This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

END OF TRIAL STUDY SUMMARY REPORT

MK-0457

Generic Name: tozasertib	Protocol 008
EudraCT Number:	2006-004535-30
Dosage Form: Intravenous	Phase: IIa
Indication: LEUKAEMIA	Study Design: Open-label, non-randomized
Sponsor Name:	Merck & Co., Inc.
Clinical Monitor:	[redacted]
Study Initiation Date (FPI):	18-Dec-2006
Study Early Termination Date (if applicable):	02-Nov-2007 (enrollment suspended)
Study Completion Date (Global LPO):	27-May-2009
Investigator Name/Affiliation:	Multicenter, 24 countries

MERCK RESEARCH LABORATORIES

END OF TRIAL STUDY SUMMARY REPORT

MK-0457
tozasertib, Intravenous
LEUKAEMIA

PROTOCOL TITLE/NO.: A Phase II Study of MK-0457 in Patients with BCR-ABL T315I Mutant Chronic Myelogenous Leukemia and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia #008

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter

PRIMARY THERAPY PERIOD: every 14 days | **CLINICAL PHASE:** IIa

DURATION OF TREATMENT: 5-Day continuous infusion

OBJECTIVE(S):

Primary:

(1) To evaluate the efficacy of MK-0457, as defined by major cytogenetic response in chronic phase CML and as major hematological response in accelerated phase CML, blastic phase CML, and Ph+-ALL, when given as a 5-day CIV infusion every 14 days.

(2) To evaluate the safety of MK-0457 with dose and regimen.

Secondary:

(1) To evaluate the durability of responses with MK-0457.

(2) To assess the time to initial hematological response and best hematological response after treatment with MK-0457.

(3) To measure the overall hematological response rate in advanced T315I mutant leukemias (i.e. accelerated phase CML, blastic phase CML, and Ph+-ALL), and complete hematological response rate in T315I mutant chronic phase CML.

(4) To measure the cytogenetic response rates after treatment with MK-0457.

(5) To measure overall survival after treatment with MK-0457.

[redacted]

DIAGNOSIS/INCLUSION CRITERIA:

Patients must meet all of the following criteria to participate in the study.

1. Patient is male or female, and ≥18 years of age on day of signing informed consent.

2. ECOG performance status:

   a) For Accelerated Phase CML, Blastic phase CML, and Ph+-ALL patients: ECOG ≤3

   b) For Chronic Phase CML patients: ECOG ≤ 2

3. The interval from prior treatment (standard or investigational) to time of study drug administration should be at least 2 weeks for cytotoxic agents or at least 5 half-lives for non-cytotoxic agents. The only exception is hydroxyurea which can be used to control peripheral leukemia cell counts prior to initiating study drug and during the first treatment cycle. Persistent clinically significant chronic toxicities from prior chemotherapy must not be greater than Grade 2 (except alopecia).

4. Patients must have the following laboratory values unless considered due to leukemia:

   a) ALT and AST ≤ 3 x upper limit of normal (ULN)

   b) Serum total bilirubin ≤ 1.5 x ULN (except for known Gilbert's syndrome)

   c) Serum creatinine ≤ 2.0 x ULN

5. Patient, or patient's legal representative, has voluntarily agreed to participate by giving informed consent.

6. Patients with active CNS disease may be included and will be treated concurrently with intrathecal therapy.

7. Patients under consideration for inclusion into this study must have Ph+ (or BCR-ABL+) CML or ALL.

8. Patients with BCR-ABL T315I mutation documented within the Screening period (within 28 days of study drug administration). The choice of assay used for documenting the BCR-ABL T315I mutation is at the discretion of the investigator.

STUDY STATUS:

STUDY DESIGN: Multicenter, open label, nonrandomized single treatment design

PATIENT DISPOSITION: (Preliminary and unaudited)

SCREENING FAILURES:		
RANDOMIZED:	52	
Male	34	(Ages: 22-78)
Female	18	(Ages: 30-70)
COMPLETED:	0	
DISCONTINUED:	50	
Clinical adverse experience:	10	
Laboratory adverse experience	0	
Other :	40	

DOSAGE/FORMULATION NOS.:

	formulation #	packaging lot #
500mg	[redacted]	
500mg		
75mg		
75mg		
500mg		
500mg		
75mg		
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EVALUATION CRITERIA:

Efficacy:
All patients will have peripheral blood and bone marrow obtained for MK-0457-related molecular studies. Hematologic, cytogenetic, and molecular responses will be evaluated from peripheral blood, bone marrow, and lumbar puncture (when applicable) throughout the study.

Safety:
Physical examinations, vital signs, chest x-ray, ECOG performance status, laboratory safety evaluations, ECG, two dimensional echocardiogram or MUGA scan, and assessment of adverse experiences will be conducted prior to drug administration and at designated intervals throughout the study. Toxicity will be graded and recorded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events-CTCAE, Version 3.0.

Other:
Clinical evaluations including physical exam and Eastern Cooperative Oncology Group (ECOG) performance status will also be used in assessment. Pharmacodynamic measurements will include measurement of BCR-ABL activity biomarkers and Aurora kinase activity biomarkers. Blood samples for plasma levels of MK-0457 and metabolites (if appropriate) will be obtained during the first cycle of therapy. Urine samples for levels of MK-0457 and potential metabolites (if appropriate) will be obtained during the first cycle of therapy from those patients enrolled into the study in Japan.

Data Analysis Summary:
The primary endpoints of this protocol is major cytogenetic response (MCyR) for chronic phase CML patients and major hematological response (MHR) for accelerated phase CML, blastic phase CML, and Ph+-ALL patients. Each of the four populations will be considered an independent sub study and any of the four that succeeds will be analyzed and filed for registration independently.

RESULTS:

Of the 37 patients with accelerated phase (AP) CML, blastic phase CMP, or Ph+ ALL, only one AP patient initially treated at 40-mg/m^2/hr achieved a confirmed major hematological response. Two (2) of the 15 Chronic Phase (CP) patients, both initially treated at 40-mg/m^2/hr, achieved a major cytogenetic response.

AUTHORS:

[redacted]