

2) Patients who enroll in registries may be different in important ways from patients who decline to enroll in registries (selection bias), thus limiting the representativeness of the findings.

3) A primary problem is that registries lack controls limiting interpretation of results. In the situation of U.S. patients exposed to prasugrel, the U.S. population site specific cancer incidence rates obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data could be used to compare the rates in prasugrel users with those for the U.S. population. However, this comparison is crude and often not acceptable since individuals indicated to receive prasugrel may be unlike the general population in ways that may predict cancer outcome. Variables that affect outcome are not factored into such an analysis.

4) Ascertainment of disease, death, and causes of death in registries is often incomplete.

5) Registries often have considerable loss to follow-up of patients over time.

6) Data are often incomplete or missing for important variables that affect outcomes.

7) Data are often not verified by medical records, death certificates, and autopsy reports.

6) The logistics of following patients longitudinally and tracking their health outcomes are difficult.

#### 3.4 The Use of a New Randomized Clinical Trial (TABY) to Address the Carcinogenicity of Prasugrel

The company is planning to conduct a new randomized clinical trial referred to as TABY in which prasugrel will be compared to clopidogrel in patients with unstable angina or non-ST-segment elevation myocardial infarction who are medically managed. In this study, the number of study subjects is planned to exceed 13,000. The sponsor proposes lowering the loading dose to 30 mg for patients needing a loading dose and lowering the maintenance dose from 10 mg to 5 mg in patients  $\geq 75$  years old or weighing  $< 60$  kg.

The comments of Dr. Hicks about this study are as follows: "Based on our preliminary analysis which suggests there may be an increased rate of malignancy in the prasugrel treatment group, the sponsor will need to carefully collect all information related to neoplasia and bleeding. Perhaps cancer screening could be incorporated into the trial following the index hospitalization. Additionally, the sponsor will need to clearly distinguish neoplasia as past medical history from a new diagnosis in the clinical trial. Patients with worsening of their underlying malignancy should also be followed closely."

Dr. Hicks also states, \_\_\_\_\_  
 \_\_\_\_\_ the Division of Cardiovascular and Renal Products has recommend that the sponsor reformulate prasugrel and use this reformulated drug product in Study TABY."

b(4)

This study might have a better chance of resolving the question of the induction of carcinogenesis of prasugrel than the use of a Registry. However, if the drug is reformulated, the results would be pertinent to the reformulated drug.

To determine if prasugrel compared with clopidogrel increases the risk of incident cancer, a large randomized controlled clinical trial of individuals who have no history of

cancer diagnoses and no preexisting cancer would be required. Subjects having previous or current cancer diagnoses and current signs and symptoms of cancer at baseline would need to be excluded from entry. While the subjects will be randomized and presumably the risk factors for cancer would be balanced, the subjects should be queried about the risk factors for cancer and imbalances in risk factors should be adjusted for in the analyses. To determine increases in site-specific cancers (e.g., lung, breast, or colon) as opposed to overall cancer, a sample size would need to be calculated that might exceed the planned 13,000 subjects. The company should supply its calculations for its estimates of sample size and study duration to the FDA and a biostatistician should be consulted to determine if the calculated sample size and study duration seems adequate.

As stated above, 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), 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 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.

Note that some of the important risk factors for coronary disease are similar to those for breast and colon cancer. This overlap of risk factors might supply an explanation for an increase of these cancers with both clopidogrel and prasugrel, but not with a difference between these two drugs.

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). Tobacco use (collected 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.

Subjects would need to be followed closely throughout the study for the development of any symptoms suggestive of cancer.

### 3.5 Other Studies to Address the Carcinogenicity of Prasugrel

The promotional effect of prasugrel on carcinogenesis has been questioned. If within the bounds of ethical standards for clinical trial investigations, patients with histories of treated cancer (who are at high risk of cancer reoccurrence) could be randomized to clopidogrel or prasugrel and monitored for the development of new cancer. Also, as explained in the paragraphs below, patients at high risk of site-specific cancers of interest

(lung, breast and colon) could be randomized to clopidogrel or prasugrel and followed for new cancer development.

To determine if prasugrel compared with clopidogrel promotes colon cancer in those at high risk of colon cancer, individuals with a history of documented benign colonic polyps and who meet the other requirements for study entry, could be randomized to clopidogrel or prasugrel and followed to determine bleeding rates and colon cancer (via colonoscopy and biopsy) in subjects in the two arms.

To determine if prasugrel compared with clopidogrel promotes lung cancer in those at high risk of lung cancer, individuals with documented chronic obstructive pulmonary disease or who have a history of long-term, heavy cigarette smoking and who meet the other requirements for study entry, could be randomized to clopidogrel or prasugrel and followed to determine the development of lung cancer (via chest x-ray) in subjects in the two arms.

To determine if prasugrel compared with clopidogrel "promotes" breast cancer in those at high risk of breast cancer, individuals with a documented family history of breast cancer in first degree relatives (mother or sister) and who meet the other requirements for study entry, could be randomized to clopidogrel and prasugrel and followed to determine the development of breast cancer in the two arms.

Animal studies to measure promotion of tumor growth by randomizing animals with tumors to clopidogrel, prasugrel, excipients of each drug, and placebo, might also be considered and undertaken before drug marketing approval.

Also, in vitro carcinogenesis studies of clopidogrel, prasugrel, excipients of each drug, and placebo might be considered and undertaken before drug marketing approval.

If not already accomplished, FDA chemists should be asked to weigh in concerning their analysis of the structure and of the potential for carcinogenesis of the molecules of clopidogrel and prasugrel, and for their assessment of the differences between the two drugs that could explain a carcinogenic effect.

#### 4 RECOMMENDATIONS

We suggest that the sponsor be asked to try 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 text above have been made. 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 use their data to make the case for or against the carcinogenicity of their drug. In brief, we suggest the sponsor provide comparative individual and 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 preexisting 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 above Results section should be consulted for 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 cancer 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.

## 5 REFERENCES

1. Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2005/](http://seer.cancer.gov/csr/1975_2005/), based on November 2007 SEER data submission, posted to the SEER web site, 2008.

Diane K. Wysowski, Ph.D.

cc: HicksK/MarciniakT/UngerE/Pease-FyeM/DCVRP

Akhavan-ToyserkaniG/DempseyM/KarwoskiC/DRISK

WysowskiD/BrinkerA/IyasuS/DEPI

KortepeterC/HoustounM/WisemanC/AviganM/DAAEI

MannB/DDOP

Atiar/Biostatistics

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/s/

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6/12/2008 09:06:00 AM  
DRUG SAFETY OFFICE REVIEWER

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This study was a Phase 3, multicenter, randomized, parallel-group, double-blind (DB), double-dummy, active-controlled study. The study population included subjects with ACS who were to undergo PCI. ACS was defined as unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) with thrombolysis in myocardial infarction (TIMI) risk score  $\geq 3$  or ST-segment elevation myocardial infarction (STEMI). Subjects were treated with study therapy for a median follow-up period of at least 12 months, until they had completed at least 6 months of follow-up, and until at least 875 UA/NSTEMI subjects had reached the primary endpoint. The length of the study was 33 months. The first subject was assigned to therapy on November 5, 2004 and the last subject completed the study on July 22, 2007. The primary objective of this study was to test the hypothesis that prasugrel co-administered with aspirin was superior to clopidogrel co-administered with aspirin in the treatment of subjects with ACS who were to undergo PCI, as measured by a reduction in the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at study end.

A secondary efficacy endpoint was to evaluate the incidence of major and minor bleeding events.

Prasugrel, supplied as 10-mg tablets, were administered orally as a one-time 60-mg loading dose, followed by a once-daily 10-mg maintenance dose. Subjects were treated until study termination or 464 days from randomization, whichever was earlier.

There were no particular concerns about the clinical investigators chosen for inspection. However, the definition of myocardial infarction was changed towards the end of the study in January, 2006, and "nonfatal MI" is what drives the primary endpoint of the study.

The three sites that were chosen for inspection were all selected primarily because they were the largest sites in their respective countries/continents, and they showed the most favorable results for the drug under study.

There was one protocol inspected:

**H7T-MC-TAAL: A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects who are to Undergo Percutaneous Coronary Intervention (PCI)/TIMI 38**

**II. RESULTS (by Site):**

Name of CI, IRB, or Sponsor City, State or Country	Indication: Protocol #: and # of Subjects:	Insp. Date	Interim Classification  <i>NAI/VAI/OAI</i>	Final Classification  <i>NAI/VAI/OAI/ Pending</i>
William E. Downey, M.D. LeBauer Cardiovascular Research Foundation	H7T-MC-TAAL 108 enrolled 94 completed	4/21/08- 4/25/08	NAI	NAI

1200 North Elm Street Greensboro, NC 27401				
Johannes Paulus Remigius Herrman, M.D., M.P.H. Onze Lieve Vrouwe Gashuis Eerste Oosterparkstraat 279 Amsterdam, 1091 HA	H7T-MC-TAAL 121 enrolled 108 completed	5/19/08- 5/23/08	NAI	Pending
Saleem Y. Dawood, M.B., Ch.B. Vincent Palloti Hospital Dick Williamson Medical Centre Suite 2012, First Floor Alexandra Road Pinelands, W. Cape 7405	H7T-MC-TAAL 64 enrolled 53 completed	5/26/08- 5/30/08	NAI	Pending

Key to Classifications

NAI = No deviation from regulations.

VAI-No Response Requested= Deviations(s) from regulations.

VAI-R = Response Requested = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. William E. Downey, M.D.

LeBauer Cardiovascular Research Foundation  
1200 North Elm Street  
Greensboro, NC 27401

- a. **What was inspected:** At this site, 108 subjects were enrolled in protocol H7T-MC-TAAL. Out of these, 12 subject records were reviewed. The source records contained medical histories, examination visit data, lab reports and signed consent forms. The case report forms from 12 subjects were reviewed and compared with the source documents. No deviations were noted. Efficacy (cardiovascular death, nonfatal MI or nonfatal stroke) and safety (major and minor bleeding events) endpoints were reviewed and compared with source records. No discrepancies were noted. All SAE's were documented and reported properly.
- b. **General observations/commentary:** There were no significant protocol violations affecting data validity and efficacy, no underreporting of SAE's, and no enrollment of ineligible subjects. No form 483 was issued.
- c. **Assessment of data integrity:** Data from this site are acceptable.

2. Johannes Paulus Remigius Herrman, M.D., M.P.H.

Onze Lieve Vrouwe Gashuis  
Eerste Oosterparkstraat 279  
Amsterdam, 1091 HA

- a. **What was inspected:** Out of 121 subjects who were enrolled at this site, 108 completed the study. About a third (41) of the records were reviewed. CRF's were compared with the source records and no discrepancies were found. There was no evidence that AEs were under-reported.
- b. **General observations/commentary:** There were no significant protocol violations affecting data validity and efficacy, no underreporting of SAE's, and no enrollment of ineligible subjects. No form 483 was issued.
- c. **Assessment of data integrity:** Data from this site are acceptable. Preliminary review does not indicate any serious deviations or findings that would impact the validity or reliability of the submitted data.

3. Saleem Y. Dawood, M.B., Ch.B.  
Vincent Palloti Hospital  
Dick Williamson Medical Centre  
Suite 2012, First Floor  
Alexandra Road  
Pinelands, W. Cape 7405

- a. **What was inspected:** There were 92 subjects screened at this site, and 64 of these subjects were enrolled, with 53 completing the study. Half (32) of the enrolled subject's CRFs were reviewed. The source records contained medical histories, examination visit data, lab reports and signed consent forms. The case report forms from 12 subjects were reviewed and compared with the source documents. No deviations were noted. Efficacy (cardiovascular death, nonfatal MI or nonfatal stroke) and safety (major and minor bleeding events) endpoints were reviewed and compared with source records. No discrepancies were noted. All SAE's were documented and reported properly.
- b. **General observations/commentary:** There were no significant protocol violations affecting data validity and efficacy, no underreporting of SAE's, and no enrollment of ineligible subjects. However, there was one issue noted by the inspector. The patient, 270495-11003 had a pre-PCI CK-MB value of 19.6 at 7:15AM on 6/3/2005. Their PCI value was 18.9 at 8:00AM on 6/3/05. Their 6, 12, and 18 hour post PCI CK-MB values were 2.1, 8.1, and 16.7, respectively (values are in ng/ml.) The inspector thought this should have been coded as a peri-procedural MI. However, after carefully reviewing the protocol, it seems that this does not qualify as a peri-procedural event. The protocol states that "if the suspected event is within 48 hours of a percutaneous coronary intervention (PCI), the creatine kinase-myocardial bands (CK-MB) value (on at least two samples) must be >3x the upper limit of normal (ULN)." In this laboratory, the ULN is 5 ng/ml, so there is only one qualifying value, and only one sample. No form 483 was issued.

- c. **Assessment of data integrity:** Data from this site are acceptable. Since the adjudicators did not assess the case in question as a peri-procedural MI as per protocol, there could be an issue with the protocol design. However, the determination of the clinical significance of this finding will be deferred to the review division. A preliminary review does not indicate any serious deviations or findings that would impact the validity or reliability of the submitted data.

The preliminary inspection results for Dr. Hermann's and Dr. Dawood's sites noted above are based on communication from the field investigator. Further review and evaluation of the observations will be made when the EIR and exhibits are submitted. An inspection summary addendum will be generated if our assessment changes upon receipt and review of the EIR.

#### IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, for the two study sites inspected, it appears that there is sufficient documentation to assure that all study subjects audited did exist, signed informed consent documents, study eligibility criteria were fulfilled, and adverse events were adequately reported. Primary efficacy and safety endpoints were captured in accordance with protocol requirements. Based on preliminary review, the data are considered reliable in support of the proposed indication.

Follow-up action: An inspection summary addendum will be generated if conclusions changes significantly upon receipt and review of the EIRs and evidence exhibits from the international sites.

*{See appended electronic signature page}*

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