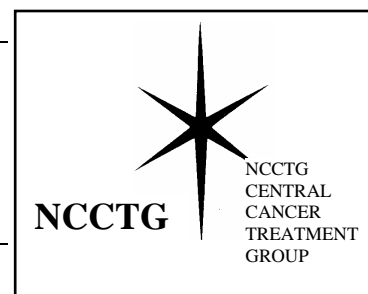

Operations Office

Telephone (507) 266-3549



Date: August 26, 2005

To: NCCTG Primary Clinical Research Associates

From: Lori K. Kelly
Protocol Development Coordinator

Re: N0272, Phase II Trial of STI-571 in Treatment of Recurrent Oligodendroglioma and Mixed Oligoastrocytoma

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with STI-571 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_1014473

Please note that all risks currently cited in the NCCTG consent form can not be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Lori K. Kelly at 507/266-3549.

lkk
enclosure



DATE: August 8, 2005
FROM: Alice Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: STI571 (imatinib mesylate, Gleevec®) IND Safety Report, AE# 1014473
TO: Investigators Using STI571, IND 61135

apc 8/8/05

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agent STI571 (IND 61135).

Please complete the following:

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

CTEP's evaluation of this IND Safety Report in light of previous experience with STI571 does not require a change in the clinical protocols for this agent at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The Adverse Events Assessment that describes the following adverse events, previous experience under this IND, and the total number of patients enrolled in trials under this IND is attached:

A 41-year-old male with gastrointestinal stromal tumor experienced grade 4 ALT/SGPT while on a phase 3 trial using the investigational agent STI571.

ADVERSE EVENTS ASSESSMENT

IND 61135 NSC 716051 STI571 (imatinib mesylate, Gleevec®)	ADVERSE EXPERIENCE REPORT NO. # 36 IND Safety Report: Initial Event: Gr. 4: ALT/SGPT Protocol: ACOSOG-Z9001
AE: 1014473	

The patient is a 41-year-old male with gastrointestinal stromal tumor (GIST) who experienced elevated ALT/SGPT levels while on a phase 3 study using the investigational agent STI571 or placebo. He began his first course of treatment on December 13, 2004 receiving STI571 (or placebo) 400 mg PO daily, every 28 days for 1 year. He received his last dose on June 5, 2005 (Course 7, Day 6) and was removed from the study on June 24, 2005. At that time, the patient was unblinded and had received STI571 therapy.

The patient was diagnosed with GIST in October 2004 and was status post surgical resection for a 10 cm GIST at that time. On December 13, 2004, he started treatment with STI571 and had completed 5 courses of therapy. On May 2, 2005 (Course 6, Day 1), routine laboratory analysis revealed a slightly elevated ALT/SGPT level of 128 IU/L (reference range: 0-40 IU/L) and an AST/SGOT level of 83 IU/L (reference range: 0-40 IU/L). The patient continued on STI571 without any dose modifications. On June 6, 2005 (Cycle 7, Day 7), the patient was found to have an increased ALT level of 579 IU/L and AST level of 308 IU/L. The study agent was withheld, and the patient was monitored weekly thereafter. The patient's transaminase levels continued to rise despite termination of the investigational therapy. He did not have a history of hepatitis, blood transfusion prior to 1990, alcohol abuse, or IV drug use, although he had episodes of vomiting (one to two times weekly) and crampy abdominal pain during his STI571 therapy, which increased as therapy continued; however, he reported improvement since treatment termination. A magnetic resonance cholangiopancreatography (MRCP) on June 24, 2005 indicated no liver or bile duct abnormalities, and blood tests at that time were negative for hepatitis A, B, and C antibodies/antigens.

On June 28, 2005, the patient was hospitalized for nausea and fatigue, with an ALT level of 3000 IU/L and an AST level of 2247 IU/L. A CT scan and Doppler ultrasound of the abdomen were unremarkable. His blood tests were negative for cytomegalovirus and antinuclear antibodies. A liver biopsy revealed severe active hepatitis with extensive periportal and centrilobular necrosis, which was felt to be drug-induced vs. autoimmune induced hepatitis. The patient was started on prednisone and discharged on June 30, 2005, with a decrease in his transaminase levels noted. As of July 27, 2005, the patient's ALT level was 517 IU/L and AST level was 328 IU/L, and he reports that he feels well, has more energy and an increased appetite. He continues on prednisone at a lower dose.

The patient's past medical history is significant for hypertension and saliva gland removal secondary to infection. Medications at the time of the event included lisinopril, Excedrin®, ibuprofen, Pepto-Bismol®, Robitussin®, Tums®, Tylenol Cold®, Tylenol Sinus®, and a multivitamin.

Although elevated ALT/SGPT levels are expected with STI571 therapy, this case was unusually severe with worsening of toxicity despite having the agent stopped. The liver biopsy could be consistent with drug-induced hepatitis. There have been 2,243 patients enrolled in NCI-sponsored clinical trials under this IND.

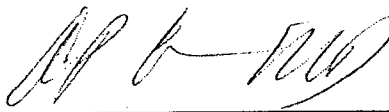
	ALT/SGPT
STI571	Probable
Gastrointestinal stromal tumor	Unrelated

CONFIDENTIAL

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Date: 8/8/05

Signature:



Alice Chen, M.D.
(IDB Monitor for STI571)

If this assessment is changed, we will notify your office.

cc: Faith Williams and Clinical Safety & Epidemiology
Novartis Pharmaceuticals Corporation

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2 of 2

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