



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_PHHO2006CA16505

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



To: All Investigators in Imatinib (ST1571) Studies*

Date: 11 October 2006

Re: Investigator Notification for Imatinib (ST1571): **Fatal Angioedema** – PHHO2006CA16505

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements we wish to inform you of a serious, unexpected, possibly related adverse report of fatal angioedema that occurred in a patient being treated with Imatinib during the course of a clinical study.

For the current case, details of the adverse event are provided in the attached CIOMS form, which contains the available information as reported to Novartis.

To summarize briefly,

Initial report received on 02 October 2006: A 76 year-old patient was enrolled in study protocol CSTI571 ACA07, a phase I-II study evaluating the safety and efficacy of imatinib mesylate (Gleevec) combined with reinduction chemotherapy using mitoxantrone, etoposide and cytarabine in patients with relapsed/refractory c-kit positive acute myeloid leukemia (AML). The patient received her first dose of the study medication on 22 September 2006. The patient's medical history includes previous pneumonia (with initial 'chemo' given July 2006), pulmonary oedema (associated with ischaemia possibly), an allergy to penicillin, arthritis and hypothyroidism. An onset date of 24 September 2006 was reported for this event. On 27 September 2006 the patient noted mild discomfort in her throat, however she was eating, drinking and swallowing well. The patient also experienced increasing oedema and facial swelling. On 30 September 2006, the patient experienced increased oral secretions, a thick coating on the lining of her mouth and tongue, increasing swelling of the tongue and difficulty swallowing. On 30 September 2006, the study medication was temporarily interrupted. On 01 October 2006, the patient suffered cardiopulmonary arrest with pulseless electrical activity. The patient was resuscitated and intubation was difficult due to airway oedema and angioedema which were thought to be secondary to the study medication. The patient's treatment included Lasix, Benadryl and steroids. At the time of reporting the patient's condition was still present and unchanged. The investigator described the patient as 'palliative only'. This event was assessed as life-threatening. The investigator did suspect the event to be related to the study medication.

Follow-up received on 04 October 2006: The investigator confirmed that the onset date of this event was 27 September 2006 (previously incorrectly reported as 24 September 2006). The patient died on 03 October 2006 due to the cardiopulmonary arrest and angioedema. No autopsy was performed. The investigator did suspect the event to be related to the study medication..

A search of the Novartis Clinical Safety database for MedDRA SMQ Angioedema with fatal outcome and suspected causality has not identified any further cases.

We will keep you informed if further medically significant information becomes available. We ask that you please inform your Institutional Review Board or Ethics Review Board of this event, if you have such an obligation. For clinical trials in the U.S. only, if you are utilizing the services of a central

Institutional Review Board (IRB) that has been contracted through Novartis, Novartis will submit the Investigator Notification on your behalf to the central IRB.

Sincerely,

Sumita Rai, MD
PVL, Integrated Safety, Novartis Pharmaceuticals
One Health Plaza 419, Rm 1258
East Hanover NJ 07936, USA
862-778-6370 (phone)

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.

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year	76 Years	Female	69.90 kg	Day	Month	Year	
											<input checked="" type="checkbox"/> PATIENT DIED Date: 03-OCT-2006 <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input checked="" type="checkbox"/> LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Airway oedema / Angioedema [Angioneurotic oedema] ([Tongue coated], [Dysphagia], [Swollen tongue], [Oral discharge], [Swelling face], [Throat irritation]) Cardiopulmonary arrest [Cardio-respiratory arrest] ([Electromechanical dissociation], [Resuscitation], [Intubation complication]) Case Description: Initial report received on 02 Oct 2006: This patient (centre number XXX, patient number XX) was enrolled in study protocol CST1571 ACA07, a phase I-II study evaluating the safety and efficacy of imatinib mesylate (Gleevec) combined with reinduction chemotherapy using mitoxantrone, etoposide and cytarabine in patients with relapsed/refractory c-kit positive (continue)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1 GLEEVEC(STI571/CGP57148B T35717+TAB)Tablet		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) #1 400 mg, QD	16. ROUTE(S) OF ADMINISTRATION #1 Oral	
17. INDICATION(S) FOR USE #1 Acute myeloid leukaemia		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
18. THERAPY DATES(from/to) #1 22-SEP-2006 00:00 / 30-SEP-2006 00:00	19. THERAPY DURATION #1 9 days	

III. CONCOMITANT DRUG(S) AND HISTORY (Continued on Additional Information Page)

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 AMLODIPINE (AMLODIPINE) ; ; Unknown #2 IRBESARTAN (IRBESARTAN) ; ; Unknown #3 THYROXINE (LEVOTHYROXINE SODIUM) ; ; Unknown	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates JUL-2006 to Unknown	Type of History / Notes Description Pneumonia Previous pneumonia with initial 'chemo' given Pulmonary oedema Associated with ischaemia possibly

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
24b. MFR CONTROL NO. PHHO2006CA16505		
24c. DATE RECEIVED BY MANUFACTURER 04-OCT-2006	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	25b. NAME AND ADDRESS OF REPORTER
DATE OF THIS REPORT 10-OCT-2006	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

ADDITIONAL INFORMATION**7+13. DESCRIBE REACTION(S) continued**

acute myeloid leukemia (AML). The patient received her first dose of the study medication on 22 Sep 2006. The patient's medical history includes previous pneumonia (with initial 'chemo' given Jul 2006), pulmonary oedema (associated with ischaemia possibly), an allergy to penicillin, arthritis and hypothyroidism. An onset date of 24 Sep 2006 was reported for this event. On 27 Sep 2006 the patient noted mild discomfort in her throat, however she was eating, drinking and swallowing well. The patient also experienced increasing oedema and facial swelling. On 30 Sep 2006, the patient experienced increased oral secretions, a thick coating on the lining of her mouth and tongue, increasing swelling of the tongue and difficulty swallowing. On 30 Sep 2006, the study medication was temporarily interrupted. On 01 Oct 2006, the patient suffered cardiopulmonary arrest with pulseless electrical activity. The patient was resuscitated and intubation was difficult due to airway oedema and angioedema which were thought to be secondary to the study medication. The patient's treatment included Lasix, Benadryl and steroids. At the time of reporting the patient's condition was still present and unchanged. The investigator described the patient as 'palliative only'. This event was assessed as life-threatening. The investigator did suspect the event to be related to the study medication.

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Novartis Comment: Serious adverse event report "angioedema", (death), assessed as unexpected according to the Investigator's Brochure. It is Novartis' policy to assess a case with a fatal outcome as unexpected unless the label specifically mentions death as a possible outcome of the listed risks. Investigator causality is suspected.

Serious adverse event report "Cardiopulmonary arrest", (Death), assessed as expected according to the Investigator's Brochure. Investigator causality is suspected.

13. Relevant Tests

(date unknown) Heart rate (HR): 101
 (date unknown) Blood pressure (BP): 133/56
 (date unknown) Arterial Oxygen Concentration (SaO2): 1002 40%
 (date unknown) Respiratory rate (RR): 19 ACV
 (date unknown) Temperature (T): 35

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#4 METFORMIN (METFORMIN) ; ; Unknown
 #5 ROSIGLITAZONE (ROSIGLITAZONE) ; ; Unknown
 #6 CYTARABINE (CYTARABINE) ; ; Unknown
 #7 PREDNISOLONE (PREDNISOLONE) ; ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Penicillin	Drug hypersensitivity
Unknown		Arthritis
Unknown		Hypothyroidism