

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 06 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_1068486

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/dkf
enclosure



DATE: September 25, 2006 *AP 9/27/06*
FROM: A. Dimitrios Colevas, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: STI571 (Imatinib Mesylate, Gleevec™) NCI IND Safety Report, AE# 1068486
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(s), previous experience under this IND, and the total number of patients enrolled in trials under this IND is attached:

A 42-year-old female with acute lymphoblastic leukemia experienced grade 3 hypocalcemia and elevated SGPT (ALT) levels while on a phase 2 trial using the investigational agent STI571 following chemotherapy, irradiation, and an allogeneic peripheral blood stem cell transplant.

ADVERSE EVENTS ASSESSMENT

IND 61135 NSC 716051 STI571 (imatinib mesylate, Gleevec™)	ADVERSE EXPERIENCE REPORT NO. 37 IND Safety Report: Initial Event: Gr. 3: Hypocalcemia Gr. 3: SGPT (ALT) serum glutamic pyruvic transaminase Protocol: CALGB-10001
AE: 1068486	

The patient is a 42-year-old female with acute lymphoblastic leukemia (ALL) who experienced hypocalcemia and elevated SGPT (ALT) while on a phase 2 trial using the investigational agent STI571 following chemotherapy, irradiation, and an allogeneic peripheral blood stem cell (PBSC) transplant. The patient was to receive allopurinol 300 mg PO daily on Days -8 to -2; fractionated total body irradiation on Days -7 to -4; etoposide 60 mg/kg IV over 4 hours on Day -3; Prograf® (tacrolimus) 0.05 mg/kg/day via continuous IV infusion on Days -1 to 3 and 0.03 mg/kg/day via continuous IV infusion on Days 4 to 56; allogeneic PBSC transplant on Day 0; methotrexate 10 mg/m² IV on Day 1 and 5 mg/m² IV on Days 3 and 6; G-CSF 5 µg/kg/day SC beginning on Day 4 until ANC > 1500; and STI571 400 mg daily for 28 days, every 28 days, beginning on Day 30 post-transplant and continuing until obtaining two negative reverse transcriptase-polymerase chain reaction (RT-PCR) assays 3 months apart or experiencing relapse. The patient underwent a PBSC transplant on May 23, 2006 and began therapy with STI571 on June 27, 2006. She received the last dose of tacrolimus on August 11, 2006 and the last dose of STI571 on August 16, 2006.

The patient was initially diagnosed with Philadelphia chromosome positive ALL in November 2005 and had received no other therapies prior to starting the CALGB-10001 protocol. She began her allogeneic transplant course on May 15, 2006 (Day -8) and underwent a PBSC transplant on May 23, 2006 (Day 0), but did not begin STI571 therapy until June 27, 2006 (Day 35). Treatment was complicated by elevated tacrolimus blood levels (up to 26.1 ng/mL on June 27, 2006), despite receiving small doses of the agent (0.5-1 mg daily), and subsequent neurotoxicity (including blurry vision and mild tremors) resulting in a dosage decrease of 0.5 mg every other day. In addition, the patient experienced grade 3/4 graft versus host disease diagnosed by skin biopsy on July 21, 2006 (Day 59 post-transplant), for which she was treated with prednisone with improvement in symptoms by July 28, 2006 (Day 66 post-transplant). However, the patient then experienced sleep problems and depression, for which Lexapro® and amitriptyline were initiated on July 28, 2006, and mental status changes (including confusion, disorientation, positive Romberg test, and some dysmetria on finger-to-nose and heel-to-shin examination) on August 11, 2006 (Day 80 post-transplant). Tacrolimus was terminated that day.

On August 15, 2006 (Day 84 post-transplant), the patient was noted to have a markedly elevated SGPT/ALT level, accompanied by a gradual increase in confusion, and profound hypocalcemia, associated with severe vitamin D deficiency; these events were attributed to prednisone administration and her previous gastric bypass surgery, and possibly exacerbated by mucositis associated with the transplant. The patient was treated with IV calcium and vitamin D supplements while being weaned off prednisone. STI571 therapy was discontinued on August 16, 2006 (Day 85 post-transplant). A liver biopsy performed on August 17, 2006 (Day 86 post-transplant) showed central venous congestion with hepatocyte dropout and marked hemosiderosis. There was no evidence of graft versus host disease. Although no venoocclusive disease was identified, it could not be completely excluded. On August 22, 2006 (Day 91 post-transplant), the patient was noted to have a markedly elevated parathyroid hormone level of 3394 pg/mL and was hospitalized on August 26, 2006 (Day 95 post-transplant) after a severe anxiety attack and orthostatic syncopal episode resulting in a fall. Upon admission, the patient was anxious, her lip was quivering, and there were some oral movements reminiscent of tardive dyskinesia. Her neurologic evaluation revealed a mild tremor of the right upper extremity with a pill-roll activity. All psychotropic drugs were discontinued, except Lexapro®. Blood and urine cultures showed growth of coagulase-negative *Staphylococcus epidermidis*. In addition, her urine cultures were positive for growth of *Enterococcus* species. She was treated with trimethoprim, Fluconazole®, vancomycin, and acyclovir. The electrolyte imbalance was corrected, and the patient was administered vitamin D 50,000 units PO weekly. After adenovirus was cultured from her central catheter and hematuria was identified, cidofovir and probenecid were

added to the patient's therapy. An MRI of the brain on August 27, 2006 revealed mucosal thickening in the ethmoid sinuses, but was otherwise unremarkable. Her mental status began to rapidly improve after Zyprexa® treatment was initiated on August 31, 2006. Cerebrospinal fluid evaluation from August 31, 2006 showed 96% lymphocytes (reference ranges: 40-80) and was otherwise normal. By September 1, 2006, the patient's condition had significantly improved. She was discharged on September 4, 2006 after completing her 10-day course of vancomycin in stable condition.

Pertinent laboratory values are as follows:

	6/29/06 Day 37 post-transplant	7/14/06 Day 45 post-transplant	7/21/06 Day 59 post-transplant	8/8/06 Day 79 post-transplant	8/15/06 Day 85 post-transplant	8/26/06 Day 94 post-transplant (Admission)	9/3/06 Day 103 post-transplant (prior to discharge)
Calcium (mg/dL) (reference ranges: 8.5-10.5 mg/dL)	7.8	7.5	7.5	Within normal limits	6.1	8.2	7.9
Total protein (g/dL) (reference range: 6.7-8.6 g/dL)	6.4	4.5	4.9	Within normal limits	5.2 (6.4-8.2 g/dL)	6.3	3.8
Albumin (g/dL) (reference range: 3.5-5.5 g/dL)	3.1	2.7	2.9	Within normal limits	3.5 (3.4-5.0 g/dL)	3.6	2.3
ALT/SGPT (U/L) (reference range: 0-45 U/L)	Within normal limits	159	117	582	1142 (30-65 U/L)	615	140
AST/SGOT (U/L) (reference range: 15-41 U/L)	Within normal limits	133	63	141	247 (30-65 U/L)	142	28
Total bilirubin (mg/dL) (reference range: 0.00-1.00 mg/dL)	Within normal limits	Within normal limits	Within normal limits	Within normal limits	1.76 (0.10-1.00 mg/dL)	1.8	0.9
Parathyroid hormone, PTH (reference range: 10-65 pg/mL)	-	-	-	-	3394 (8/22/06)	674 (8/29/06)	-
Total 25-OH vitamin D (D2+D3) (reference range: 25-80 ng/mL; < 10 ng/mL = severe deficiency)	-	-	-	-	< 6.0 (8/18/06)	<6.0	-
Tacrolimus level, ng/mL (therapeutic range: 5-10 ng/mL)	9.3	11.8	5.2	6.4	-	-	-

The patient's past medical/surgical history is significant for gastric bypass surgery in 1995, abdominoplasty in 1996, cesarean sections, and a toxic reaction to morphine (hallucinations). Medications taken at the time of the event included Levaquin®, Micro-K®, Septra®, acyclovir, magnesium supplement, Provera®, Florinef®, fluconazole, Atarax®, prednisone, Lidex® cream, amitriptyline, Haldol®, and Neurontin®.

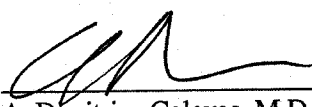
Elevated SGPT level is an event known to be associated with STI571. There have been seven other incidences of hypocalcemia reported to the NCI as serious adverse events through AdEERS under this IND, which are summarized in the table below.

Event	Grade	Attribution
Hypocalcemia (n = 7)	4	1 Possible, 1 Unlikely
	3	1 Possible
	2	2 Unlikely, 1 Unrelated
	1	1 Possible

In this case, it is felt that a possible relationship between the hypocalcemia and STI571 therapy cannot be excluded, and the elevated SGPT level is considered probably related to STI571 therapy. There have been 2,794 patients enrolled in NCI-sponsored clinical trials under this IND.

	Hypocalcemia	SGPT
ST1571	Possible	Probable
Acute lymphoblastic leukemia	Unlikely	Unlikely
Tacrolimus	Possible	Possible
Graft versus host disease	Unlikely	Possible
Hyperparathyroidism	Probable	Unrelated

Date: 9/27/06

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