

# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** April 21, 2006  
**To:** NCCTG Primary Clinical Research Associates  
**From:** Lori K. Bratvold  
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\_1957747

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. Bratvold at 507/266-3549.

lkb  
enclosure



**DATE:** April 12, 2006 *AK*  
**FROM:** A. Dimitrios Colevas, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** STI571 (Imatinib Mesylate, Gleevec™) IND Safety Report, AE# **1957747**  
**TO:** Investigators Using STI571, IND 61135

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).

The following must be completed by all investigators using STI571 under NCI IND 61135:

- 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 78-year-old male with a gastrointestinal stromal tumor experienced grade 3 syncope while participating in a phase 3 randomized double-blinded study using the investigational agent STI571 or placebo.

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## ADVERSE EVENTS ASSESSMENT

IND 61135 NSC 716051 STI571 (imatinib mesylate, Gleevec™) AE: 1957747	ADVERSE EXPERIENCE REPORT NO. 35 IND Safety Report: Initial Event: Gr: 3 Syncope Protocol: ACOSOG-Z9001
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The patient is a 78-year-old male with a gastrointestinal stromal tumor (GIST) who experienced syncope while on a double-blind phase 3 trial using the investigational agent STI571 or placebo. He began his first course of treatment on January 10, 2006 receiving STI571 (or placebo) 400 mg PO daily, every 28 days for 1 year. He received the last dose of STI571 or placebo prior to the event on January 19, 2006 (Cycle 1, Day 10).

The patient was initially diagnosed with GIST in November 2005 and was status post tumor resection. He began the investigational therapy on January 10, 2006. On January 19, 2006, the patient presented to the emergency department reporting several episodes of weakness and confusion with altered consciousness. He stated that the episodes were associated with diplopia and urinary incontinence and reported waking up on the floor with bilateral arm and leg weakness and bilateral subconjunctival hemorrhages. Upon further investigation, the patient stated that he checked his blood glucose before one of these episodes and may have taken more insulin than required. An initial evaluation demonstrated the patient to be alert and oriented x 3, and pupils were equal, round, and reactive to light (PERRL) with extraocular muscles intact. The patient's gag reflex was normal and speech and language were intact, but a mild central weakness with tongue deviation to the right was noted. The patient exhibited right arm and leg 4/5 strength and left arm and leg 5/5 strength with an ataxic tandem gait, 1+ pretibial edema, a right pronator drift with decreased tone on the right side and severe right upper extremity dysmetria. Sensory examination was intact to light touch, pinprick and proprioception. His physical examination was essentially normal except for an elevated blood pressure of 162/58, bilateral subconjunctival hemorrhages, facial bruising, and left arm and shoulder pain with bruising. Laboratory values upon admission were unremarkable except for an elevated glucose (162 mg/dL; reference range: 70-105 mg/dL). The patient was admitted to the neurology service for evaluation of possible seizure activity and started on Keppra®. An EEG and brain MRI were negative. A CT scan of the brain showed hyperintensity in the posterior and lateral cerebellar lobes, periventricular leukomalacia, calcification of basal ganglia and basilar system, and atrophy of the frontal, temporal and parietal lobes. An MRA had findings of possible atherosclerotic plaque versus artifact at the carotid siphon. An EKG showed normal sinus rhythm with a right bundle branch block, left ventricular hypertrophy and an old infarct. A cardiac angiogram was negative for significant stenosis, and an echocardiogram revealed normal left ventricular systolic function with an estimated ejection fraction of 55-60% and moderate concentric left ventricular hypertrophy with impaired relaxation suggestive of mild diastolic dysfunction. A chest CT scan completed for comparison with a previous study (December 20, 2005) identified a soft tissue abnormality in the right upper lobe, which had decreased from 2.8 cm to 1.9 cm; a calcified granuloma at hepatic segment 7; a left renal cyst, which was stable from the previous study; an adrenal mass with minimal increase in size from 2.5 cm to 2.9 cm; and a 3.5 cm x 3 cm ill-defined filling defect at the gastric fundus.

The patient was monitored on telemetry throughout his hospitalization with no arrhythmias or abnormal cardiac events recorded. His blood pressure remained stable with systolic ranges from 130-175 mmHg and diastolic ranges from 50-85 mmHg. The patient's blood glucose fluctuated from 147-280 mg/dL, and he was treated with an insulin sliding scale. The patient was discharged to home on January 27, 2006 on Keppra® and seizure precautions with a presumptive diagnosis of epilepsy. He will be followed in the neurology clinic. The patient resumed STI571 or placebo therapy on February 1, 2006. The treating site has not reported any additional serious adverse events for this patient; however, he was taken off study on March 29, 2006.

The patient's past medical history is significant for hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, arthritis, and prostate cancer. Medications taken at the time of the event included alendronate, ascorbic acid, atenolol, Avandia®, Coumadin®, doxepin, gabapentin, insulin, iron sulfate, Lasix®, loratidine, Lortab®, omeprazole, potassium chloride, valsartan and Zocor®.

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There have been 7 other incidences of syncope (4 unlikely and 3 unrelated to the investigational agent) and 23 incidences of seizures (20 unlikely and 3 unrelated to the investigational agent) reported to the NCI as serious adverse events under this IND.

In this case, it is felt that a possible relationship between the syncope and STI571 cannot be excluded. There have been 2,625 patients enrolled in NCI-sponsored clinical trials under this IND.

	<b>Syncope</b>
<b>ST1571</b>	Possible
<b>Gastrointestinal stromal tumor</b>	Unrelated
<b>Alendronate</b>	Unrelated
<b>Ascorbic acid</b>	Unrelated
<b>Atenolol</b>	Unlikely
<b>Avandia<sup>®</sup></b>	Unrelated
<b>Coumadin<sup>®</sup></b>	Unrelated
<b>Doxepin</b>	Unlikely
<b>Gabapentin</b>	Unlikely
<b>Insulin</b>	Unlikely
<b>Iron sulfate</b>	Unrelated
<b>Lasix<sup>®</sup></b>	Unrelated
<b>Loratadine</b>	Unrelated
<b>Lortab<sup>®</sup></b>	Unlikely
<b>Omeprazole</b>	Unrelated
<b>Potassium chloride</b>	Unrelated
<b>Valsartan</b>	Unrelated
<b>Zocor<sup>®</sup></b>	Unrelated

Date: 9/12/06

Signature:   
A. Dimitrios Colevas, M.D.  
(IDB Monitor for STI571)

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

cc: Clinical Safety & Epidemiology  
Faith Williams  
Novartis Pharmaceuticals Corporation