TIMI Study Group Downgrades and Upgrades:

A. Downgrades

The TIMI Study Group downgraded 195 subjects, including 92 prasugrel and 103 clopidogrel subjects. Per FDA analysis, of 195 subjects downgraded, 76 subjects (42 prasugrel, 34 clopidogrel) had no clinical syndrome consistent with stent thrombosis, 19 subjects (5 prasugrel, 14 clopidogrel) had elective or staged procedures, and 50 subjects (25 prasugrel, 25 clopidogrel) had non target vessel revascularization and no history of PCI. This left a total of 50 subjects (20 prasugrel, 30 clopidogrel) that were downgraded from investigator reported stent thrombosis. Please see Figure 1 which describes the 195 downgrades in the subject population who had a stent placed at the index PCI and Figure 2 which describes the downgrades in the subject population who had a stent placed at any time in the study.

B. Upgrades

The TIMI Study Group upgraded 65 subjects, including 24 prasugrel and 41 clopidogrel subjects.

C. Sensitivity Analyses

Per the FDA analysis, the worst case analysis with downgrades still shows a statistically significant reduction in stent thrombosis with prasugrel, but the worst case analysis with upgrades does not. However, the point estimate still favors prasugrel.

Table 3. FDA Analysis: Subjects with Thrombosis in Stents Placed During Index Procedure in TRITON by Definition of Stent Thrombosis: All ACS Subjects

Number of Subjects with Stent Thrombosis	Prasugrel N=6422 n (%)	Clopidogrel N=6422 n (%)	RR	95% CI
CEC adjudicated (ARC definite or probable)	58 (0.90)	116 (1.8)	0.50	(0.37, 0.68)
Investigator Reported (Subject Population limited to those who had a stent placed at the index PCI)	135 (2.1)	200 (3.1)	0.67	(0.54, 0.84)
Concordant (CEC and Site Reported)	58/135 (42)	116/200 (58)	0.74	(0.59, 0.93)
Downgrades	20	30		
Upgrades	24	41		
Worst case analysis I: (restore downgrades to prasugrel group only)*	78 (58 + 20)	116	0.67	(0.51, 0.89)
Worst case analysis II: (remove upgrades from clopidogrel group only)**	58	75 (116-41)	0.77	(0.55, 1.09)

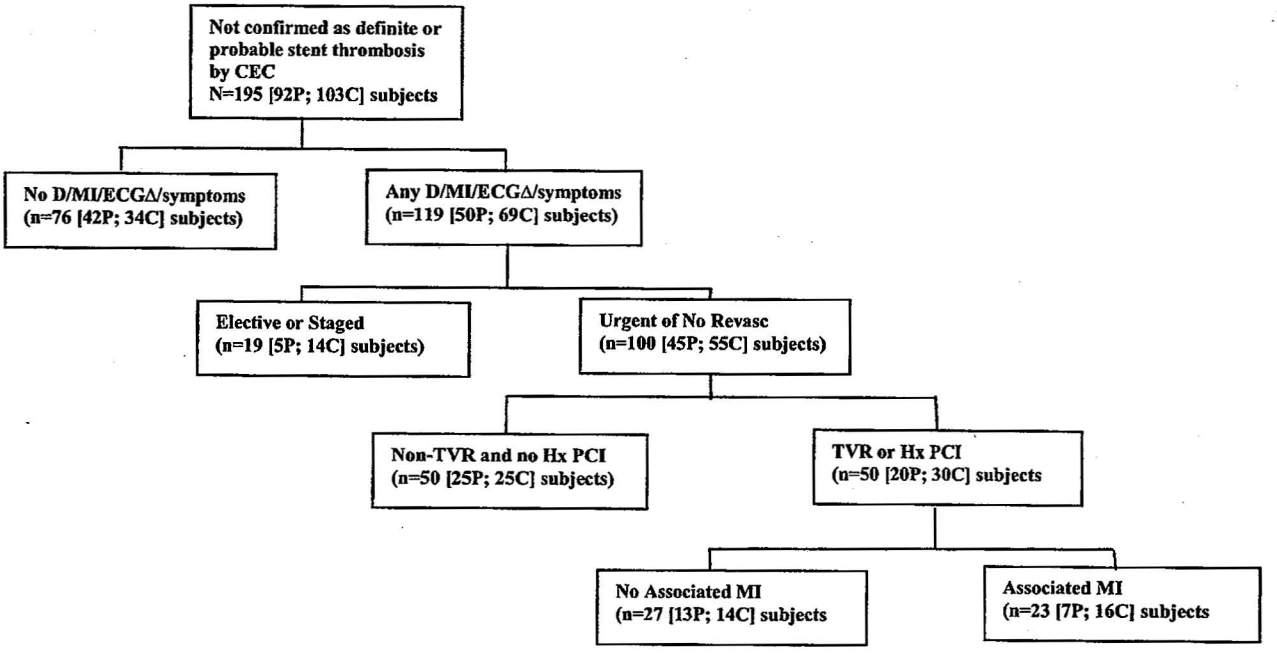
[a]Kaplan-Meier percentage at 15 months

***assumes all prasugrel events in question are stent thrombosis and all clopidogrel events in question are assumed to not be stent thrombosis.**

****assumes none of the events in question are stent thrombosis, but only in clopidogrel group.**

Analysis by Karen A. Hicks, M.D. and Ellis Unger, M.D.

Figure 1: FDA Analysis: Characteristics of Downgraded Events (Subject Population who had Stent Placed at Index PCI) (Investigator Reported Stent Thrombosis in Any Stent)

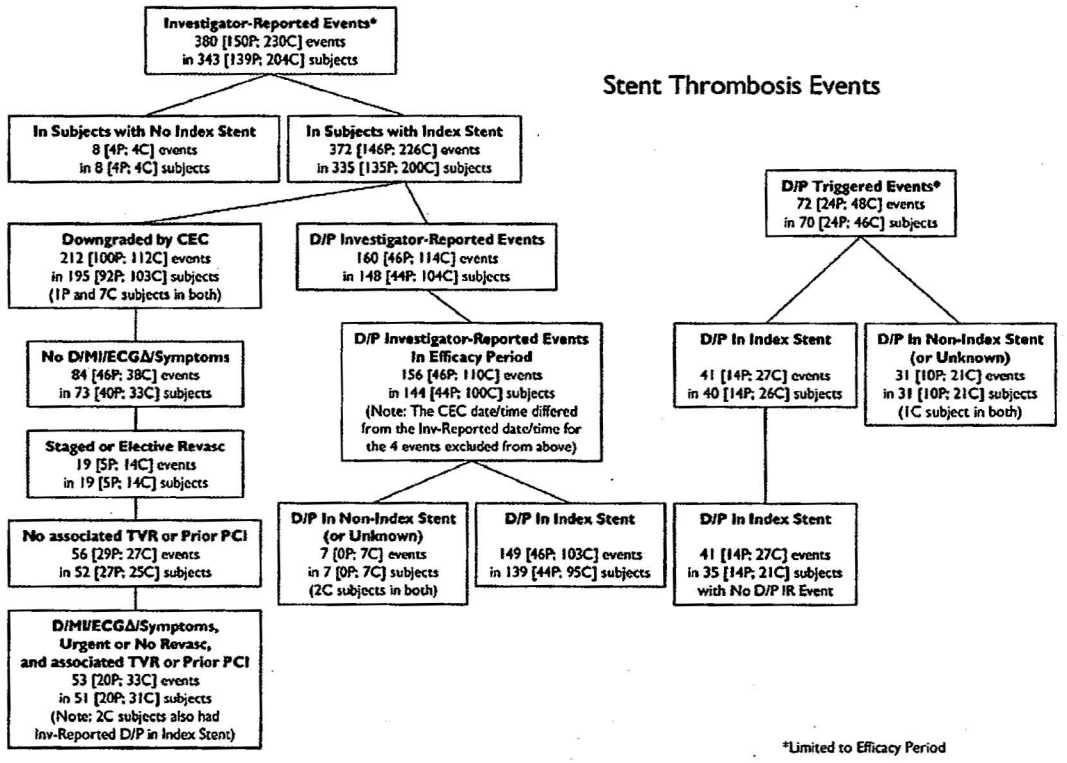


Source: 10533_1ssthl11_inadj_index.rtf, 10531_1ssthl1 1_invadj.xls

CEC: Clinical Endpoints Committee; D: Death; ECGΔ: electrocardiographic change; Hx: history; MI: myocardial infarction; PCI: percutaneous coronary intervention; Revasc: revascularization; TVR: target vessel revascularization;

(Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA)

Figure 2: Characteristics of Downgraded Events (All Randomized Subjects) (Investigator Reported Thrombosis in Any Stent)



Source: l0532_lssthl11_invadj.rtf, l0533_lssthl11_invadj_index.rtf

CEC: Clinical Endpoints Committee; D/P: Definite/Probable; D: Death; MI: myocardial infarction; ECGΔ: electrocardiographic changes; PCI: percutaneous coronary intervention; Revasc.: revascularization; TVR: target vessel revascularization

(Analysis verified by Ququan Liu, M.D., M.S., Biometrics, FDA)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Hicks
2/2/2009 08:09:02 PM
MEDICAL OFFICER

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Secondary Review of Cancer Adverse Events and Risk/Benefit

NDA:	22,307
Drug:	prasugrel (Effient)
Indication:	reduction of atherothrombotic events and stent thrombosis in acute coronary syndromes managed by percutaneous coronary intervention
Sponsor:	Eli Lilly and Company
Review date:	December 31, 2008
Reviewer:	Thomas A. Marciniak, M.D. Medical Team Leader

Background

This review is a special secondary review of the findings in this NDA submission related to cancer adverse events and risk/benefit. I initiated the analyses because of my assignment as the clinical reviewer for the prasugrel IND, a professional interest in exploring cancer rates in large outcome trials, and the suggestive results (in my interpretation) of the mouse carcinogenicity study. Because my preliminary analysis raised the issue of increased cancer rates with prasugrel in a large outcome study, the Cross Discipline Team Leader for this submission requested that I complete and formally submit my analyses. For a general background on prasugrel and this NDA submission and discussions of the formulation issues, please see the primary clinical review, the other discipline primary reviews, and the Cross Discipline Team Leader review. This version is an updated version based on a series of exchanges with the sponsor regarding the cancer events and includes the data collected by the sponsor in response to those exchanges; it replaces all prior versions.

Recommendation and Conclusions

I recommend approval of prasugrel for the indication of reduction in myocardial infarctions in acute coronary syndromes managed by percutaneous coronary interventions with a boxed warning regarding cancer and a duration of treatment limited to 30 days. In the large outcome study TAAL, new solid cancer rates were more than 40% higher in the prasugrel group than in the clopidogrel control group. The solid cancer rates began diverging after about 4 months and continued diverging for the duration of the study. They were associated with substantial death rates. It is impossible to decide whether these findings are real drug effects or artifactual or chance variations from TAAL alone; another study is needed. Until such a study is completed I believe it is prudent to approve prasugrel, because of its beneficial impact upon an important endpoint (myocardial infarction), but to limit its duration of use. The sponsor is planning another large outcome study in acute coronary syndrome patients who are medically managed. A description of the TAAL cancer results must be incorporated into the informed consent for the new trial, patients with a history of solid cancers must be excluded, complete follow-up for cancer events must be detailed, and the trial must be sized (including a blinded interim analysis of cancer event rates with resizing if needed) to have 90% power of detecting a 50% increase in the rate of development of new solid cancers.

Materials Used in Review

1. Submissions for NDA 22,307, particularly the reports and data sets for the rodent carcinogenicity studies, the data sets and case report forms for the large TAAL outcome trial, and the supplementary regulatory responses on neoplasms from March 25 through November 12, 2008
2. Primary Clinical review by Karen A. Hicks, M.D., dated April 28, 2008
3. Statistical Review of the Rodent Carcinogenicity Studies by Mohammad Atiar Rahman, Ph.D., dated February 19, 2008
4. Pharmacology/Toxicology Review by Belay Tesfamariam, Ph.D., dated April 26, 2008

Relevant Chemistry and Metabolism

Prasugrel is a thienopyridine prodrug for an irreversible antagonist of the platelet $P2Y_{12}$ receptor. It is functionally and structurally similar to the approved thienopyridine platelet $P2Y_{12}$ receptor antagonist clopidogrel and, in fact, the large TAAL outcome trial in this submission compared prasugrel to clopidogrel rather than placebo. However, prasugrel is neither structurally nor metabolically identical to clopidogrel as shown in the structure diagrams in Figure 1 and Figure 2 and the metabolic pathways of prasugrel in Figure 3 and the major and active metabolites of clopidogrel in Figure 4.

Figure 1: Prasugrel Structural Formula

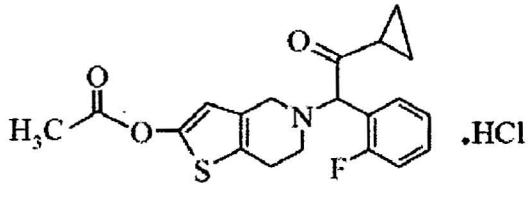


Figure 2: Clopidogrel Structural Formula

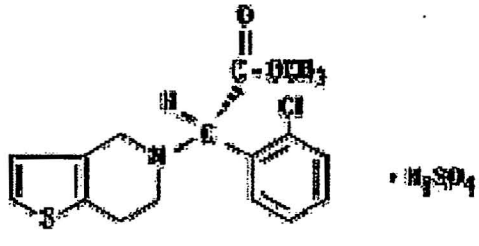


Figure 3: Prasugrel Proposed Metabolic Pathways

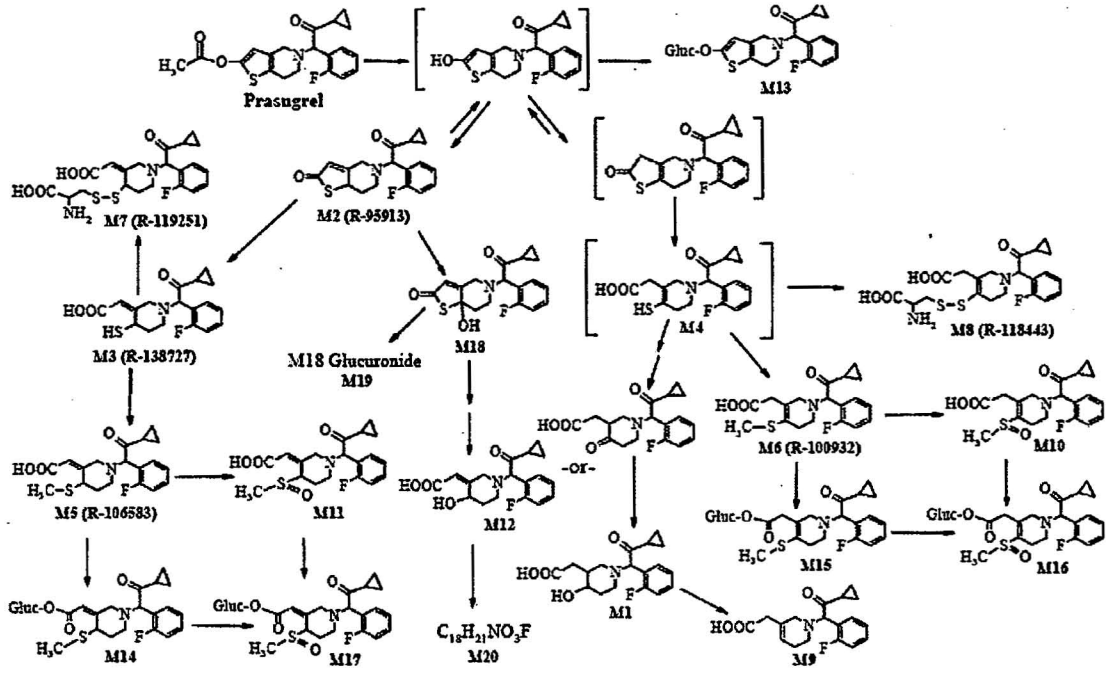
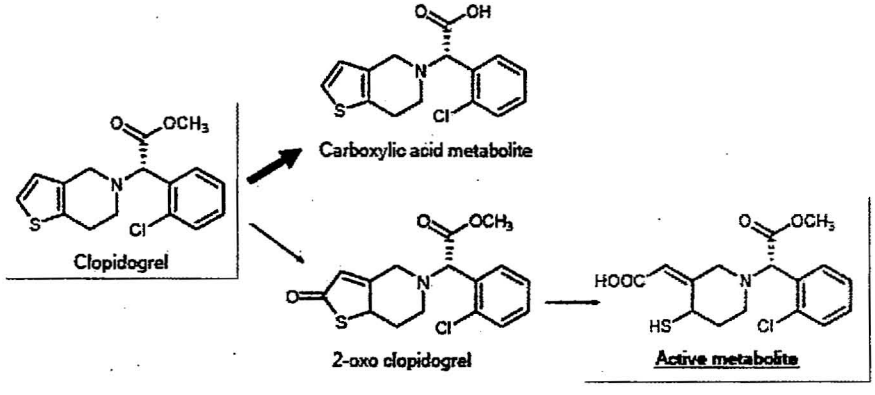


Figure 4: Clopidogrel Major and Active Metabolites*



*from http://www.inertsil.com/Technical_Data/Titansphere/ASMS2006/A061099.pdf

Both prasugrel and clopidogrel are prodrugs. Prasugrel is rapidly hydrolyzed to the inactive metabolite R-95913. R-95913 is then converted by various CYP isoenzymes to the thiol active metabolite R-138727. Clopidogrel undergoes rapid hydrolysis to its carboxylic acid derivative, the major metabolite in plasma. It also undergoes an alternate pathway of oxidation through CYP isoenzymes to a thiol active metabolite. Both prasugrel and clopidogrel undergo extensive other metabolism.

COMMENT: While structurally similar, there are sufficient structural and metabolic dissimilarities between prasugrel and clopidogrel such that an adverse affect of one can not be automatically assumed to be an adverse effect of the other. The metabolic pathways of each are diverse enough that one can not elucidate from typical clinical or pre-clinical studies what metabolite can produce an adverse effect.

Rodent Carcinogenicity Studies

Included in the NDA submission are two two-year carcinogenicity studies, one in mice and one in rats. The studies are similar, each with 55 animals per dosing and control groups, except that the dosages are lower in the rat study because of a lower tolerability limit in rats compared to mice: The mice dosages tested were 30, 100, and 300 mg/kg and the rat dosages were 10, 30, and 100 mg/kg. The suggestive carcinogenicity findings are predominantly in the mouse study. I show the distributions of neoplasms (benign and malignant) by site, sex, and dosing group in Table 1 and by sex and dosing group for both sexes combined in Table 2.

Table 1: Neoplasms with Frequency > 4 by Site, Sex, and Dosing Group in the Prasugrel Mouse Carcinogenicity Study (NOTE: All Group Sizes Were 55)

Group	Female				Male			
	Control	30	100	300	Control	30	100	300
Harderian gland	5	3	7	6	5	8	2	2
Intestinal cancer	0	2	2	1	1	0	0	2
Liver adenoma	5	5	20	39	20	11	26	44
Liver carcinoma	1	4	2	5	11	12	13	16
Liver cancer*	2	6	3	5	11	15	14	17
Liver hemangioma	1	2	0	0	6	3	1	1
Lung adenoma	1	2	4	3	5	5	5	6
Lung cancer	2	2	1	2	3	3	8	4
Lymphorecticular ca	19	24	20	16	5	12	4	6
Pituitary adenoma	2	3	4	3	1	0	0	0
Skin benign	2	0	0	1	2	0	0	1
Skin cancer	4	1	2	2	0	0	1	0
Spleen sarcoma	1	3	0	1	0	0	1	0
Spleen hemangioma	2	3	0	1	4	0	1	0
Uterus neoplasm†	1	3	3	2	0	0	0	0

*including hemangiosarcoma, hepatoblastoma; †one carcinoma in 30 mg/kg group, the rest polyps

Table 2: Neoplasms with Frequency > 4 by Site and Dosing Group in the Prasugrel Mouse Carcinogenicity Study

Group	Control	30	100	300
Harderian gland	10	11	9	8
Intestinal cancer	1	2	2	3
Liver adenoma	25	16	46	83
Liver carcinoma	12	16	15	21
Liver cancer*	13	21	17	22
Liver hemangioma	7	5	1	1

Group	Control	30	100	300
Lung adenoma	6	7	9	9
Lung cancer	5	5	9	6
Lymphorecticular ca	24	36	24	22
Pituitary adenoma	3	3	4	3
Skin benign	4	0	0	2
Skin cancer	4	1	3	2
Spleen sarcoma	1	3	1	1
Spleen hemangioma	6	3	1	1
Uterus neoplasm†	1	3	3	2

*including hemangiosarcoma, hepatoblastoma; †one carcinoma in 30 mg/kg group, the rest polyps

In addition to the neoplasms, there were two other hepatic histologic findings worth noting, shown in Table 3.

Table 3: Other Hepatic Histologic Findings in the Prasugrel Mouse Carcinogenicity Study

Group	Female				Male			
	Control	30	100	300	Control	30	100	300
Central hypertrophy	0	0	0	0	0	0	9	22
Altered cell focus, eosinophilic	6	6	18	36	9	17	23	24

Prasugrel is an enzyme inducer that, in mice, produces an increase in liver size. The central hepatocytic hypertrophy seen in the male mice at the higher dosages (mild to moderate at the 100 mg/kg dosage and moderate in 7 mice at the 300 mg/kg dosage) is attributed to this enzyme induction. (See also the discussion regarding carcinogenicity in the Comment below.) The National Toxicology Program has suggested that presence of the altered cell foci may form part of weight-of-evidence considerations used by regulatory bodies when accompanied by a concomitant liver tumor response. (Maronpot, Harada et al. 1989)

COMMENT: The most striking finding is the increase in liver adenomas. This neoplasm appears to have a high background rate in this species—note the 20 adenomas in the male control group, although this number appears to be anomalously high. While the increase in adenomas is the most statistically significant finding, the increase in the closely related liver carcinomas is also striking. Whether one counts only carcinomas or all cancers (there were also more cases of hemangiosarcomas and hepatomas in the prasugrel groups) the increase in liver malignancies is roughly 50% with prasugrel. There are also more cases of lung cancer and intestinal cancer in the prasugrel groups with suggestions of dose-response relationships.

The FDA's statistical reviewer of these studies judged the increases in adenomas and combined adenomas and carcinomas to be statistically significant: The standard statistical analysis 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 mid and high dose groups in females

compared to their respective controls. (Per the Society of Toxicologic Pathology the incidences of benign and malignant neoplasms arising from the same cell type are usually combined for statistical analyses. (Boorman, Dixon et al. 2004)) The Executive CAC judged the mouse study to be positive for hepatocellular adenomas in both sexes.

I have the following additional comments on this study:

- *An increase in the rates of the most prevalent cancers of 50% or more is not consistent with the sponsor's explanation of the findings, that the liver adenoma increases are the result of enzyme induction similar to that seen with phenobarbital.*

- *The increase in uterine neoplasms, mainly polyps, by itself wouldn't appear very concerning or even unlikely—one more polyp in the control group would make all of the groups indistinguishable. However, it is consistent with the one suggestive finding in the rat study.*

- *The increase rates of altered cell foci may be consistent with the increased rates of adenomas. However, the triumvirate of liver adenoma increases, altered cell foci increases, and cancer increases appears consistent with a tumor promotion effect.*

- *Skin cancers and combined skin neoplasms were more frequent in the control group.*

While the increases in cancers with prasugrel are not statistically significant, they do not appear to be random effects. There are no comparable random increases in cancers for the placebo group. The neoplasms for which the count in the placebo group is higher are skin neoplasms, liver hemangiomas, and spleen hemangiomas. The fewer liver and spleen hemangiomas in the prasugrel groups are hardly reassuring because there are more hemangiosarcomas in these organs in the prasugrel groups.

The prasugrel rat carcinogenicity study does not show an increased rate of liver adenomas. Nor does it show any increased rates of cancers with prasugrel, either by site or in total. To the contrary, it showed lower rates with prasugrel for two malignancies: large granular lymphocytic leukemia and mesothelioma as shown in Table 4. The one finding consistent with the mice study findings is a higher rate of uterine neoplasms (due to high rates of polyps) in the prasugrel groups as also shown in Table 4.

Table 4: Neoplasms Differing by Dosing Group in the Prasugrel Rat Carcinogenicity Study

Group	Female				Male			
	Control	10	30	100	Control	10	30	100
Leukemia	14	13	6	1	8	8	3	2
Mesothelioma	0	0	0	0	4	3	1	1
Uterus neoplasm	20	26	29	30				

Exposure to prasugrel and its metabolites differed between the two rodent carcinogenicity studies. The exposures for the active metabolite and the main human metabolite are shown in Table 5.

Table 5: Exposure (Mean AUC_{0-24} µg·h/mL) for Main/Active Metabolites in the Prasugrel Carcinogenicity Studies (Compared to Human 0.3/0.05 for 10 mg Daily Dose)

	Female				Male			
	10	30	100	300	10	30	100	300
Mouse		23/6	85/26	201/68		23/2	87/16	206/41
Rat	4/7	18/28	43/59		4/5	7/14	22/58	

Main human metabolite R-106583/active metabolite R-138727

In addition to the neoplasms, the similar findings to the two other hepatic histologic findings found in the mouse study were also observed in the rat study as shown in Table 6.

Table 6: Other Hepatic Histologic Findings in the Prasugrel Rat Carcinogenicity Study

Group	Female				Male			
	Control	10	30	100	Control	10	30	100
Diffuse hypertrophy	0	0	0	15	0	0	0	20
Altered cell focus, eosinophilic	27	31	31	36	43	41	44	51

COMMENT: The rat carcinogenicity does not support the mouse study in suggesting that prasugrel is carcinogenic. Alone it might be interpreted as suggesting that prasugrel has a protective effect, e.g., the lower rates of leukemia. There are some similarities between the two studies for other findings, such as the endometrial polyps and the hepatocytic hypertrophy. There are also definite differences in exposure, both regarding the higher high dose exposure in the mice and the different ratios of active to main metabolite.

Because of the highly significant difference in hepatic adenomas, the moderately suggestive trend in hepatic cancers, the weakly suggestive trends in intestinal and lung cancers, the supportive data of the altered cell foci, and the absence of any tumors showing a clear reverse trend, I would still interpret the mouse study as suggestive of a carcinogenic effect of prasugrel in one species. The difference in measured exposures between the mouse and humans is not completely reassuring because we have no idea of what metabolite could be carcinogenic. The rat study is not supportive of carcinogenicity but neither does it contradict the possibility. However, by itself the results of the mouse study do not prohibit approval—the critical issue is what the human studies show. Regardless, these studies are very useful for hypothesis generation: The hypothesis they suggested to me is that prasugrel may be a tumor promoter for a variety of solid cancers—it is this hypothesis that I tested in my initial analysis of the TAAL study data.

Cancer Adverse Events in TAAL

The only human study in the submission large and long enough to provide any insight into cancer rates is TAAL. Hence I limit my analyses to that study.

TAAL (or TRITON) was a large, international, multicenter, randomized, double-blind, double dummy, active-controlled (vs. clopidogrel) of prasugrel in patients with ACS undergoing PCI. The labeled regimen for clopidogrel (300 mg loading, 75 mg maintenance) was compared to prasugrel 600 mg loading, 10 mg maintenance. About 13,608 patients (74% male) were randomized 1:1 and followed for 6-15 months. Baseline characteristics were well-balanced