

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: November 03 2006

To: NCCTG Primary Clinical Research Associates

From: Janis Wobschall
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_1550203

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 Janis Wobschall at wobschall.janis@mayo.edu or 507/284-4852

JW/dkf
enclosure



DATE: October 23, 2006
FROM: A. Dimitrios Colevas, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: STI571 (Imatinib Mesylate, Gleevec®) NCI IND Safety Report, AE# 1550203
TO: Investigators Using CTEP-supplied Investigational STI571, NSC 716051

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.

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.

If your study is not covered under IND 61135, it is strongly recommended that you follow the instructions above.

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 event, previous experience under this IND, and the total number of patients enrolled in trials under this IND is attached:

A 64-year-old female with gastrointestinal stromal tumor (GIST) experienced grade 4 profound depression while on a phase 3 trial utilizing the investigational agent STI571/placebo in the adjuvant setting. It is unknown at this time whether the patient was receiving STI571 or placebo.

ADVERSE EVENTS ASSESSMENT

IND 61135	ADVERSE EXPERIENCE REPORT NO. 37
NSC 716051	IND Safety Report: Initial
STI571 (imatinib mesylate, Gleevec®)	Event: Gr. 4: Mood alteration: Depression
AE: 1550203	Protocol: ACOSOG-Z9001

The patient is a 64-year-old female with gastrointestinal stromal tumor (GIST) who experienced profound depression while on a phase 3 trial utilizing the investigational agent STI571 in the adjuvant setting. She began her first course of adjuvant treatment on February 2, 2006 and was to receive STI571 or placebo 400 mg PO daily x 28 days, every 28 days, for 1 year. On April 24, 2006, the study drug was dose reduced to 300 mg daily due to severe gastro-esophageal reflux. She received the last dose of STI571 on September 21, 2006 (Cycle 9, Day 8).

The patient was initially diagnosed with GIST in November 2005 and is status post pancreatic duodenectomy. She began adjuvant therapy with STI571/placebo on February 2, 2006 with a performance status of 0. Severe gastro-esophageal reflux prompted a dose-reduction of the study drug to 300 mg daily, as well as initiation of Reglan® starting April 24, 2006. On June 30, 2006, the patient reported a 3- to 4-week history of new onset listlessness. She also stated that she felt increasingly uncomfortable being alone and complained of losing pleasure in activities she used to enjoy; however, she denied having depressive thoughts regarding her disease or prognosis. Her physical examination was unremarkable, and laboratory evaluation showed no evidence of significant myelosuppression. Daily Celexa® was initiated, and she was referred to psychiatry. However, she discontinued the Celexa® shortly after starting it because her symptoms worsened. On July 12, 2006, during her psychiatry evaluation, the patient reported feeling anxious and terrified to be alone. Her mental status evaluation showed a depressed and anxious patient, with an abnormal attitude (tearful and sad) and agitation (terrified of being alone). As a result, she was started on treatment with Effexor® on July 12, 2006; however, it was stopped on July 19, 2006 because she experienced increased anxiety and insomnia. Therefore, she was started on Remeron® with some improvement over the next 2 weeks. The patient's 6-month evaluation on July 24, 2006 revealed no evidence of disease recurrence or distant metastases, and she was continued on STI571/placebo. Due to the persistence of her depressive symptoms, the dose of Remeron® was increased on August 9, 2006 and again on September 13, 2006 (Cycle 8, Day 28). Additionally, oxazepam was started for anxiety.

The patient began Cycle 9 of STI571/placebo on September 14, 2006. On September 20, 2006 (Cycle 9, Day 7), the patient experienced severe mood alterations that were interfering with her daily functions. She also stated that she had suicidal ideations, but no suicidal plans. She began a Remeron® taper and started on desipramine and Klonopin®. On September 21, 2006 (Cycle 9, Day 8), the patient discontinued her STI571/placebo and was removed from protocol treatment on September 22, 2006 (Cycle 9, Day 9). At a follow-up visit on September 25, 2006, the patient described improvement in her mood and functioning and will continue with psychiatric therapy. Based on the severity of the event, a request was made to break the study blind; however, this information is pending.

The patient's past medical history is significant for asthma, anxiety, hypertension, hypercholesterolemia, and uterus prolapse. In addition, the patient had a family history of anxiety (brother) and depression (mother and brother). Medications taken at the time of the event included Albuterol®, Flovent®, Benadryl®, aspirin, oxazepam, Protonix®, Reglan®, Cogentin®, Remeron®, and magnesium supplement.

There have been three other incidences of depression reported to the NCI as serious adverse events through AdEERS under the STI571 NSC, as shown in the table below.


	Grade	Attribution
Depression (n=3)	4	1 Unlikely
	3	1 Unlikely
	2	1 Possible

The patient was receiving STI571/placebo in the adjuvant setting and had no known recurrence of GIST throughout her adjuvant therapy. Therefore, it was unlikely that the depression was secondary to GIST. However, because she developed severe gastro-esophageal reflux, her STI571/placebo was dose reduced and she was started on Reglan[®], an agent which has been associated with depression in patients with and without prior history of depression, with symptoms ranging from mild to severe and including suicidal ideation and suicide. According to the patient, by June 30, 2006, she had been experiencing listlessness, anxiety, and depressive thoughts for 3-4 weeks duration, which coincided with approximately 6 weeks of Reglan[®] administration and a decrease in her adjuvant therapy. Therefore Reglan[®] therapy has a possible causal relationship to the severe depression and a possible relationship between the event and STI571/placebo cannot be ruled out at this time.

There have been 3,170 patients enrolled in NCI-sponsored clinical trials under the STI571 NSC 716051.

	Mood alteration:
	Depression
STI571/Placebo	Possible
GIST	Unlikely
Reglan[®]	Possible

Date: 10/25/06

Signature: 
A. Dimtrios 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