Figure 15: Sponsor's Breakdown of Non-Benign Neoplasms

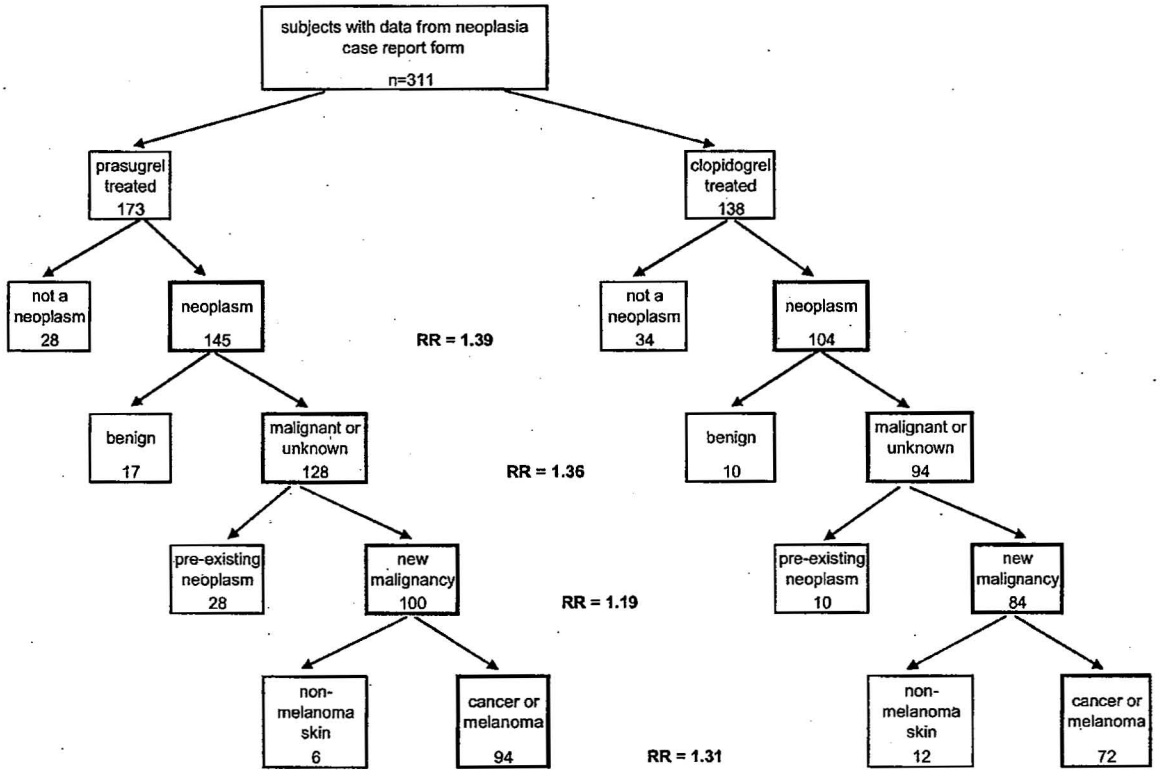

Table 15 (left) shows the sponsor's tabulation of these neoplasms, and is identical to Table 10 from the sponsor's May 9, 2008 Regulatory Response, except that a final line was added to remove the non-melanomatous skin cancers.

In terms of the sponsor's original hypothesis, that excess bleeding events in the prasugrel group led to ascertainment bias, the numbers of new, non-benign neoplasms where bleeding or anemia led to a diagnosis were 37 and 33 in the prasugrel and clopidogrel groups, respectively. Thus, the RR was largely unchanged when such cases disallowed (data not shown).

Cancer Mortality: There were 27 and 19 cancer deaths in the prasugrel and clopidogrel groups, respectively, for a RR of 1.42. If cancer deaths in subjects with pre-existing cancers are included in the totals, the numbers of deaths are 33 and 21, respectively (RR=1.57). The sponsor commented as follows:

> "The proportion of subjects diagnosed with a new nonbenign neoplasm that died due to malignancy was similar between treatment groups (27 of 100 subjects, 27% prasugrel; 19 of 84 subjects, 23% clopidogrel)."

Reviewer's Comments: Although the numbers of events are small, the imbalance in cancer deaths is concerning. The fact that similar proportions of subjects with cancer had a fatal outcome is not

Table 15: Sponsor's May 9, 2008, Analysis of New, Non-Benign Neoplasms

Analysis per:	sponsor		CDER	
neoplasm location	**prasugrel**	**clopidogrel**	**prasugrel**	**clopidogrel**
brain	0	1	0	1
eye	0	1	0	1
oral cavity and pharynx	1	2	1	2
breast	4	1	5	1
lung and bronchus	18	14	18	15
other respiratory/thoracic	1	0	1	0
any GI site	35	25	37	25
colorectal, stomach, esophagus	31	21	33	21
colorectal	20	11	22	11
esophagus	4	3	4	3
stomach	7	7	7	7
pancreas	2	3	2	3
liver	0	1	0	1
gallbladder/biliary	2	0	2	0
any GU site	20	19	23	21
kidney	5	4	5	4
bladder	5	8	6	8
prostate	10	7	12	9
gynecologic	2	1	2	1
malignant melanoma	3	2	3	2
non-melanomatous skin	6	12	5	12
endocrine	2	0	2	0
any hematologic	4	4	5	5
leukemia	2	1	2	2
lymphoma	2	2	2	2
other hematologic	0	1	1	1
metastasis unknown primary	3	0	3	1
other unknown primary	0	1	1	1
unknown	1	1		
other			2	
all	100	84	108	88
all, excluding non-melanomatous skin	94	72	103	76

reassuring. Moreover, if ascertainment bias were operational in the study and contributed to the imbalance in cancers, it would not account for additional deaths in the prasugrel group.

FDA Analysis:

The Division added three cancers that were not included in the sponsor's tabulation of malignancies. The "Neoplasm" CRF was not returned for subject 1013520854, but the original CRFs provided unambiguous documentation of the existence of a new bladder carcinoma; therefore, CDER categorized this case as a new cancer. Subject 61051813568 had a history of prostate cancer that antedated study entry, but underwent a right hemicolectomy on ——— for adenocarcinoma of the colon. (The pathology was described as showing "...moderately differentiated adenocarcinoma infiltrating through the full thickness of the muscularis propria.") This tumor was classified as malignant in the dataset cantea2.xpt, but for some reason had been reclassified as benign in the dataset neoplasm.xpt. CDER considered this subject to have a new malignancy as well. Finally, subject 1010413222 had an adverse event of "multiple skin cancer on both arms & hands" that the Division reclassified from benign to malignant.

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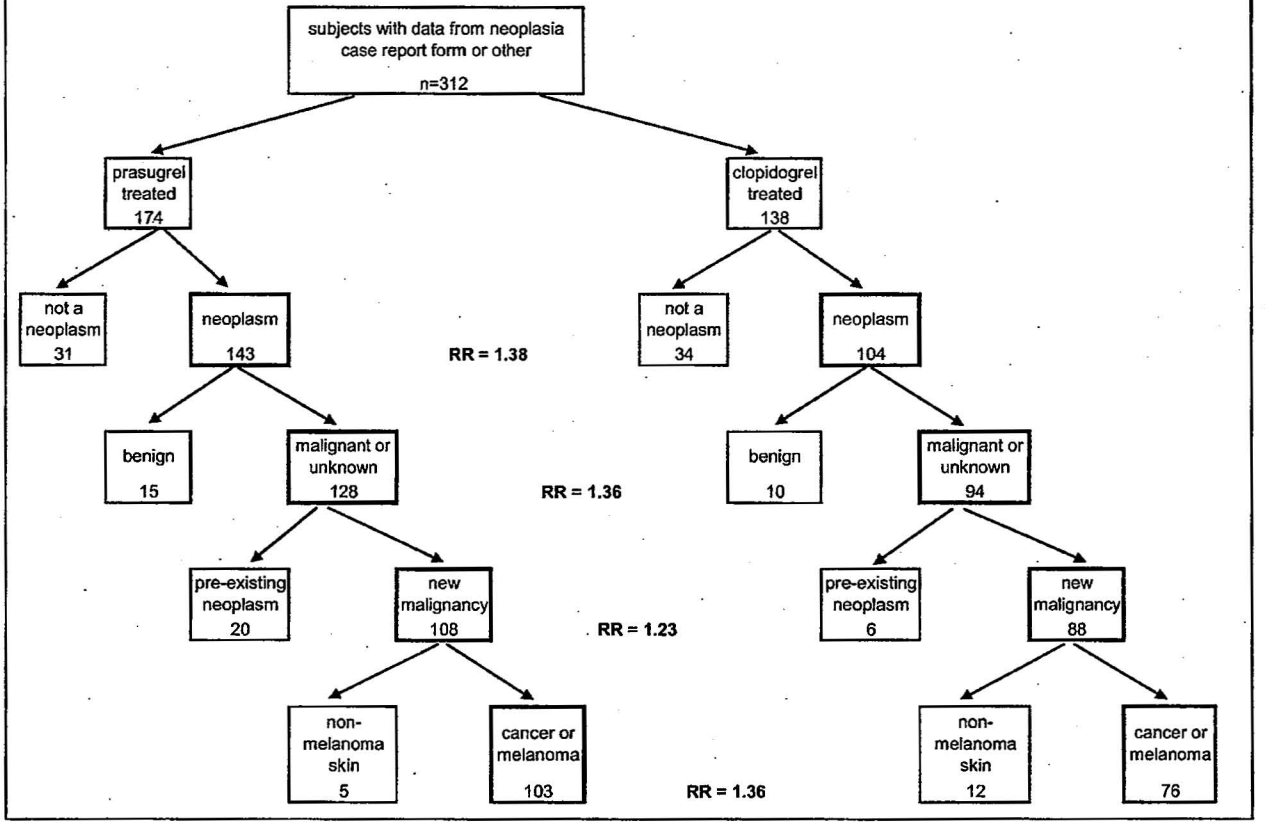
The Division then undertook a blinded review of CRFs for subjects with non-benign neoplasms where the sponsor had made a final determination that the neoplasm was pre-existing. Through

this process, the Division identified 3 subjects the sponsor had classified as having a pre-existing neoplasm (subjects 1017116675, 1018815272, and 1020015221) where the Division was not convinced there was sufficient evidence to substantiate either a change in status of the neoplasm, or an adverse event related to the neoplasm. The Division reclassified these 3 cases as "not a neoplasm."

There were 10 subjects whom the sponsor categorized as having a pre-existing neoplasm, where the Division disagreed. These were subjects 1004412788, 1022617856, 1027316242, 31073511345, 39067618325, 39068617832, 39069712358, 46060416222, 46066313229, and 97099323020. Many had symptoms or signs suggesting an abnormality (i.e., pain, bleeding, a hard prostate), but no actual diagnosis of malignancy prior to enrollment. Others had a pre-existing neoplasm, but developed a new neoplasm on study that was distinct from the first.

Having reclassified these subjects, the results of the Division's analysis are shown in Table 15 (right) and Figure 16. FDA's results are not importantly different from those of the sponsor.

Figure 16: FDA Breakdown of Non-Benign Neoplasms

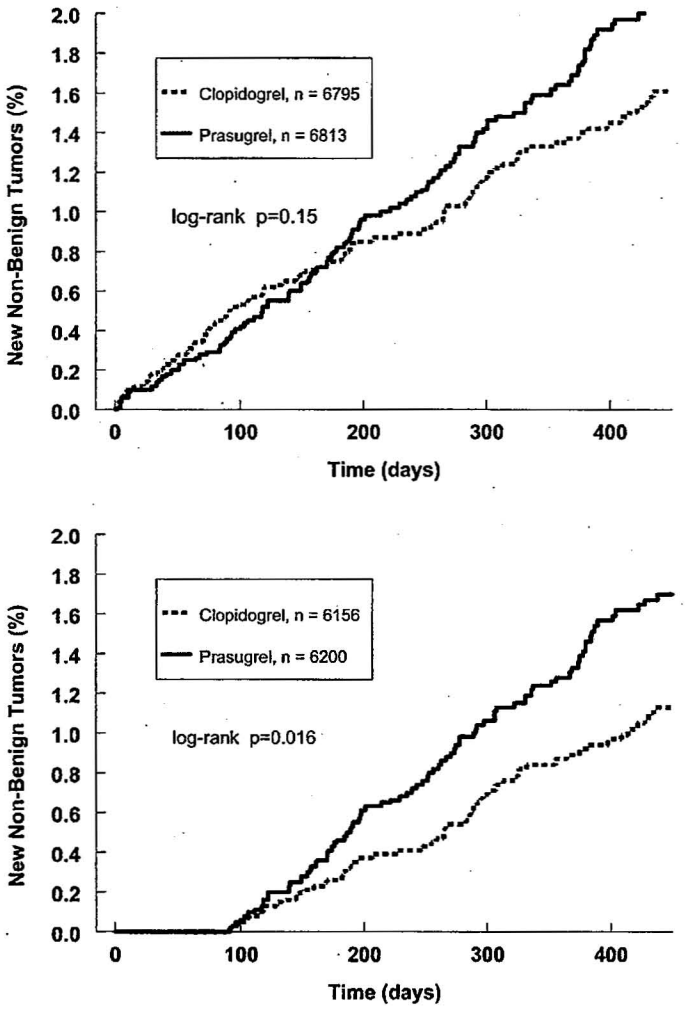


One hundred three (103) and 76 subjects in the prasugrel and clopidogrel groups, respectively, experienced a new neoplasm, characterized histologically as malignant or unknown, for a RR of 1.36 (non-melanomatous skin cancers excluded). Kaplan-Meier time-to-event analyses for cancer are displayed in Figure 17. The top panel shows a standard analysis, including all subjects, and the log-rank is 0.15. Because tumors that were detected very early, perhaps

through 90 days, were extremely unlikely to be causally related to prasugrel through any potential mechanism, the bottom panel shows the Kaplan-Meier analysis with events through the first 90 days excluded. Here the log-rank is 0.016. Had prasugrel-associated excess bleeding led to ascertainment bias, one would have expected the cancer rate in the prasugrel group to have exceeded the rate in the clopidogrel group during the earlier weeks of the study, when bleeding was more frequent and subjects were evaluated more frequently. In fact, the opposite tended to be true. Thus, the time-to-event analysis does not support the concept that ascertainment bias importantly influenced the findings.

Dr. Marciniak reviewed the data from the clopidogrel development program, and found no apparent effect of clopidogrel on cancer rates. CURE showed a doubling in the rate of colorectal cancer with clopidogrel compared to placebo (16 versus 8), but this was not observed in CAPRIE or CHARISMA. Clopidogrel was associated with excess lung cancer in CURE (12 versus 7) and CREDO (5 versus 0), but not in the larger CAPRIE (72 versus 74) or CHARISMA Studies (70 versus 63).

Figure 17: New, Non-Benign Neoplasms – Top Panel: All; Bottom Panel: Events After Day 90



The Division also sought the expertise of the Division of Drug Oncology Products, and their consult team (B. S. Mann, J. R. Johnson, and P. Cortazar) highlighted the following points (paraphrased here):

1. In terms of supporting the concept that prasugrel causes cancer, no analyses based on TAAL can be conclusive:
   a. TAAL was not designed to compare the cancer incidences between study arms, so the Type I error rate for this exploratory significance testing is essentially unknown.
   b. The absence of cancer at entry was not a requirement. There was no baseline cancer screening evaluation of study subjects.

c. The clinical significance of the statistical findings obtained by combining of different cancers in the comparisons is hard to interpret given differing etiologies and natural histories of the diverse types of cancers.

2. There are no data in TAAL to support a belief that prasugrel is a "promoter" in humans. Given the absence of a well defined cancer screening at study entry, short drug exposure to the study drugs (6 to 15 months), and no specified follow up to detect specific cancers, the cancers diagnosed on study are more likely to be incidental.

3. To determine whether worsening of cancer was related to study drugs or was spontaneous, one would need to study the progress of known cancers when exposed to study drugs and a placebo to address this issue. Such trials are not possible in humans for clinical, statistical, and ethical reasons.

4. Epidemiologic comparison with the SEER data may be helpful; however, the results are of limited value and likely to be inconclusive as the study population in TAAL is drawn from several different countries. SEER data come from US populations from selected cities/regions.

5. A definitive study would require a screened population (cancer free) of adequate size, randomly assigned to the study treatments and followed up for adequate time.

Cancer – Conclusions:
Prasugrel was associated with an excess number of new malignant tumors. Compared to clopidogrel, the relative risk of cancer was 36%, and the absolute risk was 0.4%. The distribution of tumor types was typical of the patient population, and little affected by prasugrel. According to United States Cancer Statistics, National Program of Cancer Registries, the leading types of cancer by incidence are: prostate, breast, lung/bronchial, and colorectal (http://apps.nccd.cdc.gov/uscs/, searched 7/2/08). In TAAL, the numbers of new cancer cases in these categories for prasugrel and clopidogrel were 12 versus 9, 5 versus 1, 18 versus 15, and 22 versus 11, respectively (Table 15). Because females comprised only ~25% of the subjects enrolled in TAAL, the numbers of breast cancer cases would be roughly doubled if extrapolated to a 50% female population.

Safety analyses are observational in nature and conducted without the benefit of pre-specified hypotheses or correction for multiplicity; therefore, there is always the possibility of a false positive finding. False positive results are, of course, *expected* under these circumstances. Beyond a mere association between prasugrel and excess cancers, therefore, biological plausibility, exposure-response, and other factors are helpful to support causality.

Considering the diverse biologies of these tumor types and the relatively brief 15-month time frame of TAAL, it is simply not plausible for carcinogenicity effects to underlie these trends in cancer cases (moreover, the results of carcinogenicity studies in the prasugrel development program were not positive). If in fact prasugrel is causally related to the excess cancers, a tumor promoter effect is much more likely. The time course of the incidence of new tumors (Figure 17) is consistent with some of the observations with exogenous erythropoietins and in patients with cancer.[3]

[3] Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *JCO*. 2005; 23:1-13.

There is a paucity of non-clinical data suggesting a role for prasugrel in tumor promotion. One could hypothesize that platelet aggregation and thrombosis provide natural defenses against tumor development and metastasis (processes with which prasugrel interferes), that prasugrel is pro-angiogenic, mitogenic, or that it acts as a tumor cell growth factor; however, all of this is purely speculative.

Given that prasugrel and clopidogrel share a number of similarities in their mechanisms of action, Dr. Marciniak re-visited the large clopidogrel outcome trials, CAPRIE, CREDO, CURE, and CHARISMA, with a combined sample size of over 39,000 subjects. He found no consistent trends suggesting that clopidogrel is a cancer promoter. This is reassuring, actually. Had clopidogrel been associated with a slight increase in cancer rates, it would suggest a class effect, which would make a stronger case for a causal role of prasugrel in cancer.

In summary, the difference in cancer rates raises concern. The time-to-event relation is reasonably consistent with a tumor promoter effect, and cancer deaths (27 for prasugrel versus 19 for clopidogrel, RR = 1.42) provide another reason for consternation. Conversely, the lack of an identifiable mechanism of action and the multiplicity of potential safety issues analyzed assuage our apprehension, at least to some extent.

Finally, if we assume a causal relation between prasugrel and excess cancers, the point estimate for the absolute risk is 0.4%. To place this risk into perspective with efficacy (Table 5), prasugrel was associated with a 2.1% absolute reduction in the triple efficacy endpoint, primarily due to a reduction in non-fatal myocardial infarction. Thus, for each 1000 patients treated with prasugrel, one might expect to prevent 21 myocardial infarctions, at a cost of 4 cancers. This trade seems advantageous, at least for many patients.

This reviewer suggests a warning in labeling regarding the excess cancers and cancer deaths. The labeling should suggest that consideration be given to use of alternative agents in patients with known cancer, but I would not go as far as to suggest that patients without a history of cancer switch to other agents after some arbitrary period in time (see below). This reviewer also suggests a postmarketing requirement to study the issue more carefully in a randomized controlled trial. This is consistent with the advice the Division received from the Division of Drug Oncology Products, Office of Oncology Drug Products, OND. The advice we have received from the Division of Epidemiology, OSE is that because of the limitations of registry data, including missing data, typically low and possibly biased enrollment, and the absence of controls, a registry is not likely to answer the question of cancer etiology.

6.2.5. QT Prolongation

The sponsor performed a thorough QT study in normal volunteers (Study TAAP), which was deemed negative and largely adequate by the Division's Interdisciplinary Review Team for QT Studies (S. Balakrishnan, Y. Chen, J. Zhang, N. Mehrotra, and C. Garnett). TAAP was a single-center, randomized, three-period crossover study wherein 60 healthy volunteers received either an 80-mg single dose of prasugrel or placebo. Subjects also received a single 400-mg oral dose of moxifloxacin, administered open label. Delta QTcF for moxifloxacin was 10.7 ms, with 90% C.I. 8.3 ms, 13.0 ms, demonstrating assay sensitivity, i.e., the study was adequately designed and conducted to detect an effect of a QT-prolonging drug on the QT interval. For prasugrel 80 mg, ΔQTcF was 2.1 ms, 90% C.I. -1.3 ms, 5.4 ms. Because the upper limit of the two-sided C.I. for the mean difference between prasugrel and placebo was <10 ms, the threshold for regulatory concern (per ICH E14 Guideline), the study was considered negative in the context of a positive moxifloxacin control.

The review team identified two key study limitations: 1) the 80-mg dose used in the study did not adequately emulate "worst-case" scenarios (based on intrinsic and extrinsic factors) for the 60-mg LD, although it did cover the expected high exposure scenario for the 5-or 10-mg MD; and 2) the ECG sampling schedule did not capture the t_{max} for metabolites, except for R-106583.

Because the lack of a QT effect fact could have been a function of dose and/or timing of ECG sampling, the QT Team compared R-119521 and R-106583 exposures achieved in TAAL to those achieved in TAAP, and concluded that prasugrel is unlikely to prolong QT interval after clinically relevant exposures.

In light of the QT Team's conclusion, and given that QT effects are inherently less important when the benefit of a drug is improvement in a cardiovascular outcome, no additional evaluation is needed for QT.

6.2.6. Discussion of primary reviewer's comments and conclusions

1. The primary clinical reviewer noted, "There appears to be a potential for drug-drug interaction with atorvastatin. One healthy subject in Study TAAV (Subject 115) experienced acute hepatic failure after co-administration of high-dose atorvastatin and prasugrel. Liver function abnormalities resolved after the discontinuation of both medications."

Reviewer's Comments: As noted in section 5.3, it is difficult to know the extent to which prasugrel was contributory, and the interaction occurred in only one subject. Thus, placement of a precaution in labeling seems unnecessary.

2. The primary clinical reviewer suggested that "...prasugrel should probably not be the treatment of choice in patients ≥ 75 years of age," noting that such patients appeared to receive less benefit from prasugrel, compared to clopidogrel.

Reviewer's Comments: In CURE, the study of clopidogrel versus placebo in the setting of ACS, triple endpoint event rates (cardiovascular death, MI, or stroke) for subjects ≥75 years of age were 17.8% and 19.2%, respectively. In TAAL, efficacy for subjects ≥75 years of age was similar in the prasugrel and clopidogrel groups (16.0% versus 17.0%, respectively). Thus, efficacy is marginal for both products in patients ≥ 75 years old. Importantly, however, the risk of bleeding is much higher in the elderly, and this appears to be particularly true with prasugrel. The frequencies of fatal bleeding in subjects 75 years of age and older were 1.01% for prasugrel and 0.11% for clopidogrel. The respective frequencies of ICH were 0.79% and 0.34%. With increased risks of bleeding in patients ≥ age 75 in the face of marginal efficacy, the primary reviewer's recommendation seems reasonable. Some advice to the effect that prasugrel's efficacy is limited and its bleeding risk is increased in patients over the age of 75 would be appropriate for labeling.

Although the sponsor proposes a reduction in the MD from 10 mg to 5 mg daily in the over age 75 population, retention of efficacy is not assured. If prasugrel is approved for all age groups, physicians will need to carefully balance the risks versus benefits when prescribing prasugrel in patients ≥75 years of age.

3. With regard to the claim the sponsor is seeking for the prevention of stent thrombosis, the primary clinical reviewer opined that the claim should not be allowed. "Furthermore, I recommend that the sponsor participate in a randomized, prospective clinical trial to evaluate

the effect of prasugrel on stent thrombosis and to determine the optimal duration of dual antiplatelet therapy. Such a trial should use the standardized ARC definitions and incorporate histopathological confirmation as well as angiographic core laboratory review."

Reviewer's Comments: It is not clear to this secondary reviewer that a new randomized controlled trial is needed to assess stent thrombosis. The primary clinical reviewer believes that the sponsor's conclusions may be erroneous because clinical *reports* of angiograms were used to determine the presence or absence stent thrombosis. In retrospect, the actual angiogram *images* should have been reviewed by a blinded core laboratory. As such, it is this reviewer's belief that the prevention of stent thrombosis claim should be denied for the time being; however, the sponsor should be encouraged to collect the angiograms and have them reviewed by a blinded core laboratory. It would be important to review ALL angiograms obtained after the initial PCI, and not limit the analysis to cases that had been classified as stent thrombosis. Moreover, because the goal is primarily to corroborate the sponsors' initial conclusions, a review of only a subset of the subjects may be sufficient to support the claim.

4. Given the concern about cancer, as well as increased bleeding risks with prasugrel over time, the clinical reviewer recommended "...limiting therapy with prasugrel to short-term use (i.e., one week), so that patients may receive the benefits of this therapy while avoiding some of the possible risks."

Reviewer's Comments: A number of members of the review team, including Drs. Hicks and Marciniak, have suggested that the package insert recommend a limited duration of use for prasugrel, because of the risks of cancer and bleeding. In terms discontinuing prasugrel, it is important to recognize that the population for whom this would be approved, i.e., patients with recent PCI, predominantly with stents, should probably not discontinue their thienopyridine, as this may lead to stent thrombosis, which is associated with poor outcomes. Thus, if the label were to encourage a limited duration of use, it would be critical for patients to switch seamlessly to another approved inhibitor of ADP-induced platelet aggregation, which presents practical problems of its own. Because continued therapy is critical, and because the risk management strategy of "switching" has not been tested, this reviewer is not enthusiastic about limiting length of use. The specific risks noted by Dr. Hicks are discussed below:

Cancer: The cancer risk is discussed extensively, above. If prasugrel is causally related to excess cancer, it would be fair to say that patients with pre-existing cancer, and possibly those at high risk of cancer (the latter would need to be carefully defined) should consider alternative drugs, or limiting length of use in a general way. Although some general advice about cancer risk may be appropriate, this reviewer does not believe that the cancer data support a recommendation for a *specific* maximum length of use. Certainly, the data do not seem to support a limit of one week.

Bleeding: Placing bleeding events into context with efficacy (Figure 14), the benefit-risk, i.e., the tradeoff in myocardial infarctions prevented per bleeding event incurred, increases from Day 0 through Day 12, appears to plateau through approximately Day 30, and declines thereafter. Thus, if labeling were to recommend a limited duration of prasugrel's use, 30 days seems most reasonable based on the tension between bleeding and efficacy.

7 Advisory Committee Meeting

An advisory meeting is not planned for the NDA.

8 Conclusions and Recommendations

Although the prasugrel development program included only a single adequate and well-controlled trial to support efficacy (TAAL), the study had many of the hallmark features that provide reassurance regarding its evidence of effectiveness. TAAL was a large multicenter study with findings that were statistically persuasive, robust to exploration, and consistent across subgroups. Because TAAL demonstrated prasugrel's superiority, not to a placebo, but to an active drug (clopidogrel), prasugrel's efficacy seems beyond question. There are two key safety concerns: 1) the risk of bleeding, which is well-understood and well-characterized; and 2) the risk of cancer. The association between prasugrel and cancer is difficult to understand mechanistically and may represent a chance finding. Nevertheless, risk of cancer is always of great interest to practitioners and patients, and cannot be ignored.

Much has already been written in the literature regarding prasugrel's risk of bleeding. Although bleeding can cause serious morbidity and mortality, the most critical consequences of bleeding, i.e., those that cause irreversible morbidity or mortality (exsanguination, MI, and stroke), were included in the primary efficacy endpoint, where prasugrel was superior to clopidogrel. Thus, the tradeoff between efficacy and bleeding is between avoidance of permanent morbidity versus causation of temporary morbidity. When evaluating the risk-benefit for a population, this seems like a reasonable trade. Under these circumstances, the problem in practice is that the practicing physician knows only when the drug harms a patient (i.e., when the patient experiences a bleeding event); they do not know when the drug has prevented an MI in a particular patient.

The CMC review team has serious and valid concerns regarding conversion of the product from the salt form to the free base, in that the manufacturing process fails to ensure consistent product quality. On the other hand, efficacy appears consistent in all lots tested and across a spectrum a tablet age. In light of the efficacy of the product, the demonstration of prasugrel's superiority against an active comparator on the endpoint of nonfatal MI, it would be shortsighted to deny approval on the basis of this product issue, despite its considerable magnitude. b(4)

8.1 Recommended regulatory action

This reviewer recommends approval of prasugrel for reduction of myocardial infarction in patients with ACS who are managed with PCI. The claim sought by the sponsor, the reduction of "atherothrombotic events," is ambiguous and implies reductions in all 3 components of the TAAL primary endpoint. The indication should be restricted to reduction of myocardial infarction, the component where efficacy was actually demonstrated.

It could be argued that the results of TAAL show prasugrel to be non-inferior to clopidogrel in ACS, such that it is appropriate for prasugrel to enjoy the same claims as its comparator. Clopidogrel has the indication "for the reduction of atherothrombotic events as follows: ACS:...to decrease the rate of the combined endpoint of cardiovascular death, MI, or stroke....".

Although clopidogrel has a claim for "reduction of atherothrombotic events," the phrase seems inappropriate in retrospect. For cardiovascular death and stroke, the rates with clopidogrel were only marginally better than placebo, and the differences were not statistically significant. The ambiguity in the phrase "atherothrombotic events" mostly serves to encourage loose association and extrapolation.

This reviewer is not enthusiastic about limiting the length of prasugrel's use to manage the risk of bleeding and the concern regarding cancer. As noted in this review, there is no clear rationale for selecting a specific length of time. Moreover, mandating or encouraging a limited duration of therapy requires switching to another drug, and this type of risk management strategy has not been tested in the post-PCI setting. By avoiding use of prasugrel in patients at higher risk of bleeding (patients over the age of 75, patients with prior stoke or TIA, and patients who are planned to undergo CABG or other surgery), much of the excess bleeding risk will have been avoided. In terms of cancer risk, lacking definitive data, the strategy of limiting length of use seems ill advised.

The reduction of stent thrombosis is an important claim, and would give the product a competitive advantage over existing products, if granted. Dr. Hicks raised concerns regarding the materials adjudicated by the CEC, in that the CEC considered reports of cardiac catheterizations, and not the original angiographic images. Thus, TAAL did not use current standard definitions for stent thrombosis developed by the Academic Research Consortium. Although the difference in the incidence of stent thrombosis between prasugrel and clopidogrel was compelling, some degree of ascertainment bias is operational when contemplating the diagnosis of stent thrombosis. In other words, investigators considered stent thrombosis when subjects had an acute MI that was removed in time from the index PCI. Given that the overall RR of nonfatal MI was 0.76 in favor of prasugrel in TAAL, if the adjudicators made determinations of stent thrombosis for all MIs in a random fashion, the overall risk of stent thrombosis would be determined to be 0.76 as well.

To address these issues, the stent thrombosis claim should be denied for now, but the sponsor should be given the opportunity to have source materials adjudicated by a blinded core laboratory. A random subset of angiograms of subjects that were classified as stent thrombosis should be examined, along with an equal number of angiograms from subjects who experienced a myocardial infarction but who were not adjudicated for stent thrombosis. If re-adjudication of source angiographic images by a blinded core lab substantiates the original finding, the labeling claim should be allowed.

8.2 Safety concerns to be followed postmarketing

The cancer concern should be addressed through a randomized, controlled clinical trial. A registry may be supportive, but can not substitute for a randomized controlled trial.

8.3 Risk Minimization Action Plan, if any

None seems necessary.

8.4 Postmarketing studies, voluntary or required

1. Studies will be needed to further evaluate the risk of cancer, as above. The details of the study will need to be worked out and agreed upon prior to approval.

b(4)

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/s/

Ellis Unger
7/10/2008 07:19:34 PM
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