For female adolescents of childbearing potential, patient has a negative serum or urine pregnancy test prior to enrollment into the study and will subsequently use adequate birth control measures as defined by the investigator (Note: oral contraceptives should not be used as the sole method of birth control because the effect of MK-0991 on the efficacy of oral contraceptives has not yet been established).

Patient has a functioning central venous catheter in place at screening.

Patient or guardian understands the procedures and

agrees to the patient's participation by providing written informed consent.

Assent will also be obtained from minors capable of understanding.

Must not have proven invasive fungal infection at the time of enrollment .

Must not have abnormal laboratory values including Platelet counts less than 5,000 units per liter; INR 1.6 (INR greater than 4.0, if patients are receiving anticoagulants); AST or ALT greater than 3 times the upper limit of normal (for age); Alkaline phosphatase greater than 5 times the upper limit of normal for age. (Note: Patients with an elevated alkaline phosphatase greater than 5 times the ULN which is thought to be related to bony metastases or other suspected bony processes may be enrolled on a case by case basis following discussion with the sponsor).

Must not be hemodynamically unstable, exhibit hemodynamic compromise or not expected to survive at least 5 days.

Must not be pregnant or breast feeding.

Must not have a diagnosis of acute hepatitis or cirrhosis due to any cause.

Must not be participating in any other clinical study involving the administration of an investigational antibiotic or antifungal drug within 14 days prior to study. (Note : other phase I trials of investigational cancer agents are prohibited during the course of study therapy. Patient may continue to receive any routine antineoplastic agent or medication for supportive care of his underlying disease).

Must not have previously enrolled in this study.

Must not have any condition or concomitant illness which, in the opinion of the investigator, might confuse the results of the study or pose additional risk in administering the study drugs to the patient.

Must not be taking rifampin, cyclosprin A, phenytoin, carbamazepine, or phenobarbital.

Must not have documented HIV infection of any stage.

Must not have a history of allergy, hypersensitivity, or any serious reaction to echinocandin antifungals.

Special Instructions: Currently Not Provided

Keywords:
Pediatric
Antifungal
Echinocandin
Neutropenic
Pharmacokinetic

Recruitment Keywords:
Pediatric
Cancer
Neutropenia
Antibacterial Therapy

Conditions:
None

Investigational Drug(s):
MK-0991

Investigational Device(s):
None

Contacts:
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Citations:
Engelhard. 1998. Bacterial and fungal infections in children undergoing bone marrow transplantation, Bone Marrow Transplant, Vol. 21, p. S78

Pizzo. 1982. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and

granulocytopenia, Am J Med, Vol. 72, p. 101

Chanock. 1996. Evolving Concepts of Prevention and Treatment of Invasive Fungal Infection sin Pediatric Bone Marrow Transplant Recipients, Bone Marrow Transplant, Vol. 18, p. S15

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If you have:

* Questions about participating in a study, please contact the Patient Recruitment and Public Liaison Office, CC.
* Questions about specific studies, or the database in general, please contact the Protocol Coordination Service Center, CC.
* Technical questions regarding the Clinical Center web site, please contact the Information Systems Department, CC.