



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: August 11, 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_PHH02005GB03990

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



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: August 1, 2006

FROM: A. Dimitrios Colevas, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: STI571 (Imatinib mesylate; Gleevec™) Investigator Notification: **Multiple Sclerosis**
Novartis Report # PHHO2005GB03990

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. An investigator notification, which describes multiple sclerosis in a patient participating in a Novartis-sponsored clinical study utilizing the investigational agent STI571, was recently distributed to investigators.

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

- Send a copy of this letter to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of this letter 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 Dear Doctor Letter and Suspect Adverse Reaction Report that describe the following adverse event are attached:

A 34-year-old male with chronic myelogenous leukemia developed multiple sclerosis while participating in a phase 3 study utilizing the investigational agent STI571.

There have been no incidences of multiple sclerosis, 11 incidences of muscle weakness, and 20 neurological events reported to the NCI as serious adverse events under the STI571 NSC 716051, which are summarized in the table below.

Adverse Event	Grade	Attribution
Muscle weakness (n=11)	4	1 Possible, 1 Unlikely, 1 Unrelated
	3	1 Possible, 3 Unlikely, 2 Unrelated
	2	2 Unlikely
Neurological events (n=28)		
Fall (n=1)	3	1 Unrelated
Hemiparesis/hemiplegia (n=5)	4	1 Unrelated
	3	2 Unlikely, 2 Unrelated
Mental status changes (n=2)	2	1 Possible, 1 Unlikely
Motor (n=7)	4	1 Possible, 1 Unlikely
	3	3 Unlikely, 1 Unrelated
	2	1 Unlikely
Motor-face (n=1)	4	1 Unlikely
Possible ALS (n=1)	3	1 Unlikely
Sensory (n=3)	3	1 Possible, 1 Unrelated
	2	1 Unrelated
Speech Impairment (n=6)	4	1 Unlikely, 1 Unrelated
	3	1 Unlikely, 1 Unrelated
	2	2 Unlikely
Weakness (n=1)	3	1 Unlikely
Tremor (n=1)	2	1 Unlikely

A total of 3125 patients have been enrolled in NCI-sponsored trials under NSC 716051.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

On an unspecified date the patient suffered Bell's palsy. Magnetic resonance imaging of the head revealed the patient to have multiple plaques of demyelination. At the time of reporting the Bell's palsy had resolved, the outcome of the multiple plaques of demyelination was not known. The investigator did not provide an assessment of causality, however, the sponsor's medical safety expert provided a provisional causality assessment of not suspected.

Follow-up received on 22 Apr 2005: The patient commenced study medication on 5 Jul 2000. The patient developed Bell's Palsy on 7 Jan 2005 and multiple plaques of demyelination on 24 Jan 2005 which were both considered to be medically significant. The patient completely recovered from the Bell's Palsy on an unknown date and the outcome of the multiple plaques of demyelination was unknown. The investigator did not suspect a relationship between the event and the study medication.

Follow-up received on 06 May 2005: The patient had made a completely recovery from the Bell's Palsy by 15 Jan 2005. The outcome of the multiple plaques of demyelination was not known as the patient had not been re-scanned.

Data reconciliation received 26 Sep 2005:
The end date of the Bell's Palsy was 31 Jan 2005, not 15 Jan 2005 as previously reported.

Follow-up received on 08 Mar 2006: The investigator now considers the Bell's Palsy and plaques of demyelination to be related to the study medication.

Follow-up received on 15 Mar 2006; prior to circulation of previous follow-up: The investigator reported that occasional symptoms of the demyelination persist and the patient still has extensive brain magnetic resonance imaging (MRI) abnormalities consistent with ongoing demyelination. The study medication was continued. At the time of reporting, a cerebro-spinal fluid (CSF) oligoclonal band analysis was pending. In the investigator's opinion, this event was suspected to be related to the study medication because there was no other obvious cause.

Follow-up received on 16 Jun 2006: The investigator reported that the patient was experiencing minimal and variable symptoms of the demyelination at present. There had been some visual deficit, but little other sensory or motor disturbance at the time of reporting. Tests carried out in March 2006 were positive for oligoclonal bands, diagnostic of multiple sclerosis.

Follow-up received on 22 Jun; prior to circulation of previous follow-up: The investigator considered that the multiple sclerosis was quite possibly related to Glivec therapy.

Novartis Comment: Serious adverse event report: (other significant medical event), assessed as unexpected according to the Investigator's Brochure.

The information provided in this individual case does not warrant a change to the Investigator's Brochure. The topic will be monitored closely. Investigator causality is suspected.

13. Relevant Tests

(Date Unknown) Magnetic resonance imaging of the patient's head revealed multiple plaques of demyelination.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1 STI 571 vs IFN-ALPHA + CYTARABINE (STI 571 vs IFN-ALPHA + CYTARABINE) Capsule; Regimen #1	400 mg, QD; Oral	Chronic myeloid leukaemia	05-JUL-2000 00:00 / Ongoing; Unknown

To: All Investigators in Imatinib (STI571) Studies*

DATE: 28 June 2006
Re: Investigator Notification for Imatinib (STI571)
Manufacturer Case ID PHHO2005GB 03990
Multiple sclerosis, Demyelination, Facial palsy
Study CSTI571 0106

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements, we wish to share with you medically significant follow up information concerning the above report initially circulated on 17 March 2006.

To summarize again,

A 34-year-old male was enrolled in study protocol CSTI571 0106, a Phase III study of STI571 versus interferon-alpha combined with Cytarabine in patients with newly diagnosed, previously untreated chronic myelogenous leukaemia in chronic phase. The patient started the study medication on 5 July 2000. On an unspecified date the patient suffered Bell's palsy. Magnetic resonance imaging of the head subsequently revealed multiple plaques of demyelination. The patient had made a completely recovery from the Bell's palsy by 31 Jan 2005. The investigator did not provide an assessment of causality; however, the sponsor's medical safety expert provided a provisional causality assessment of not suspected.

Follow-up received on 08 and 15 Mar 2006 indicated that the investigator now considers the plaques of demyelination to be related to the study medication.

It was reported that occasional symptoms of the demyelination persist and the patient still has extensive brain magnetic resonance imaging (MRI) abnormalities consistent with ongoing demyelination. At the time of reporting, a cerebro-spinal fluid (CSF) oligoclonal band analysis was pending. The study medication was continued. In the investigator's opinion, this event was suspected to be related to the study medication because there was no other obvious cause.

Follow-up received on 16 and 22 June 2006: Tests carried out in March 2006 were positive for oligoclonal bands, i.e. diagnostic of multiple sclerosis. The investigator reported that the patient was experiencing minimal and variable symptoms of the demyelination. There has been some visual deficit, but little other sensory or motor disturbance at the time of reporting. The investigator considered that the multiple sclerosis was quite possibly related to Glivec therapy.

We ask that you please inform your Institutional Review Board or Ethics Review Board of this event, if you have such an obligation.

* 00005

Yours sincerely,

Richard Pilot, MD, MPH
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United States

Attachment: CIOMS case report

* Novartis Investigator Notification: International Guidelines for Good Clinical Practice as well as specific health authority regulations require that clinical investigators be informed of any adverse drug reaction which is serious (according to specific regulatory criteria), unexpected (i.e. not specifically mentioned in the Investigator's Brochure) and which has a 'reasonable possibility' (in the opinion of the reporter and/or the Company) of being related to the study medication. While Novartis tries to obtain all meaningful information as soon as possible, we are required to communicate all available information within a specified time of its receipt. Since initial data is frequently incomplete, further information must be sent in the form of follow-up reports. Where they have such an obligation, investigators are expected to inform institutional review boards/ethics committees, of each investigator notification. Should Novartis believe that a change in protocol or other action needs to be taken on the basis of clinical reports or other available data, the company will communicate such changes to involved investigators.