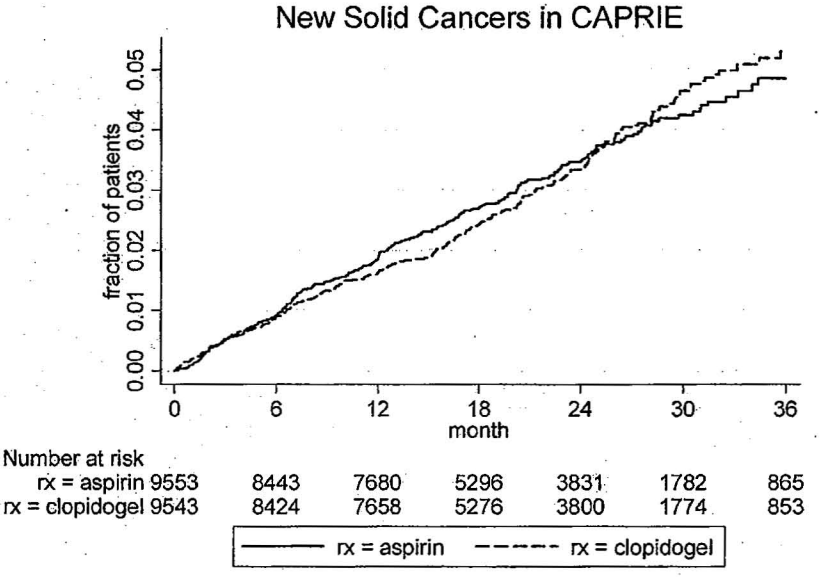
bladder, and unknown in the placebo group. In CREDO there was a 5 vs. 0 excess of lung cancers (*post hoc* p = 0.03 commented upon in the study report) but overall new solid cancers were less frequent with clopidogrel (20 vs. 12). Hematologic malignancies and brain tumors did not show any noteworthy variations except a 4 vs. 1 excess of lymphomas in the placebo group in CURE.

I show the new solid cancer incidence plots for CAPRIE in Figure 13 and for CHARISMA in Figure 14; I show the types of cancers for CAPRIE in Table 19 and for CHARISMA in Table 20.

Figure 13: K-M Incidence Plot of New Solid Cancers in CAPRIE



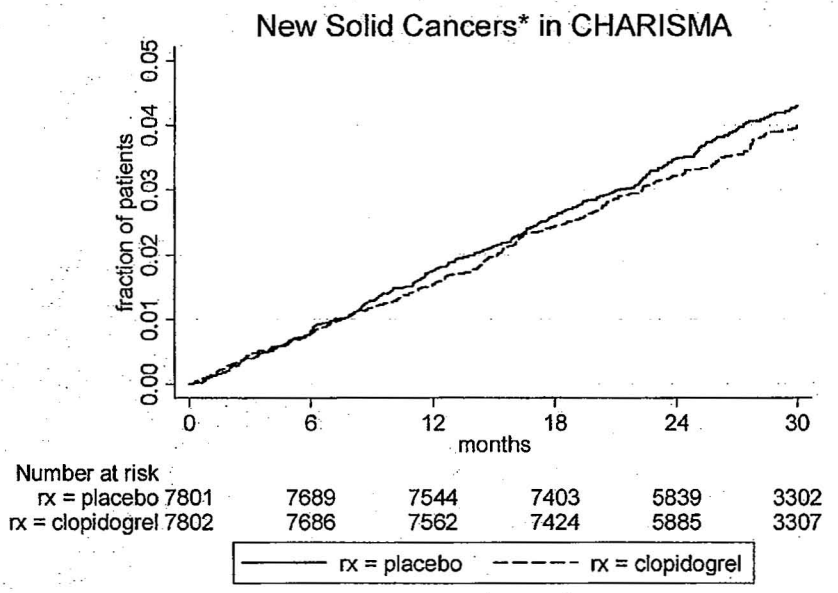
*excluding non-melanoma skin cancers and brain tumors; p = 0.9 by log rank

Table 19: Numbers of Cancers by Site and Treatment in CAPRIE

	aspirin	clopidogrel
patients	9599	9586
bladder	28	26
breast	15	11
cervix	2	2
colorectal	40	33
esophagus	4	4
gall bladder	3	0
head & neck	11	16
kidney	10	10
liver	4	3
lung	74	72
melanoma	13	11
mesothelioma	0	1
ovary	1	3

	aspirin	clopidogrel
pancreas	11	3
prostate	46	61
sarcoma	1	4
stomach	5	13
unknown	11	8
uterus	5	1
total new solid cancers	284	282
skin	71	76
pituitary	4	0
brain	3	9
leukemia	4	5
lymphoma	12	7
myeloma	0	4
polycythemia	4	3

Figure 14: K-M Incidence Plot for New Solid Cancers in CHARISMA



*excluding non-melanoma skin and brain; p = 0.35 by log rank

Table 20: Numbers of Cancers by Site and Treatment in CHARISMA

	clopidogrel	placebo
patients	7,802	7,801
bile duct	3	1
bladder	26	19
breast	13	22
cervix	0	2
colon	0	1

	clopidogrel	placebo
colorectal	41	39
esophagus	6	5
gall bladder	0	1
gi	2	0
head & neck	16	22
kidney	11	13
liver	5	7
lung	70	63
melanoma	9	13
mesothelioma	2	1
myeloma	4	2
other	2	1
ovary	1	3
pancreas	5	10
pelvis	2	1
prostate	52	52
sarcoma	1	0
small intestine	3	2
stomach	8	10
testis	2	0
thyroid	1	1
unknown	9	15
uterus	3	4
vagina	0	1
total new solid cancers	297	311
brain	7	3
leukemia	9	4
lymphoma	4	15

The K-M incidence plots show no significant differences in the rates of new solid cancers in either CAPRIE or CHARISMA. The plot for CAPRIE looks like it might be starting to trend unfavorably for clopidogrel but the plot for CHARISMA looks like it might be trending favorably for clopidogrel. The distributions of cancer types by treatment group also show random differences in the rates, e.g., slightly more prostate and stomach cancers with clopidogrel in CAPRIE but less colorectal cancer; more bladder and lung cancers with clopidogrel in CHARISMA but less breast cancer.

One final comment about CHARISMA: bleeding rates were higher in the clopidogrel group as shown in Table 21.

Table 21: Bleeding in CHARISMA

Type of Bleeding (GUSTO)	No. % With Event		Difference Clopidogrel - Placebo (%) (95% CI)	p-Value
	Clopidogrel (N=7802)	Placebo (N=7801)		
Any	2827 (36.23)	1616 (20.72)	15.52 (14.12,16.91)	<0.001
Severe/Moderate [a]	290 (3.72)	197 (2.53)	1.19 (0.65,1.74)	<0.001
Severe [a]	130 (1.67)	104 (1.33)	0.33 (-0.05,0.71)	0.087
Moderate [ab]	164 (2.10)	101 (1.29)	0.81 (0.40,1.21)	<0.001
Other bleeding [c]	2646 (33.91)	1487 (19.06)	14.85 (13.49,16.22)	<0.001

COMMENT: Clopidogrel does not appear to have an appreciable effect upon cancer rates. The exposure in the clopidogrel studies is much higher than that for prasugrel in TAAL and should be sufficient for detecting an effect comparable to that seen in TAAL. I believe the clopidogrel studies are good examples of what variations in results to expect when analyses like those I performed for TAAL are done for a drug that has good substantiation of a lack of carcinogenic potential. Furthermore, the fact that in CHARISMA there was substantially more bleeding in the clopidogrel group than in the control group but similar cancer rates does not support the hypothesis that the differences in bleeding rates observed in antiplatelet trials lead to cancer ascertainment biases.

Prasugrel Efficacy Robustness

Because I have been asked to recommend approvability of prasugrel and labeling for it, I also performed some independent analyses of prasugrel efficacy in TAAL. I was interested in understanding the robustness of the prasugrel effect for comparison to the risk of cancer promotion. The sponsor's analyses of the TAAL use Clinical Endpoint Committee (CEC) adjudications of site-reported and lab value-triggered events. As a measure of robustness I also analyzed the TAAL results using site-reported events only.

CEC Adjudication and Peri-Procedural Myocardial Infarctions

The CEC adjudicated all important endpoint events, including MIs, strokes, and CV deaths as well as stent thromboses, and bleeding events for TAAL. What the study report and other reviews do not state prominently is that there were two distinct paths for an event to be referred to the CEC: (1) by the site; and (2) "triggered" by a review of adverse events or lab values. (In addition, the CEC could find an event in a CRF or other documentation submitted for a different type of event, but such CEC-detected events were rare.) For MIs the majority of triggered events were peri-procedural MIs (PPMIs). There were far more potential PPMI events adjudicated by the CEC (2,583) than investigator reported MI events (483). However, because the CEC adjudicated the minority of potential PPMIs as MIs, the number of adjudicated MIs submitted in some fashion by the sites (705—in addition to MIs the sites also submitted other potential cardiac ischemic events) exceeded the number of adjudicated MIs based on PPMI triggers (512, with 11 additional MIs being otherwise triggered or CEC determined.)

The CEC adjudicated higher percentages of clopidogrel events as MIs than prasugrel events as shown in Table 22.

Table 22: CEC MI Adjudications by Type of Referring Event

	clopidogrel		prasugrel	
referring event	n	% MI	n	% MI
site MI event	303	80%	180	76%
site other ischemic event	984	19%	903	15%
triggered PPMI*	1022	21%	1049	19%

*PPMI = peri-procedural myocardial infarction

Note also that site referred MI events were substantially higher in the clopidogrel group than in the prasugrel group while triggered potential PPMIs were equal between the two groups. However, there are problems with the determination of MI adverse events as I describe below.

Adjudication in a clinical study always raises at least three sets of issues: (1) whether the adjudication rules were pre-specified and appropriate; (2) whether referral for adjudication was comparable; and (3) whether the adjudication was performed fairly or, at least, how adjudication affects the results. Regarding the first set of issues, incomplete criteria for the endpoint definitions, particularly the definition of an MI, were provided in the original protocol. The original protocol did not describe how screening would be done for PPMIs or how PPMIs would be distinguished form the index ACS event. Additionally, Protocol Amendment (a) dated January 10, 2006, modified the criteria for PPMIs (and adjudication of MIs started after this amendment on January 24, 2006.) This amendment was stated to have been developed after blinded evaluation of the data by the Study Operations Committee—TAAL reached 50 per cent enrollment in December 2005. The PPMI criteria modification highlighted by the sponsor in Amendment (a) was the following: The original definition of PPMI required an elevation of creatine kinase-myocardial band (CK-MB) to > 3x upper limit of normal (ULN) on a minimum of two samples within 48 hours of PCI. The modified definition retained the original definition and extended PPMIs to a CK-MB > 5x ULN on one sample if it was the last available sample and was drawn ≥ 12 hours after PCI. While this change does not appear to be problematic (see the *post-hoc* analysis in the primary clinical review), there was a second change to the PPMI definition that was not discussed by the sponsor but vaguely worded: "A peri-procedural event must be distinct from the index event." How the PPMI must be distinct from the index event was not specified operationally in Amendment (a).

One of the major problems with PPMIs in TAAL is distinguishing them from the index event. The protocol does not include a description of how PPMIs were screened and adjudicated. The sponsor (or their agents) eventually developed complicated procedures for screening for PPMIs and attempting to distinguish them from the index event. The sponsor eventually added a footnote to two of the five "major sets of criteria" "used for the diagnosis of nonfatal MI" in the main body of the CEC Charter: "Cannot be determined within 12 hours of onset of qualifying STEMI" (regarding PPMIs with PCI and CABG.) The main body of the CEC Charter does not mention how a PPMI is distinguished from an index NSTEMI. The algorithm to screen for PPMIs and to distinguish them from the index event was detailed in a CEC Charter appendix submitted to the NDA and is extremely complex and nonstandard—see Table 23.

Table 23: CEC Charter Appendix Algorithm for Identifying PPMIs and Distinguishing Them from the Index Event

Algorithm for identifying unreported potential peri-procedural Myocardial infarctions

Clinical presentation*	Intervention	Pre-Intervention CK-MB	Conditions that needs to be met to trigger
UA/NSTEMI/STEMI>12h	PCI	All normal	1
UA/NSTEMI/STEMI>12h	PCI	At least one >ULN	1,2, and 3
STEMI≤12h	PCI	Normal or abnormal	1,2, and 3
UA/NSTEMI /STEMI>12h	PCI	Missing	1
STEMI ≤12h	PCI	Missing	1 and 3
UA/NSTEMI /STEMI>12h	CABG	Normal or Abnormal	4
STEMI ≤12h	CABG	Normal or Abnormal	3 and 4
UA/NSTEMI /STEMI>12h	Medical	All visit 1 CK-MB Normal	5
STEMI ≤12h	Medical	All visit 1 CK-MB Normal	3 and 5
UA/NSTEMI /STEMI>12h	Medical	At least one visit 1 CK-MB>ULN	2 and 5
STEMI ≤12h	Medical	At least one visit 1 CK-MB>ULN	2, 3 and 5
UA/NSTEMI /STEMI>12h	Medical	Missing	5
STEMI≤12h	Medical	Missing	3 and 5

* If clinical presentation is missing, subject will be conservatively considered as UA/NSTEMI.

Conditions

1. At least one post-PCI CK-MB>3* ULN
2. Maximum post-PCI CK-MB>1.5* (minimum CK-MB during the peri-procedural period) up to 48 hours after PCI.
3. Evidence of resolution of index MI
    a. Sort CK-MB from central laboratory by time
    b. Assign the sign of change, increase in CK-MB (+) or decrease in CK-MB (-) to each time point leaving the sign change for last measurement missing.
    c. Follow (a) and (b) for CK-MB from local laboratories (from CRF)
    d. Merge central and local laboratory data, sort them by time and count the number of sign changes.

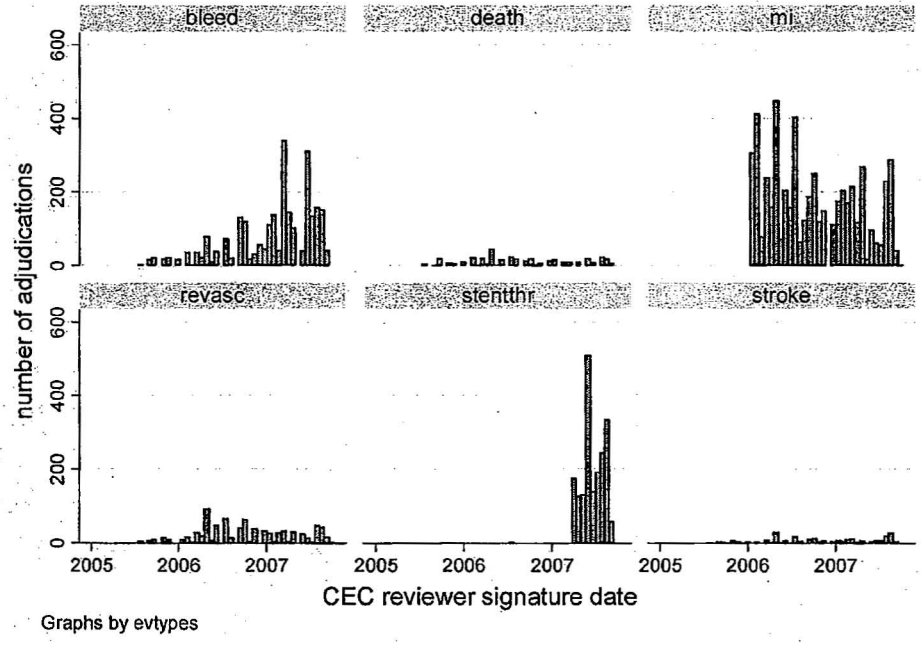
If the initial sign of change in CK-MB is positive, then 3 or more runs (sequential Sign of Change) will be considered as evidence of resolution of Index MI (see Examples below: +++ or ----). If the initial sign of change in CK-MB is negative, then 2 or more runs will be considered as evidence of resolution of Index MI.

4. At least one post-CABG CK-MB>10*ULN
5. At least one Visit 3 CK-MB >ULN

This algorithm was not submitted to the IND until April 16, 2007 (3 months after the last patient was enrolled), when it was included in a submission of the CEC Charter describing stent thrombosis changes (with stent thrombosis adjudications beginning April 5, 2007.) The CEC Charter also describes the screening for triggered events being performed by the Contract Research Organization (CRO) but otherwise how or when the algorithms were developed and how they were implemented is not detailed. How well the screenings and adjudications adhered to the algorithm in Table 23 is not documented in the materials submitted to the NDA. However, a mitigating factor regarding the problems with ascertaining PPMIs is that they were more evenly distributed than MI events between the two treatment groups: PPMIs account for about 47 per cent of the MIs but only about 21 per cent of the difference in numbers of MIs between the two groups.

I show the timing of CEC adjudications in TAAL in Figure 15.

Figure 15: Timing of CEC Adjudications in TAAL



The timing of adjudications shows several patterns:

- Bleed adjudications were performed predominantly in the later stages of the study.
- Adjudications for deaths and strokes were distributed throughout the study period.
- MI adjudications did not start until the end of January 2006 following the Amendment (a) modifying the definition of PPMIs.

- The majority of revascularization adjudications were delayed until after March 2006.

- Stent thrombosis adjudications were performed starting April 2007 following the CEC Charter amendment providing definitions of them.

COMMENT: Of these patterns, the one that does not have a ready explanation is that for bleeds. The reasons for the timing of revascularization adjudications is also not obvious. Both suggest that there were evolutions in the CEC adjudication definitions or processes that have not been revealed.

The referral of site-determined events is complicated by another problem: Sites were to assign an "AEID" (e.g., E01, E02, etc.) to each active medical problem at baseline and to each adverse event. Despite the AEIDs being required on many different forms filled out at many different times, the sites were not supposed to use the same AEID for different events or problems. Not surprisingly, sites made mistakes. For a general description of this problem (and how I handled it for cancer events) see **Cancer Adverse Events in TAAL**, numbered paragraph 2, above. AEIDs were also entered on the CEC adjudication forms. Most of these AEID references appear reasonable, but some are bizarre: Referenced investigator terms include "arthritis", "hyperlipidemia", and "hypothyroidism". How this AEID problem affected referrals for adjudication I do not know, but I performed the following analyses to attempt to elucidate the impact.

In this first data set provided by the sponsor with initial and final values (AETERMCH), I counted 201 MI events for which the final value was not an MI. I counted 724 final MI events so that about 21% (201/925) of the MI events may have been lost. However, the potential loss does not appear to be biased because a similar percentage of the potential loss cases were clopidogrel (54%) as of the final value cases (56%). This first data set did not provide other details of the cases such as event dates so that further analysis of it is not helpful.

The sponsor submitted later more complete data sets of initial and final values (OEVENTSA and OVENTSB split because of size—I combined them into one data set OEVENTS). OEVENTS is the most complete description of adverse events for TAAL submitted by the sponsor. I classified MI and stroke events in OEVENTS by both the originally reported and final event terms. As a check of the completeness of the referral for adjudication of potential events, I cross-checked the MI events from OEVENTS with the adjudicated events in the CEC adjudication dataset and with the investigator-reported events in CIE1. I found 62 MI events from OEVENTS that did not have records in CEC. Of these 62 events 61% were in clopidogrel patients, 85% had a flag set (CRF field) that they had been submitted for adjudication, and 25% of the prasugrel cases and 12.5% of the clopidogrel cases were not classified as having an MI based on another event. Hence the absolute number of cases that may have missed adjudication is small (10 cases for MIs by this analysis).

I also analyzed OEVENTS for an endpoint identical to the primary endpoint but not utilizing the CEC adjudications. I did the OEVENTS analyses as sensitivity analyses to determine the robustness of the results and to compare the site-reported results with the adjudicated results.

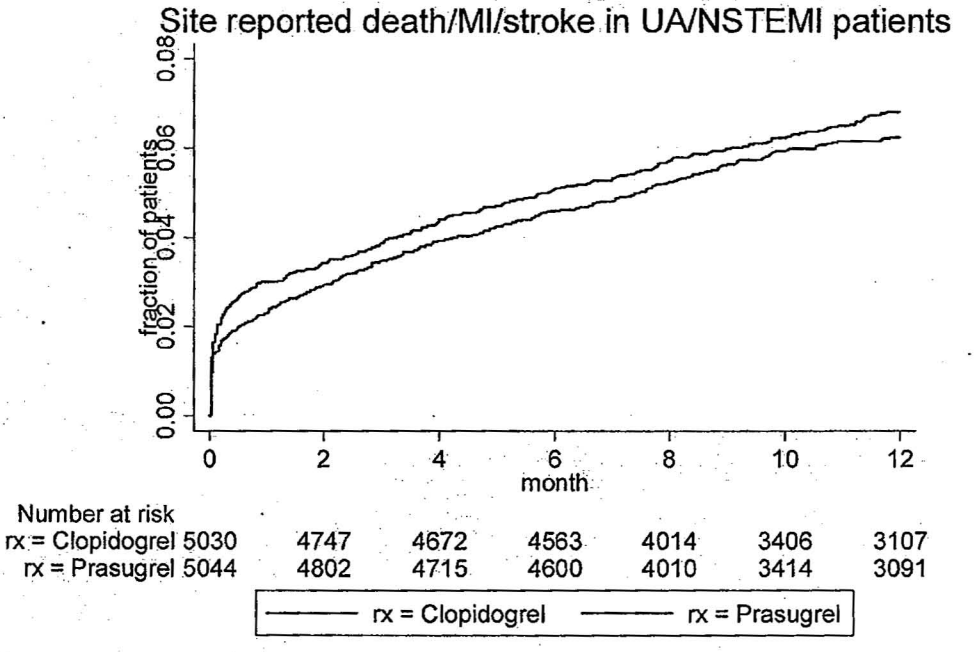
The endpoint I tested was the composite of all-cause mortality, site-reported MIs, and site-reported strokes. I present the results below.

Site-Reported Endpoint Results

For the following analyses I accepted the site's description of the event as reported in the verbatim term, i.e., AEMODIFY in the SAS data sets. Sites reported many events as MIs and I counted them as such; however, for some cardiac events the sites described the events as "new Q wave", "acute coronary syndrome", "cardiac ischemia", or "LAD thrombosis". The CEC adjudicated the latter events and classified some of them as MIs; for the following analyses I counted the latter reports as not MIs (although note that vessel thrombosis reports could also be accompanied by a clinical event of MI.)

Based on site reports, the analysis corresponding to the pre-specified primary endpoint analysis (the composite of all cause mortality, site-reported MIs, and site-reported strokes for the pre-specified primary analysis (time-to-event tested by the Gehan-Wilcoxon test for the UA/NSTEMI subgroup) shows early improvement but not a statistically significant benefit with prasugrel. I show the Kaplan-Meier (K-M) failure plot in Figure 16.

Figure 16: Site-reported Death/MI/Stroke in TAAL UA/NSTEMI Patients

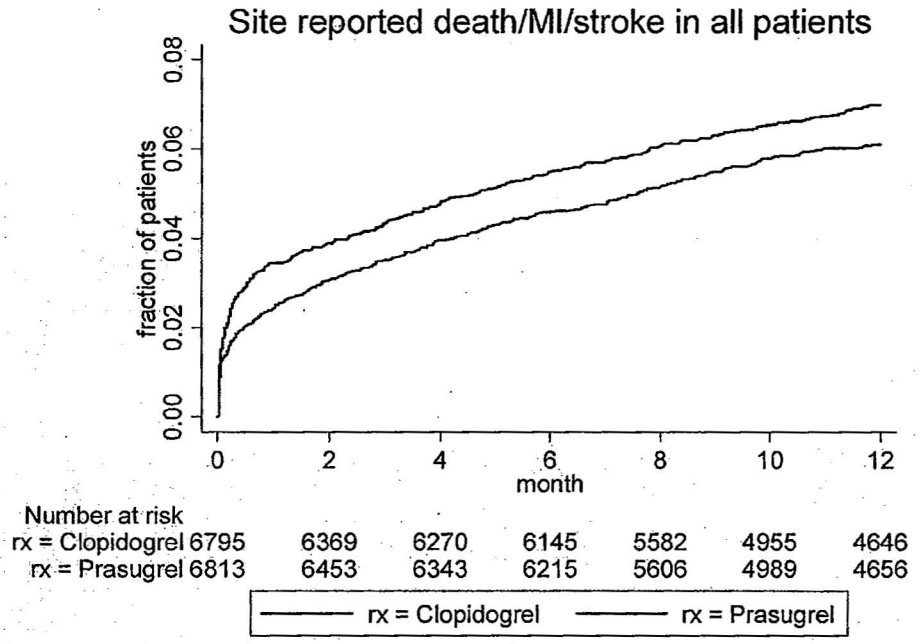


p = 0.24 by Gehan test, 0.35 by log rank test

While the benefit with prasugrel is not statistically significant for this site-reported, unadjudicated sensitivity analysis, there does appear to be a lower rate for early events. The overall risk reduction (about 9%), however, is substantially less than for the CEC-adjudicated

endpoint. While the sponsor pre-specified the UA/NSTEMI subgroup as the primary analysis, the early lower rate of events is better shown in the whole study population in Figure 17.

Figure 17: Site-Reported Death/MI/Stroke in All TAAL Patientws



p = 0.12/0.04 (stratified/unstratified) by Gehan test, 0.08/0.07 by log rank test

The results for the primary site-reported endpoint are not statistically significant by the Gehan test stratified by ACS type, i.e., UA/NSTEMI vs. STEMI, or by the log rank test stratified or non-stratified. They are by the unstratified Gehan test. The Gehan test is more sensitive to the early part of the survival or failure curve compared to the log rank test. That event rates are highest immediately after an ACS event may be the reason the sponsor pre-specified using the Gehan rather than the log rank test. This pre-specification was accepted by the Division when the statistical analysis plan was submitted.

The prasugrel benefit appears greater for the STEMI subgroup as shown in Figure 18.