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Thru:	Solomon Iyasu, M.D., Director, Division of Epidemiology, OSE
From:	Diane K. Wysowski, Ph.D., Epidemiologist, Division of Epidemiology, OSE
Subject:	Cancer in Clinical Trials of Prasugrel
Drug Name(s):	Prasugrel (Effient)
Submission Number:	N/A
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Applicant/sponsor:	Eli Lilly/Daiichi-Sankyo
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EXECUTIVE SUMMARY

Prasugrel is "a novel thienopyridine" that binds to the $P2Y_{12}$ receptor to confer antiplatelet activity. The sponsors, Eli Lilly and Daiichi Sankyo, have submitted an application to the Division of Cardiovascular and Renal Products (DCVRP) of FDA for its marketing approval for the reduction of atherthrombotic events in patients with acute coronary syndromes including patients with unstable angina or non-ST-segment elevation myocardial infarction who are managed with percutaneous coronary intervention and patients with ST-segment elevation myocardial infarction who are managed with primary or delayed percutaneous coronary intervention. The application has been reviewed by Karen Hicks, M.D., DCVRP, and Thomas Marciniak, M.D., DCVRP, and both reviewers have questioned the carcinogenicity of prasugrel as compared to clopidogrel in the clinical trial TRITON.

The DCVRP requested a consult from the Office of Surveillance and Epidemiology to comment on the recommendation that a postmarketing registry be set up to track cancer occurrence in patients administered prasugrel, to suggest other recommendations besides a registry for further evaluation of neoplasia with prasugrel, and to suggest recommendations FDA can make about the design of a planned upcoming trial called TABY to assess prasugrel's risk of neoplasia.

Several documents were provided by the DCVRP on the conduct of the trial and on the carcinogenicity issue and these were reviewed. However, some of the cancer data were preliminary in nature. The review was further hampered by data integrity issues because cancer cases were not excluded from the trial and important information on how and when the cases came to detection was not supplied.

We suggest that the sponsor be asked to attempt to resolve the question of the carcinogenesis of prasugrel with the available data from TRITON ***before*** the drug is marketed. In support of that, a number of suggestions in the Results section of the text below have been made. We believe that the sponsor should be asked to finalize data on cancer cases and submit the data to the DCVRP and other FDA staff for review. They should be asked to use their data to make the case for or against the carcinogenicity of their drug. In brief, we suggest the sponsor provide more definitive comparative summary data *for each drug* related to the following:

- unknown and other cancers,
- nonfatal cancer cases by site,
- site-specific cancer deaths,
- combined fatal and nonfatal site-specific cancer cases,
- site-specific cancers that were known to be prexisting at baseline, likely preexisting because of symptoms at baseline, and likely newly developed during the trial,
- time from study drug to breast cancer diagnosis, to lung cancer diagnosis, and to colorectal diagnosis,

- available risk factors in cases of breast cancer, lung cancer (cigarette smoking *not* tobacco use), and colorectal cancer,
- protective factors in cases of colorectal cancer (long-term aspirin use), and
- geographic clustering (country of residence) for breast, lung, and colorectal cancer cases.

The text in the Results section provides a fuller explanation of these points.

We do not believe the question of carcinogenicity of prasugrel can be adequately answered using a registry.

The planned TABY study might be useful if it is powered for site-specific cancer outcomes (lung, colorectal, and breast) as the major safety endpoints and if important risk factors for site-specific cancers are collected and analyzed.

If ethically feasible, trials of individuals with cancer or premalignant tumors, or subjects at high risk of cancer development might be undertaken to try to determine if prasugrel has a promotional effect.

Trials of animals with cancerous tumors might be undertaken to observe how tumor size varies with prasugrel, clopidogrel, excipients of each drug, and placebo exposure.

If not already done, the FDA chemists should be asked about the carcinogenicity of the prasugrel and clopidogrel molecules and differences that might explain a carcinogenicity potential of prasugrel.

1 BACKGROUND

Prasugrel is "a novel thienopyridine" that binds to the $P2Y_{12}$ receptor to confer antiplatelet activity. The sponsors, Eli Lilly and Daiichi Sankyo, have submitted an application to the Division of Cardiovascular and Renal Products (DCVRP) of FDA for its marketing approval. The application has been reviewed by Karen Hicks, M.D. and Thomas Marciniak, M.D., DCVRP, and both reviewers have questioned the carcinogenicity of prasugrel as compared to clopidogrel in the clinical trial TRITON.

As a result, a consult was sent to the Division of Drug Oncology Products (DDOP) to assess the carcinogenic potential of prasugrel. Bhupinder S. Mann, MBBS, completed the consult. In addition to other suggestions, he recommended that DCVRP seek the review of staff in the Office of Surveillance and Epidemiology (OSE), FDA.

A consult was sent from DCVRP to OSE requesting answers to the following questions:

1) "In addition to the recommendations made by Oncology which include establishment of a registry by the sponsor and labeling suggestions, what other recommendations do you have for the Division of Cardiovascular and Renal Products for further evaluation/surveillance of neoplasia with prasugrel?"

2) "The sponsor is planning on doing another 13,000 patient trial in patients with acute coronary syndromes who are medically managed (study TABY) and plans to start this trial soon. What recommendations should be made to the sponsor with respect to the conduct of this study, screening for malignancy, and follow-up of bleeding/new malignancies/worsening prior malignancies?"

The consult to OSE was sent to the Division of Epidemiology (DEPI). Results of the review follow.

2 METHODS AND MATERIALS

The following documents were reviewed:

1) Statistical Review and Evaluation of Carcinogenicity Studies (104 week Carcinogenicity in Rats and Mice) of Mohammad Atiar Rahman, Ph.D., dated December 26, 2007.

2) A memorandum entitled "Prasugrel carcinogenicity" sent from Thomas Marciniak, M.D., DCVRP, to Karen Hicks, M.D., DCVRP, dated April 22, 2008, that included graphs of new solid cancers in subjects exposed to prasugrel and clopidogrel in clinical trials.

3) A document entitled "Prasugrel: the Case for Carcinogenicity" that was sent on April 18, 2008, by Dr. Marcinaik to Dr. Hicks and others as an attachment to an email.

4) The consult from Bhupinder S. Mann, MBBS, DDOP, to the DCVRP dated April 24, 2008, that provides his assessment of the carcinogenic potential of prasugrel.

5) Selected sections of the clinical review of prasugrel by Karen Hicks, M.D., DCVRP.

3 RESULTS

3.1 Summary of Background Materials and Data

The following summarizes the main points concerning the potential carcinogenicity of prasugrel based on a review of the above documents:

1) For the preclinical mouse two-year study in which groups of 55 mice were randomly allocated to prasugrel (30, 100, and 300 mg/kg/day) and compared with placebo (0.5w/v% tragacanth solution), the FDA statisticians found "no statistically significant dose response relationship or differences in survival across treatment groups in either sex. Tests showed statistically significant positive dose response relationship in the incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in both sexes. Pairwise comparisons showed statistically significantly increased incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in high dose group in males, and medium and high dose groups in females compared to their respective control." The rat studies that involved lower doses of the study drug were generally negative.

2) TRITON (also called TAAL) is a large, international, multicenter, randomized, double-blind, active-controlled clinical trial of prasugrel versus clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Patients numbering 13,608 were randomized 1:1 and followed for 6 to 15 months. The labeled regimen for clopidogrel (300 mg loading, 75 mg maintenance) was compared to prasugrel (60 mg loading, 10 mg maintenance). All patients also took aspirin.

About 94% of patients in each drug group completed the protocol, and there were no statistically significant differences between the study drugs in the number of deaths, withdrawal of consent, incomplete follow-up of < 166 days, inability to attend the study termination visit, and lost to follow-up.

According to staff of the DCVRP, TRITON had some data integrity issues including incomplete data and confusion about whether cancer cases identified were prevalent (known at baseline) or newly diagnosed. For instance, according to Dr. Marciniak's memo, "Prasugrel: the Case for Carcinogenicity" dated April 18, 2008, his analyses were preliminary "because there are issues with the completeness of the data. Some adverse events are tersely recorded as 'LUNG MASS' and we do not yet have the details on all potential cancer cases." To attempt to take the latter problem into account, Dr. Marciniak excluded cancers diagnosed during days 0 to 7 (9 for prasugrel and 7 for clopidogrel).

With skin and brain cancers also excluded and focusing on solid tumors, Dr. Marciniak found that the number of "new first cancers" in TRITON was 104 for prasugrel and 69 for clopidogrel. A Kaplan-Meier incidence plot for all new cancers (excluding skin and brain) after 7 days in TRITON showed a clear divergence between the drugs and higher rates beginning at four months for prasugrel. Cancer sites showing the largest differences between the drugs included breast (5 for prasugrel and 1 for clopidogrel), colorectal (19 for prasugrel and 8 for clopidogrel), lung (21 for prasugrel and 13 for clopidogrel), and "unknown/other" (7 for prasugrel and 2 for clopidogrel).

The sponsor attempted to explain the excess cancers in the prasugrel group by asserting that there is detection or ascertainment bias because prasugrel appears to cause earlier bleeding than clopidogrel, thus affecting the detection of cancers. While earlier bleeding might explain an earlier detection of colorectal cancer, the sponsor's explanation would not be applicable for the detection of lung and breast cancers.

In addition to the excess occurrence of cancer cases in the prasugrel group in TRITON, Dr. Marciniak's report stated that there was an excess number of cancer deaths for prasugrel (n = 19) compared with clopidogrel (n = 11). However, there appears to be a discrepancy in the number of deaths related to malignancies because the clinical review by Dr. Hicks (page 34) states that the number was 21 for prasugrel and 17 for clopidogrel.

To address if carcinogenesis was a class effect, Dr. Marciniak obtained data from large outcome trials for clopidogrel. Combined preliminary analyses for CREDO, CURE, and CHARISMA showed excess numbers of lung cancer for clopidogrel versus placebo (87 vs. 71) and of colorectal cancer (60 vs. 50), but not of breast cancer (16 vs. 25).

For CHARISMA, the largest of the three studies, an overall excess of cancer cases occurred in the placebo group compared with clopidogrel (310 vs. 330); the Kaplan-Meier incidence plot showed no difference in cancers for the two arms. When cancers from the three studies were combined (excluding skin and brain cancers), there was a modest excess for placebo (385 for clopidogrel vs. 391 for placebo). Final data from the oldest study, CAPRIE, in which clopidogrel and aspirin were compared, were not available, but preliminary analyses of new solid cancers in CAPRIE showed Kaplan-Meier incidence plots with similar incidence rates for the two drugs through nearly 30 months of exposure.

3) Dr. Mann in DDOP reviewed these data to answer the questions from DCVRP. The highlights of his review follow: He expressed uncertainty about the statistical or clinical significance of the difference in incidence of total cancers between the arms of the TRITON study "because the Type I error rate for this exploratory significance testing is

unknown" and because the combining of different cancers with differing etiologies and natural histories is hard to interpret; he does not believe that data from TRITON support prasugrel as a promoter of cancer because subjects with cancer were not screened for cancer at entry and there was no specified follow-up to detect cancers; he states that the cancers found in TRITON are likely to be "incidental" given the absence of cancer screening at study entry and short drug exposure (6 to 15 months). He also suggested that DCVRP ask OSE for suggestions to further evaluate the possible carcinogenicity of prasugrel; that the cases be analyzed further to assess ascertainment bias; that SEER cancer data might be useful for comparison purposes; that a randomized trial of participants screened for cancer would definitively answer the question of prasugrel's carcinogenicity potential; and that a registry might be useful to track the incidence of cancer in prasugrel users.

3.2 OSE Reviewer's Recommendations to Assess Carcinogenicity of Prasugrel

There are a number of problems with TRITON that make the results on carcinogenicity difficult to evaluate and inconclusive. However, a number of actions might be taken to assess the carcinogenicity of prasugrel based on the TRITON data.

1) "Unknown/other" cancers--

The sponsor should be asked to obtain and provide more specific information about the "unknown/other" cancers (7 for prasugrel and 2 for clopidogrel). For all unknown cancers, the primary site-specific cancer should be obtained from the health care provider and medical records. The list of the number of site-specific cancers should be revised accordingly. "Other cancers" should be listed by site, and the number that remains unknown should be listed separately.

2) Cancer deaths by site specific cancer--The discrepancy in the number of cancer deaths should be resolved (19 for prasugrel vs. 11 for clopidogrel or 21 vs. 17). In addition, the sponsor should be asked to provide information on each cancer-related death including number for each drug by primary cancer site, demographic information (age, sex, race, country of residence), date of cancer diagnosis, time from drug use to diagnosis, symptoms leading to diagnosis, date of symptom onset, time from drug use to symptom onset, method of diagnosis, and risk factors for development of each cancer. Deaths from cancer should be scrutinized to determine if they are similar to the non-fatal cancer cases.

3) Baseline screening, the problem of incident vs. prevalent cancers, and the timing of diagnosis--Since the incidence of cancer was not a main safety endpoint, cancers (other than terminal cancer) at baseline were <u>not</u> excluded. Consequently, a proportion of the cancers in the prasugrel and clopidogrel groups identified during the duration of the clinical trial (from 6 months to 15 months) were preexisting and known at baseline. In another proportion of cancers, tumors were not known at baseline but were likely preexisting at baseline because of symptoms at baseline, and in a third group, tumors were not preexisting at baseline and were asymptomatic but developed during the trial.

The company should be asked to provide the number of cancers by drug, by site, and by whether each cancer was:

- preexisting and known at baseline,

- likely to be preexisting at baseline (because of symptoms at baseline) but diagnosed after drug exposure, and
- not preexisting at baseline and asymptomatic and diagnosed after drug exposure.

This would help determine if either prasugrel or clopidogrel has a predominantly inducer or a promoter effect on carcinogenesis.

4) Once the newly-diagnosed site-specific cancers are obtained for prasugrel and clopidogrel, the site-specific cases in each group should be described and compared for differences in age, sex, race, country of residence, date of diagnosis, time from drug use to diagnosis, symptoms leading to diagnosis, date of symptom onset, time from drug use to symptom onset, method of diagnosis, and risk factors for development of each cancer. While the numbers may be small, this type of analysis could uncover patterns that are, or not, suggestive of a drug-induced effect.

Important risk factors for development of female breast cancer are age, race, country of residence, ethnicity/religion, previous breast cancer history, genetic and family history of breast cancer, increased body mass index (BMI) and overweight and obesity (for postmenopausal women), reproductive history (e.g., nulliparity and older age at first term birth), current or previous use of menopausal hormones (hormone replacement therapy), and alcohol use.

Important risk factors for colon cancer are age, sex, race, country of residence, history of colonic polyps, family history of colon cancer, increased BMI and overweight and obesity, and high fat diet. Some medications such as aspirin and NSAIDS appear to be protective. A higher frequency of current or previous aspirin or NSAID use in patients randomized to clopidogrel might explain the lower incidence in the clopidogrel group for colon cancer. A higher frequency of current or previous aspirin or NSAID use in patients randomized to clopidogrel might explain the lower incidence in the clopidogrel group, so history of aspirin and NSAID use would be important information to collect.

Important risk factors for lung cancer are age, sex, race, country of residence, history of and current cigarette smoking, history of exposure to second-hand smoke, occupation and occupational exposures, asbestos exposure, radiation exposure, and chemical exposures (e.g., arsenic, benzene). Collecting information on "tobacco use" (as in TRITON) is not specific enough since the use of some tobacco products (e.g., smokeless tobacco) is not associated with lung cancer. If the prasugrel tobacco users had more cigarette smokers than the clopidogrel users, this imbalance could explain the excess lung cancers in the prasugrel group.

In addition, we note an excess number of esophageal cancer cases for prasugrel compared with clopidogrel (5 vs. 2). This would be consistent with a hypothesis of more cigarette smoking and alcohol use in subjects exposed to prasugrel compared with clopidogrel since esophageal cancer is related to these risk factors.

While a randomized trial such as TRITON should result in a balance of variables between groups, the possibility exists that some variables were not balanced between the prasugrel and clopidogrel groups. Since cancer was not an expected endpoint, information on risk factors for cancer was not collected. Any risk factors for lung, breast, colon, and esophageal cancer that were collected should be analyzed by drug to see if they fit the

usual pattern of risk factors for each cancer. Divergence from the usual pattern might be suggestive of a drug effect.

5) Site-specific incidence rates could be calculated for the cancers in TRITON and compared with site-specific cancers from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Registry to determine if the cancer rates in the drug groups are above the expected U.S. background rates. Higher than expected rates in a drug group might suggest a drug effect. About 30% of subjects in TRITON were from the U.S., but the number of cancer cases by country of residence was not found in the materials reviewed.

Assuming that, on average, patients were exposed to the drug in the trial for about one year, in TRITON the incidence rate for lung cancer was 13/6696 = 194.1/100,000 person-years (PYs) for clopidogrel and 21/6682 = 314.3/100,000 PYs for prasugrel. Based on the U.S. SEER data for years 2001-2005, the age-adjusted incidence rate for lung and bronchus cancer was 63.9/100,000 PYs, and 358.7/100,000 PYs for individuals ≥65 years old (1). Since the rates are highly age dependent (as well as sex and race dependent), obtaining the ages (and sexes and races) of the lung cancer cases in each of the clopidogrel and prasugrel groups might show if the rates in each group are higher than the U.S. population lung cancer rates.

Again, assuming one year patient exposure to drug in TRITON, the incidence rate for female breast cancer rate was 1/6696 = 14.9/100,000 PYs for clopidogrel and 5/6682 = 74.8/100,000 PYs for prasugrel. Based on the U.S. SEER data for 2001-2005, the age-adjusted incidence rate of invasive female breast cancer was 127.8/100,000 PYs, 84.9/100,000 PYs for women < 65 and 424.4/100,000 PYs for women ≥65 years old (1). The rates in TRITON appear lower than expected in each drug group when compared with the U.S. population breast cancer rates.

With the same assumption of a one year exposure, the incidence rate for colorectal cancer in TRITON was 8/6696 = 119.5/100,000 PYs for clopidogrel and 19/6682 = 284.3/100,000 PYs for prasugrel. Based on the U.S. SEER data for 2001-2005, the age-adjusted incidence rate of invasive colon cancer was 39.1/100,000 PYs and 227.6/100,000 PYs for persons ≥65 years old (1). Since the rates are highly age dependent (as well as sex and race dependent), obtaining the ages (and sexes and races) of the colon cancer cases in each of the clopidogrel and prasugrel groups might show if the rates in each group are above the U.S. population colon cancer rates.

Clustering of lung, breast, colon, and esophageal cancer cases by geographic location would suggest a non-drug effect. We suggest that the sponsor examine the site-specific cancer cases by country to determine if such clustering exists.

3.3 The Use of a Registry to Address the Carcinogenicity of Prasugrel

A registry has been proposed to track the incidence of cancer in prasugrel users. While this could be done, it is unlikely that conducting a registry of patients exposed to prasugrel will resolve the question of the carcinogenicity of the drug for the following reasons:

1) Registries often have poor enrollment of subjects and inadequate sample sizes; these factors lengthen considerably the time to deriving conclusions.