



To: All Investigators in RAD001 Studies*

Date: Jan 15, 2008

Re: Investigator Notification for RAD001
Pulmonary embolism (fatal) / PHHO2008DE110940-follow-up (downgraded to not suspected)

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements, we would like to inform you of significant follow-up information for a previously reported a serious, unexpected, possibly related adverse event of pulmonary embolism (fatal) that occurred in a 63-year-old female patient who received RAD001 in the study CRAD001C2325, a randomized, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumor receiving Sandostatin LAR and RAD001 10 mg/d or Sandostatin LAR and placebo.

Follow-up reported that this event was re-assessed by the investigator as not suspected to be related to study medications. Details of the adverse event as reported to Novartis are provided in the attached CIOMS I form.

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,

Holly Zhang, MD
Senior Pharmacovigilance Leader, Integrated Medical Safety
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey, 07936-1080
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.

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS <small>(first, last)</small>	1a. COUNTRY Germany	2. DATE OF BIRTH			2a. AGE 63 Years	3. SEX Female	3a. WEIGHT 62.00 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day 24	Month SEP	Year 1944			Day 02	Month SEP	Year 2008		
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Urosepsis [Urosepsis] ([Pyrexia], [C-reactive protein increased]) Septicaemia with Candida [Candida sepsis] Stenosis of ureter due to lymph node metastases [Ureteric stenosis] Stenosis of ureter due to lymph node metastases [Metastases to lymph nodes] Pulmonary embolism [Pulmonary embolism] Case Description: Initial report received on 12 Sep 2008: This patient (centre no. xxx, patient no. <p style="text-align: right;">(Continued on Additional Information Page)</p>										<input checked="" type="checkbox"/> PATIENT DIED Date: 24-SEP-2008 <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING	

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 Vs Placebo (RAD 666 RAD+TAB) Tablet #2) SANDOSTATIN LAR (OCTREOTIDE WITH POLY(D L-LACTIDE-CO-GLYCOLIDE)) Unknown		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
15. DAILY DOSE(S) #1) Double blind #2) Double blind	16. ROUTE(S) OF ADMINISTRATION #1) Oral #2) Unknown	
17. INDICATION(S) FOR USE #1) Carcinoid tumour (Carcinoid tumour) #2) Carcinoid tumour (Carcinoid tumour)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
18. THERAPY DATES(from/to) #1) 22-APR-2008 / Unknown #2) 22-APR-2008 / Unknown	19. THERAPY DURATION #1) Unknown #2) Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Unknown Unknown	Description Hydronephrosis (Hydronephrosis) Cardiac arrhythmia (Arrhythmia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS	
24b. MFR CONTROL NO. PHHO2008DE11094		25b. NAME AND ADDRESS OF REPORTER	
24c. DATE RECEIVED BY MANUFACTURER 05-JAN-2009	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:		
DATE OF THIS REPORT 13-JAN-2009	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP:		

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

xxx) was enrolled in the study CRAD001C2325, a randomised, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumour receiving Sandostatin LAR and RAD001 10 mg/d or Sandostatin LAR and placebo. The patient's medical history included: hypertension, strumectomy, ureter stent, dyspnoea, cardiac arrhythmia and uronephrosis. The patient received her first dose of study medication on 22 Apr 2008. On 02 Sep 2008 the patient presented with urosepsis, which resulted in hospitalisation. The study medication was temporarily interrupted. At the time of this report the patient's condition was still present and unchanged. The investigator did not suspect a relationship between this event and the study medication (RAD001 or Sandostatin).

Follow up received on 01 Oct 2008: The patient died on 24 Sep 2008 due to urosepsis. The investigator reassessed the causality and suspected a relationship between this event and RAD001, but did not suspect a relationship to Sandostatin.

Follow-up received on 14 Oct 2008: The investigator confirmed that an autopsy was not performed. The cause of death as reported on the death certificate was pulmonary embolism. The investigator suspected a relationship between the pulmonary embolism and RAD001. In the absence of the investigator's causality assessment for pulmonary embolism and Sandostatin LAR, the Novartis medical safety physician provisionally assessed this event as not suspected to be related to Sandostatin LAR pending further information.

Internal review on 20 Oct 2008: No new information. Report resubmitted following unblinding due to regulatory reporting requirements.

Follow up received on 21 Oct 2008: The patient's medical history included septicemia with Candida and stenosis of the ureter due to lymph node metastases. The investigator also stated that the carcinoid tumour was relevant history leading up to the pulmonary embolism. Signs and symptoms of the urosepsis included fever and elevated CRP. Blood cultures were performed (results not provided). Treatment for the urosepsis included Fluconazole. No diagnostic tests or treatment was given for the pulmonary embolism. The patient had a sudden and unexpected death. At the time of death the patient's disease was stable. The investigator did not suspect a relationship between the pulmonary embolism and Sandostatin LAR.

Follow-up received on 11 Nov 2008: The investigator confirmed that they did not suspect a relationship between the pulmonary embolism and Sandostatin LAR.

Follow-up received on 02 Dec 2008: The investigator clarified the onset date of the stenosis of ureter due to lymph node metastases as 04 Sep 2008 and the septicemia with Candida as 06 Sep 2008, which involved hospitalisation. The investigator did not suspect a relationship between the events and the study medication RAD001 or Sandostatin LAR.

Follow up received on 05 Jan 2009: The investigator clarified that they did not suspect a relationship between the event of pulmonary embolism and the study medication (RAD and Sandostatin LAR).

Novartis Comment: Serious adverse drug reaction report, urosepsis (death), assessed as expected according to the Investigator's Brochure for RAD001C. Investigator causality is suspected to RAD001 (not Sandostatin LAR).

New information received on 05 Jan 2009, reported that the event of pulmonary embolism has been reassessed as not suspected to the study medication (RAD001 and Sandostatin LAR) by the investigator.

All remaining reported leading events and associated symptoms were assessed as not suspected by the investigator.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Blood culture		
		results not provided		

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown		Dyspnoea (Dyspnoea);
Unknown		Ureteral stent insertion (Ureteral stent insertion);
Unknown		Strumectomy (Thyroidectomy);
Unknown		Hypertension (Hypertension);