



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: February 23, 2007
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_1280006

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: February 5, 2007
FROM: A. Dimitrios Colevas, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: STI571 (Imatinib Mesylate, Gleevec[®]) NCI IND Safety Report, AE# 1280006
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/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC is attached:

A 78-year-old male with a gastrointestinal stromal tumor developed acute colonic ulceration and rectal bleeding while on a phase 3 trial utilizing the investigational agent STI571 or placebo.

ADVERSE EVENTS ASSESSMENT

IND 61135 NSC 716051 STI571 (imatinib mesylate, Gleevec™)	ADVERSE EXPERIENCE REPORT NO. 42 IND Safety Report: Event: Gr. 3: Hemorrhage, GI: Lower GI NOS Gr. 3: Ulcer, GI Colon
AE: 1280006	Protocol: ACOSOG-Z9001

The patient is a 78-year-old male with gastrointestinal stromal tumor (GIST) who developed acute colonic ulceration and rectal bleeding while on a phase 3 trial utilizing the investigational agent STI571 or placebo. He began his first course of treatment on September 26, 2006, receiving STI571 or placebo 400 mg PO daily, on Days 1-28, every 28 days for 1 year. Prior to the events, he received the last dose of STI571 or placebo on November 27, 2006 (Cycle 3, Day 1).

The patient was initially diagnosed with GIST in July 2006 and is status post radical tumor resection, distal pancreatectomy, splenectomy, and partial resection of the stomach. He began the investigational therapy on September 26, 2006 and completed two cycles. The patient began Cycle 3 on November 27, 2006. Later that day, he presented to his physician's office with complaints of rectal bleeding and reported that earlier in the day he had a bowel movement and passed large amounts of dark blood. He denied abdominal pain or cramping with the bleeding. The patient also reported that he had two additional episodes of bright red rectal bleeding in smaller amounts. He was admitted to the hospital for further evaluation and given IV fluids. STI571 (or placebo) was placed on hold. His hematocrit at admission was 33.1% (reference range: 38.6-48.0%), which was decreased from a November 3, 2006 hematocrit of 42.2%. On November 28, 2006 his hematocrit had decreased to 29.4%. A colonoscopy performed that day was significant for multiple, medium scattered diverticula in the sigmoid colon; a few aphthous ulcers in the colon between 30 and 40 cm; and colon mucosal inflammation. No evidence of pseudopolyps or colon carcinoma was found. An esophagogastroduodenoscopy (EGD) revealed a single chronic ulcer in the body of the stomach, which showed no stigmata of recent hemorrhage, and a single large diverticulum within the esophagus. Gastric ulcer tissue samples were consistent with mild, chronic inflammation. Staining for *Helicobacter* was negative. Histological findings of the colonic tissue samples were significant for colitis found in the colonic anastomosis region, colitis with mucosal erosion or ulceration in the descending colon at 40 cm, and no abnormalities in the rectum or descending colon at 30 cm. The patient was allowed to resume his diet and treated with a proton pump inhibitor, Asacol® and Cipro®. The patient's hematocrit stabilized, and no further bleeding occurred. He was discharged to home on November 29, 2006 with instructions to follow-up with his physician in 2 weeks, resume all home medications, including the investigational therapy at a reduced dose, and start Reglan®.

The patient's past medical history is significant for diverticulitis, colon polyps, an enlarged prostate, inguinal hernia repair (30 years prior), umbilical hernia repair in 2006, and tobacco use (2 packs per week). Medications taken at the time of the event included low dose Ecotrin®, Benadryl®, and a multivitamin.

Lower gastrointestinal hemorrhage is known to be associated with STI571 therapy. There have been 48 other cases of gastrointestinal hemorrhage and 3 other cases of gastrointestinal ulcers reported to the NCI as serious adverse events through AdEERS under the STI571 NSC, as summarized in the table below. Of the three cases of reported gastrointestinal ulcers, two patients also had accompanying grade 3 lower gastrointestinal hemorrhage.

Adverse Event	Grade	Attribution
GI Hemorrhage (n=48)	5	2 Possible, 1 Unlikely
	4	3 Unlikely, 1 Unrelated
	3	4 Probable, 24 Possible, 7 Unlikely, 1 Unrelated
	2	1 Unlikely
	1	4 Possible
GI Ulcers (n=3)	4	1 Unlikely
	3	2 Possible

A total of 3289 patients have been enrolled in NCI-sponsored clinical trials under NSC 716051.

In this case, it is felt that the rectal bleeding is most likely from acute colonic ulceration, while a probable causal relationship is considered to exist between the acute colonic ulceration and STI571/placebo therapy; hence, the investigational therapy is considered to be indirectly related to the bleeding.

	Lower GI Hemorrhage	GI Ulcer: Colon
STI571 or placebo	Probable	Probable
GIST	Unlikely	Unlikely
Ecotrin [®] , low dose	Possible	Possible
Colon ulcer	Probable	N/A
Stomach ulcer	Unlikely	Unrelated

Date:

2/6/07

Signature:

AAC

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