Table 10: Non-CABG-Related TIMI Major or Minor Bleeding Events by Subgroup

	Subject population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%		
Overall		6741	303	4.5	6716	231	3.4	1.31 (1.11, 1.56)	0.002
Sex	female	1684	123	7.3	1798	97	5.4	1.38 (1.06, 1.80)	0.017
	male	5057	180	3.6	4918	134	2.7	1.31 (1.05, 1.64)	0.018
Age	<65	4149	141	3.4	4096	99	2.4	1.41 (1.09, 1.83)	0.008
	>=65	2592	162	6.3	2620	132	5.0	1.26 (1.00, 1.59)	0.046
	<70	5095	182	3.6	5041	138	2.7	1.31 (1.05, 1.64)	0.016
	>=70	1646	121	7.4	1675	93	5.6	1.35 (1.03, 1.76)	0.03
	<75	5850	223	3.8	5822	169	2.9	1.32 (1.08, 1.61)	0.006
	>=75	891	80	9.0	894	62	6.9	1.35 (0.97, 1.88)	0.078
Ethnicity	Caucasian	6196	281	4.5	6200	217	3.5	1.30 (1.09, 1.56)	0.003
	African	201	10	5.0	185	7	3.8	1.34 (0.51, 3.53)	0.551
	Hispanic	269	10	3.7	255	6	2.4	1.55 (0.56, 4.27)	0.393
	Asian	60	2	3.3	63	1	1.6	-	-
Weight	<50	45	2	4.4	45	6	13.3		
	50 - <70	1133	78	6.884	1232	61	4.951	1.41 (1.01, 1.96)	0.046
	70 - <90	3378	151	4.47	3297	107	3.245	1.39 (1.08, 1.78)	0.009
	>=90	2125	68	3.2	2081	55	2.643	1.22 (0.85, 1.74)	0.275

for prasugrel, i.e., fatal bleeding: 1.01% prasugrel, 0.11% clopidogrel; symptomatic ICH: 0.79% prasugrel, 0.34% clopidogrel. Based on these data, and given that the RR approaches unity for the 1° efficacy endpoint for subjects ≥75 years of age, the primary clinical reviewer suggested that "...prasugrel should not be the treatment of choice in patients ≥75 years of age." I agree with her reasoning and recommendation.

Table 11: Non-CABG-Related Spontaneous TIMI Major or Minor Bleeding Events From Symptom Onset Through 3 Days by Concomitant Medication Use

	Subject population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%		
GPIIb/IIIa use	any	3652	22	0.6	3697	17	0.5	1.31 (0.70, 2.47)	0.4
	never	3089	12	0.4	3089	7	0.2	1.68 (0.66, 4.27)	0.27
Antithrombin use	UFH	3455	21	0.6	3436	9	0.3	2.32 (1.06, 5.07)	0.03
	UFH+LMWH	2101	8	0.4	2161	14	0.6	0.58 (0.24, 1.39)	0.22
Fibrinolytic use	yes	210	0	0.0	218	0	0.0		
	no	6531	34	0.5	6498	24	0.4	1.41 (0.84, 2.38)	0.19
Aspirin use	none	21	1	4.8	27	2	7.4		
	>0 - <100 mg	689	7	1.0	672	3	0.4	2.28 (0.59, 8.80)	0.22
	100 - 200 mg	1703	10	0.6	1741	8	0.5	1.28 (0.51, 3.24)	0.6
	>200 mg	4328	16	0.4	4276	11	0.3	1.44 (0.67, 3.10)	0.35
PPI	yes	2760	129	4.674	2719	120	4.413	1.06 (0.83, 1.36)	0.65
	no	3981	174	4.371	3997	111	2.777	1.59 (1.25, 2.01)	<0.001

The sponsor conducted subgroup analyses to assess the effects of anti-thrombotic and related medications on the incidence of non-CABG-related bleeding events. The purpose was to investigate the relationship between these medications and the incidence of bleeding during the index hospitalization; therefore, the analysis was limited to medications administered and bleeding events experienced during first 3 days after the LD of study drug.

Table 11 provides a summary of subgroup analyses of spontaneous (non-instrumented) non-CABG-related TIMI major or minor bleeding events by the use or non-use of a GPIIb/IIIa inhibitor, antithrombin agent, fibrinolytic, aspirin, and PPI, from symptom onset through Day 3. For all of these subgroups, the data are somewhat difficult to interpret because the numbers of events are limited (the analyses are through Day 3, only). There was a significant treatment-by-subgroup interaction for anti-thrombin monotherapy, unfractionated heparin (UFH), compared to UFH plus low molecular weight heparin (LMWH). In subjects receiving only UFH, the RR for spontaneous non-CABG-related TIMI major or minor bleeding events was 2.32 (worse with prasugrel). Conversely, in subjects receiving UFH plus LMWH, the RR strongly favored prasugrel (RR=0.58). There was higher incidence of bleeding events through 3 days while at risk in subjects receiving a GPIIb/IIIa inhibitor compared to subjects not receiving a GPIIb/IIIa inhibitor in each treatment group. For subjects who received GPIIb/IIIa inhibitors, the RR (1.31, unfavorable for prasugrel) is identical to the RR for the study as a whole, suggesting that GPIIb/IIIa inhibitors do not pose a particular risk for patients who receive prasugrel.

Proton Pump Inhibitors

Use of PPI deserves special mention. The clinical pharmacology reviewer (Dr. Mishina) noted that concomitant lansoprazole administration (a PPI) reduced the Cmax of prasugrel's active metabolite by nearly 30% (Study TAAI). This interaction is thought to be a function of conversion of the product from the hydrochloride salt form to the free base form, i.e., the PPI interaction is important for the free base, but not the salt. The prasugrel used in TAAL was predominantly free base, and the primary clinical reviewer (Dr. Hicks) noted a lower RR of bleeding (prasugrel versus clopidogrel) for subjects who used PPI, versus those who did not use PPI (Table 28). Together, these observations suggest that the interaction between prasugrel and PPI is clinically important, or, more specifically, prasugrel's conversion between the salt and base forms is clinically relevant.

With that as background, the RR of bleeding was lower in subjects who received concomitant PPI (1.06) than in those who did not (1.59). However, the sponsor's analysis shows that difference was not a manifestation of a higher bleeding frequency in prasugrel-treated subjects who did not receive a PPI. In fact, the frequency of bleeding in prasugrel-treated subjects was very similar in subjects who did and did not receive a PPI, 4.7% and 4.4%, respectively (Table 11). The disparity in RR between subjects who did and did not receive a PPI was due to a lower than expected frequency of bleeding in subjects who received clopidogrel and did not receive a PPI (2.8%), versus those who received a PPI (4.4%). The data should not be interpreted as supporting the concept that that the frequency of bleeding was lower in prasugrel-treated subjects who received a PPI than those who did not. The data are, in fact, reassuring, that the conversion of prasugrel between the salt and base forms did not lead to a clinically important interaction with PPI.

CABG-Related Bleeding

The frequency of CABG-related TIMI major bleeding was higher in subjects treated with prasugrel compared to clopidogrel, and there was higher risk even when prasugrel was

discontinued more than 7 days in advance of CABG (Table 12, Top panel, adapted from the sponsor's Table TAAL 12.42, page 769). The primary clinical reviewer noted that "These data suggest prasugrel should be discontinued at least 7 days prior to undergoing CABG, if possible." This advice seems reasonable on its face, given that the frequency of TIMI major bleeding was 12.7% when CABG was performed within 7 days of the last dose of prasugrel. However, the risk of bleeding when prasugrel was stopped >7 days prior to surgery is not much lower than 12.7% (it is 8.9%), and is based on only 7 events in 79 subjects. Thus, the data do not make a strong case for discontinuing prasugrel 7 days prior to CABG.

The bottom panel of Table 12 (adapted from sponsor's Table TAAL 12.44, page 782) shows a similar analysis for both TIMI major and TIMI minor bleeding events. During the first 3 days, the data make a good case for a high risk of bleeding in the prasugrel group (through 3 days, the frequency is 12/45 = 26.7%). The frequencies after 7 days, though trending lower than those within 7 days, are based on a limited N. Specifically, the frequency of bleeding in the prasugrel group for discontinuation 4, 5, 6, and 7 days prior to CABG is 9/80 = 11.25%. For days 8, 9, and 10, the frequency is 3/31 = 9.7%. Thus, irrespective of whether TIMI major or TIMI major + TIMI minor bleeding events are considered, it is clear that a longer period of discontinuation will result in less bleeding, and that the risk within 3 days is particularly high. The support for 7 days in particular seems fairly weak. Note also that when clopidogrel was discontinued more than 5 days before CABG, there were only 2 events in 95 subjects (2.1%). Practically speaking, this impacts urgent CABG, where there is no opportunity to stop the drug. Use of prasugrel should be discouraged when coronary anatomy is unknown and CABG is a possibility. For elective CABG, it is reasonable to discontinue prasugrel within 7 days, but waiting longer may be better.

In summary, in terms of prasugrel's risk of bleeding, the risk is higher for:

- patients ≥ 75 years of age (here the greater risk is for fatal and life-threatening bleeding)
- patients with a prior history of a transient ischemic attack or cerebrovascular accident
- patients who undergo CABG, or by extension, probably any surgical procedure

This information would be appropriate for labeling.

Table 12: Effect of Time of Discontinuation of Study Drug on CABG-Related Bleeding Events

CABG-Related TIMI Major Bleeding Events

Days from last dose to CABG	Prasugrel			Clopidogrel			RR
	N	n	%	N	n	%	
0-2 days	58	7	12.1	65	3	4.6	2.6
3-5 days	30	4	13.3	41	3	7.3	1.8
5-7 days	46	6	13.0	49	0	0.0	
< 7 days	134	17	12.7	155	6	3.9	3.3
> 5 days	125	13	10.4	118	2	1.7	6.1
> 7 days	79	7	8.9	69	2	2.9	3.1

CABG-Related TIMI Major or Minor Bleeding Events

Days from last dose to CABG	Prasugrel			Clopidogrel		
	N	n	%	N	n	%
0	12	1	8.3	22	1	4.5
1	17	6	35.3	12	0	0
2	4	2	50	11	1	9.1
3	12	3	25	15	1	6.7
4	8	1	12.5	14	1	7.1
5	30	3	10	30	2	6.7
6	18	2	11.1	21	0	0
7	24	3	12.5	25	0	0
8	13	1	7.7	10	0	0
9	8	0	0	9	2	22.2
10	10	2	20	5	0	0
11	5	0	0	2	0	0
12	3	0	0	1	0	0
13	1	1	100	2	0	0
14-27	9	0	0	11	0	0
28	1	1	100	1	0	0
29-60	4	0	0	3	0	0
61-341	6	1	16.7	5	0	0

Non-Hemorrhagic Serious Adverse Events:

Respiratory failure, hypotension, colon cancer, and atrial flutter were statistically significantly higher in subjects treated with prasugrel compared to subjects treated with clopidogrel:

- Respiratory failure: 0.22% prasugrel versus 0.09% clopidogrel; p = 0.050
- Hypotension: 0.21% prasugrel versus 0.06% clopidogrel; p = 0.019
- Atrial flutter: 0.18% prasugrel versus 0.06% clopidogrel; p = 0.046

Several of the events of respiratory failure occurred in the setting of TIMI bleeding.

The incidence of cardiac failure was statistically significantly lower in subjects treated with prasugrel than clopidogrel.

Clopidogrel carries a warning for thrombotic thrombocytopenia purpura (TTP), which has been reported rarely in association with the drug, and has been fatal in some cases. In the prasugrel development program, there were no reported cases of TTP in prasugrel-treated subjects, versus one case in a clopidogrel-treated subject.

Fifteen (0.22%) subjects in the prasugrel treatment group developed abnormal hepatic function, 8 (0.12%) had abnormal hepatic function reported as a serious adverse event, and 8 (0.12%) developed ALT > 3X ULN and total bilirubin > 1.5X ULN. These compare to 18 (0.27%), 15 (0.22%), and 4 (0.06%) subjects, respectively, in the clopidogrel treatment group. Clopidogrel's labeling does not contain any specific warning or precaution for hepatotoxicity, and based on these data, none seems appropriate for prasugrel.

Twenty-four prasugrel-treated (0.36%) and clopidogrel-treated (0.36%) subjects had allergic reactions reported as serious adverse events. Four (0.06%) prasugrel subjects and 3 (0.04%) clopidogrel subjects had angioedema reported as a serious adverse event. One of the prasugrel subjects was also receiving an angiotensin converting enzyme inhibitor, begun 5 days earlier.

No adverse events of pancytopenia were reported in any subjects in the development program. Anemia was reported in 2.2% and 2.0% of subjects treated with prasugrel and clopidogrel, respectively. Leukopenia ($< 4 \times 10^9$/L) was reported in 2.8% and 3.5% of prasugrel- and clopidogrel-treated subjects, respectively. There were 4 reported cases (0.06%) of neutropenia in the prasugrel treatment group, compared with 21 cases (0.31%) in the clopidogrel treatment group. The reported frequency of thrombocytopenia was similar between the prasugrel and clopidogrel groups (0.3%). In most of the cases of thrombocytopenia, subjects were also receiving a GPIIb/IIIa inhibitor.

Pyrexia and increased tendency to bruise were reported in at least 1% of prasugrel subjects and the incidence of these adverse events was significantly higher than that in the clopidogrel treatment group. Fever may have been related to bleeding. The sponsor found that subjects treated with prasugrel who had a bleeding event were twice as likely to have fever compared to subjects treated with clopidogrel who had a bleeding event.

6.2.4. Cancer:

Proportionally greater numbers of cancers were reported in subjects in the prasugrel treatment group, and much attention was paid to this issue by the Division of Cardiovascular and Renal Products clinical (Dr. K. Hicks) and secondary (Dr. T. Marciniak) reviewers, as well as consultants from the Division of Drug Oncology Products (B. Mann) and the Division of Epidemiology, Office of Surveillance and Epidemiology (Dr. D. Wysowski).

Non-Clinical, *In Vitro*
My review of the literature found very little evidence suggesting that prasugrel, clopidogrel, or modulation of the $P2Y_{12}$ receptor would have important effects on genotoxicity, tumorigenesis, tumor promotion, metastasis, or angiogenesis.

Non-Clinical, *In Vivo*

To briefly recapitulate the results of the 2-year rodent carcinogenicity studies, the rat data do not suggest increased rates of either benign or malignant neoplasms. In the mouse, at high exposures, there was a statistically significant dose-response relationship for hepatocellular adenoma. There was also a non-statistically significant trend in favor of increased hepatocellular carcinomas at the highest dose (300 mg/kg/day). Conversely, there was no evidence of prasugrel-associated increases in malignant tumors in extra-hepatic tissues. The Pharmacology/Toxicology review team and the Executive Carcinogenicity Advisory Committee opined that there was no evidence of a prasugrel-associated increase in malignant tumors in either species, and found the results reassuring.

Clinical

The sponsor's initial description and analysis of cancer adverse events was difficult to interpret: the distinction between pre-existing neoplasms and treatment-emergent neoplasms was not always clear, there was little attempt to categorize neoplasms as malignant or non-malignant, and there was little emphasis on categorization of cancers by organ or organ system. With respect to distinguishing pre-existing from treatment-emergent neoplasms, the case report forms (CRFs) used in TAAL included a "Pre-Existing Conditions" form that was used to "list all ongoing medical conditions at the time of study entry/screening." Some confusion arose because each pre-existing condition was recorded as an "event" and given an "event code" numerically continuous with treatment-emergent adverse events recorded on the "Study Adverse Events" CRFs. There were inconsistencies in recording pre-existing neoplasms, presumably because of investigators' difficulty in deciding whether a prior cancer was "ongoing" if it was not an active medical problem. Moreover, for patients in the throes of an acute coronary event, understandably little attention was given to obtaining specific historical information regarding prior cancers.

Sponsor's Initial Analyses:

For TAAL, the sponsor's tabulation of treatment-emergent serious adverse events, system organ class (SOC) "neoplasms benign, malignant and unspecified (including cysts and polyps)," is shown as Table 13, as adapted from Table TAAL 14.99. The corresponding tabulation of non-serious adverse events is provided as Table 14, adapted from Table TAAL 14.92.

Colorectal Cancer: The sponsor found 19 colonic and rectal neoplasms in the prasugrel group and 8 in the clopidogrel group, but found reassurance in the fact that half of cases in the prasugrel group were discovered as a result of an antecedent GI bleed.

Breast Cancer: The sponsor counted 5 cases of breast cancer in the prasugrel group, versus 1 in the clopidogrel group, but the relatively short time frame between initiation of study drug and diagnosis, for at least some of the cases, assuaged the sponsor's concern.

Lung Cancer: There were 8 and 2 lung cancers reported as adverse events in the prasugrel and clopidogrel groups, respectively. However, when "lung neoplasms" were added to the

Table 13: Treatment Emergent Serious Adverse Events from TALL, SOC "Neoplasms, benign, malignant and unspecified..."

Neoplasm as serious adverse event (from TAAL Table 14.99)	Prasugrel	Clopidogrel
	n (%)	n (%)
all	87 (1.29)	60 (0.89)
colon cancer	10 (0.15)	2 (0.03)
gastric cancer	6 (0.09)	7 (0.1)
prostate cancer	6 (0.09)	7 (0.1)
breast cancer	4 (0.06)	1 (0.01)
adenocarcinoma	2 (0.03)	0 (0)
bladder cancer	2 (0.03)	4 (0.06)
brain cancer	2 (0.03)	1 (0.01)
clear cell cancer of kidney	2 (0.03)	0 (0)
lung neoplasm malignant	2 (0.03)	2 (0.03)
lung squamous cell carcinoma	2 (0.03)	1 (0.01)
metastases to lung	2 (0.03)	0 (0)
metastatic neoplasm	2 (0.03)	0 (0)
non-small cell lung cancer	2 (0.03)	2 (0.03)
prostate cancer metastatic	2 (0.03)	1 (0.01)
renal neoplasm	2 (0.03)	0 (0)
squamous cell carcinoma	2 (0.03)	1 (0.01)
acute myeloid leukaemia	1 (0.01)	0 (0)
adenoma benign	1 (0.01)	0 (0)
basal cell carcinoma	1 (0.01)	1 (0.01)
benign lung neoplasm	1 (0.01)	0 (0)
bladder neoplasm	1 (0.01)	1 (0.01)
bladder papilloma	1 (0.01)	0 (0)
bone neoplasm	1 (0.01)	0 (0)
bronchial carcinoma	1 (0.01)	2 (0.03)
cervix carcinoma	1 (0.01)	0 (0)
chronic lymphocytic leukaemia	1 (0.01)	0 (0)
colon adenoma	1 (0.01)	1 (0.01)
colon neoplasm	1 (0.01)	0 (0)
colorectal cancer	1 (0.01)	0 (0)
gallbladder cancer	1 (0.01)	0 (0)
gastrointestinal carcinoma	1 (0.01)	2 (0.03)
gastrointestinal tract adenoma	1 (0.01)	0 (0)
haemangioma	1 (0.01)	0 (0)
lung adenocarcinoma	1 (0.01)	0 (0)
lung neoplasm	1 (0.01)	1 (0.01)
malignant ascites	1 (0.01)	0 (0)
mesothelioma malignant	1 (0.01)	0 (0)

	Prasugrel	Clopidogrel
	n (%)	n (%)
metastases to bone	1 (0.01)	2 (0.03)
metastases to liver	1 (0.01)	1 (0.01)
nasal neoplasm	1 (0.01)	0 (0)
oesophageal adenocarcinoma	1 (0.01)	0 (0)
oesophageal cancer metastatic	1 (0.01)	0 (0)
oesophageal carcinoma	1 (0.01)	3 (0.04)
ovarian neoplasm	1 (0.01)	0 (0)
pancreatic carcinoma	1 (0.01)	1 (0.01)
papillary thyroid cancer	1 (0.01)	0 (0)
papilloma	1 (0.01)	0 (0)
peripheral t-cell lymphoma	1 (0.01)	0 (0)
pituitary tumour benign	1 (0.01)	0 (0)
prostatic adenoma	1 (0.01)	0 (0)
rectal cancer	1 (0.01)	0 (0)
rectal neoplasm	1 (0.01)	0 (0)
renal cell carcinoma	1 (0.01)	2 (0.03)
salivary gland neoplasm	1 (0.01)	0 (0)
sarcoma	1 (0.01)	0 (0)
small cell lung cancer	1 (0.01)	3 (0.04)
thyroid cancer	1 (0.01)	0 (0)
transitional cell carcinoma	1 (0.01)	0 (0)
uterine leiomyoma	1 (0.01)	0 (0)
adenocarcinoma pancreas	0 (0)	1 (0.01)
adrenal neoplasm	0 (0)	1 (0.01)
bladder transitional cell carcinoma	0 (0)	1 (0.01)
carcinoid tumour pulmonary	0 (0)	1 (0.01)
chronic myeloid leukaemia	0 (0)	1 (0.01)
colon cancer metastatic	0 (0)	1 (0.01)
gastric neoplasm	0 (0)	1 (0.01)
hepatic cancer metastatic	0 (0)	1 (0.01)
hepatic neoplasm	0 (0)	1 (0.01)
lymphocytic leukaemia	0 (0)	1 (0.01)
malignant melanoma	0 (0)	1 (0.01)
metastases to adrenals	0 (0)	1 (0.01)
myelodysplastic syndrome	0 (0)	1 (0.01)
non-hodgkin's lymphoma	0 (0)	2 (0.03)
small cell lung cancer metastatic	0 (0)	1 (0.01)
thymoma	0 (0)	1 (0.01)

cancers, the respective numbers were 12 and 10. The sponsor determined, therefore, that the numbers of subjects with lung neoplasm were not different between treatment groups.

Prostate Cancer: Sixteen subjects in the prasugrel group and 9 in the clopidogrel group experienced an adverse event for prostate cancer or adenoma. The sponsor took reassurance from the fact that in half of the 16 cancers in the prasugrel group, the diagnosis was made within 6 months of starting the study drug, ergo; they considered these unlikely to represent new cancers.

Table 14: Treatment Emergent Adverse Events from TAAL, SOC "Neoplasms, benign, malignant and unspecified..."

Neoplasm as adverse event (from TAAL Table 14.92)	Prasugrel	Clopidogrel
	n (%)	n (%)
all	153 (2.27)	123 (1.83)
prostate cancer	16 (0.24)	7 (0.1)
colon cancer	11 (0.16)	2 (0.03)
lung neoplasm malignant	8 (0.12)	2 (0.03)
gastric cancer	6 (0.09)	8 (0.12)
bladder cancer	5 (0.07)	4 (0.06)
breast cancer	5 (0.07)	1 (0.01)
squamous cell carcinoma	5 (0.07)	5 (0.07)
lung neoplasm	4 (0.06)	8 (0.12)
prostatic adenoma	4 (0.06)	0 (0)
skin papilloma	4 (0.06)	1 (0.01)
colon adenoma	3 (0.04)	3 (0.04)
malignant melanoma	3 (0.04)	3 (0.04)
metastases to lung	3 (0.04)	0 (0)
metastatic neoplasm	3 (0.04)	1 (0.01)
renal neoplasm	3 (0.04)	1 (0.01)
skin cancer	3 (0.04)	4 (0.06)
adenocarcinoma	2 (0.03)	1 (0.01)
basal cell carcinoma	2 (0.03)	5 (0.07)
biliary neoplasm	2 (0.03)	1 (0.01)
brain neoplasm	2 (0.03)	1 (0.01)
chronic lymphocytic leukaemia	2 (0.03)	1 (0.01)
clear cell carcinoma of the kidney	2 (0.03)	0 (0)
gastric neoplasm	2 (0.03)	1 (0.01)
lung squamous cell carcinoma	2 (0.03)	1 (0.01)
metastasis	2 (0.03)	0 (0)
mycosis fungoides	2 (0.03)	1 (0.01)
non-small cell lung cancer	2 (0.03)	2 (0.03)
ovarian neoplasm	2 (0.03)	0 (0)
prostate cancer metastatic	2 (0.03)	1 (0.01)
thyroid neoplasm	2 (0.03)	2 (0.03)
acrochordon	1 (0.01)	1 (0.01)
acute myeloid leukaemia	1 (0.01)	0 (0)
adenoma benign	1 (0.01)	1 (0.01)
adrenal adenoma	1 (0.01)	0 (0)
benign lung neoplasm	1 (0.01)	0 (0)
bladder neoplasm	1 (0.01)	3 (0.04)
bladder papilloma	1 (0.01)	0 (0)
bladder squamous cell carcinoma	1 (0.01)	0 (0)
bladder transitional cell carcinoma	1 (0.01)	0 (0)
bone neoplasm	1 (0.01)	0 (0)
bone neoplasm malignant	1 (0.01)	0 (0)
breast cancer recurrent	1 (0.01)	0 (0)
bronchial carcinoma	1 (0.01)	2 (0.03)
cardiac neoplasm	1 (0.01)	0 (0)
cervix carcinoma	1 (0.01)	0 (0)
colon neoplasm	1 (0.01)	0 (0)
colorectal cancer	1 (0.01)	0 (0)
fibroadenoma of breast	1 (0.01)	0 (0)
gallbladder cancer	1 (0.01)	0 (0)
gastrointestinal carcinoma	1 (0.01)	2 (0.03)
gastrointestinal tract adenoma	1 (0.01)	0 (0)
haemangioma	1 (0.01)	0 (0)
hepatic neoplasm	1 (0.01)	1 (0.01)
lipoma	1 (0.01)	1 (0.01)
lung adenocarcinoma	1 (0.01)	0 (0)
lymphoma	1 (0.01)	1 (0.01)
malignant ascites	1 (0.01)	0 (0)
mesothelioma malignant	1 (0.01)	0 (0)
metastases to bone	1 (0.01)	2 (0.03)
metastases to liver	1 (0.01)	1 (0.01)
metastases to lymph nodes	1 (0.01)	0 (0)
multiple myeloma	1 (0.01)	0 (0)
nasal cavity cancer	1 (0.01)	0 (0)
nasal neoplasm	1 (0.01)	1 (0.01)
oesophageal adenocarcinoma	1 (0.01)	0 (0)
oesophageal cancer metastatic	1 (0.01)	0 (0)
oesophageal carcinoma	1 (0.01)	3 (0.04)
oesophageal neoplasm	1 (0.01)	0 (0)
pancreatic carcinoma	1 (0.01)	1 (0.01)
papillary thyroid cancer	1 (0.01)	0 (0)
papilloma	1 (0.01)	1 (0.01)
peripheral T-cell lymphoma	1 (0.01)	0 (0)
pituitary tumour	1 (0.01)	0 (0)
pituitary tumour benign	1 (0.01)	0 (0)
rectal cancer	1 (0.01)	0 (0)
rectal neoplasm	1 (0.01)	1 (0.01)
renal cell carcinoma	1 (0.01)	3 (0.04)
salivary gland neoplasm	1 (0.01)	1 (0.01)
sarcoma	1 (0.01)	0 (0)
small cell lung cancer	1 (0.01)	3 (0.04)
thyroid cancer	1 (0.01)	0 (0)
transitional cell carcinoma	1 (0.01)	0 (0)
uterine leiomyoma	1 (0.01)	2 (0.03)
xanthoma	1 (0.01)	0 (0)
adenocarcinoma pancreas	0 (0)	1 (0.01)
adrenal neoplasm	0 (0)	1 (0.01)
bladder transitional cell carcinoma	0 (0)	1 (0.01)
carcinoid tumour pulmonary	0 (0)	1 (0.01)
chronic myeloid leukaemia	0 (0)	1 (0.01)
colon cancer metastatic	0 (0)	1 (0.01)
fibrous histiocytoma	0 (0)	1 (0.01)
haemangioma of liver	0 (0)	1 (0.01)
hepatic cancer metastatic	0 (0)	1 (0.01)
hypergammaglobulinaemia benign	0 (0)	1 (0.01)
monoclonal	0 (0)	1 (0.01)
laryngeal cancer	0 (0)	1 (0.01)
lentigo	0 (0)	1 (0.01)
lung carcinoma cell type	0 (0)	1 (0.01)
unspecified recurrent	0 (0)	1 (0.01)
lymphocytic leukaemia	0 (0)	1 (0.01)
melanocytic naevus	0 (0)	1 (0.01)
metastases to adrenals	0 (0)	1 (0.01)
myelodysplastic syndrome	0 (0)	1 (0.01)
myeloproliferative disorder	0 (0)	1 (0.01)
nasopharyngeal neoplasm benign	0 (0)	1 (0.01)
neoplasm	0 (0)	1 (0.01)
neoplasm malignant	0 (0)	1 (0.01)
non-hodgkin's lymphoma	0 (0)	2 (0.03)
ocular neoplasm	0 (0)	1 (0.01)
osteoma cutis	0 (0)	2 (0.03)
pyogenic granuloma	0 (0)	1 (0.01)
rectal adenoma	0 (0)	1 (0.01)
seborrhoeic keratosis	0 (0)	1 (0.01)
small cell lung cancer metastatic	0 (0)	1 (0.01)
squamous cell carcinoma of skin	0 (0)	2 (0.03)
thymoma	0 (0)	1 (0.01)
tongue neoplasm malignant	0 (0)	1 (0.01)

The sponsor's summary interpretation, as stated in the original submission, was:

> "Cases of malignancy were reported at a frequency that was higher in the prasugrel than in the clopidogrel group. In some cases, such as prostate cancer, this appears to be a coincidental finding since about half of the cases were reported within 6 months of starting drug. In the case of colon cancer, they were often discovered during a diagnostic procedure following a bleed. In summary, there is no evidence that use of prasugrel is associated with a higher risk of cancer."

Division's Concerns: In early communications between the Division and the sponsor, the Division expressed its concern regarding the excess serious adverse events for neoplasia in the prasugrel group. The sponsor espoused the view that the observed difference between prasugrel and clopidogrel in the frequency of neoplasm treatment-emergent adverse events was due to ascertainment bias, because of increased bleeding associated with prasugrel compared to clopidogrel.

This possibility seemed plausible on its face, and the Division performed its own analysis of the cases, excluding cancers where a hemorrhagic adverse event preceded the cancer *in the same organ system as the cancer*, i.e., hemoptysis for lung cancer, hematuria for genitourinary cancers, GI bleeds for GI cancers, and dysfunctional uterine bleeding for gynecologic cancers. Our analysis showed that the between-group difference in neoplasms largely persisted (results not shown).

The Division sought additional information from the sponsor, to clarify diagnoses and malignancy status for cases where it was not clear, to distinguish new from pre-existing cancers, to collect investigators' assessment of symptoms, signs, and laboratory studies that led to diagnoses of cancer, and to collect information on long-term vital status. The sponsor developed "Neoplasia" CRFs to capture this information, and sent clinical monitors to the sites to oversee collection of the data. The sites were to complete the CRFs and provide all available source documents supporting the data.

The sponsor provided a regulatory response on 9 May, 2008, wherein they identified 313 subjects reported as having experienced an adverse event within the "Neoplasms Benign, Malignant, and Unspecified" SOC, either as 1) a newly diagnosed adverse event, or 2) a pre-existing condition that increased in severity during the conduct of the trial.[2] There were 175 subjects treated with prasugrel and 138 subjects treated with clopidogrel who had one or more of these events during the study. Figure 15 shows the sponsor's breakdown of non-benign neoplasms. ("Non-benign" includes neoplasms that were characterized as malignant or "unknown.") Once the benign and pre-existing neoplasms were subtracted, the RR was 1.19; however, the sponsor included non-melanomatous skin cancers in their analyses, which are readily curable by excision and not considered to be a serious malignancy. When such cancers were excluded (Figure 15, bottom groups of boxes), there were 94 and 72 new, non-benign neoplasms in the prasugrel and clopidogrel groups, respectively, for a RR of 1.31.

[2] Two subjects were not included, because the sponsor was not able to obtain additional information from the site. Both subjects has been in the prasugrel treatment group, and one was diagnosed with a new "papillary urothelial carcinoma."