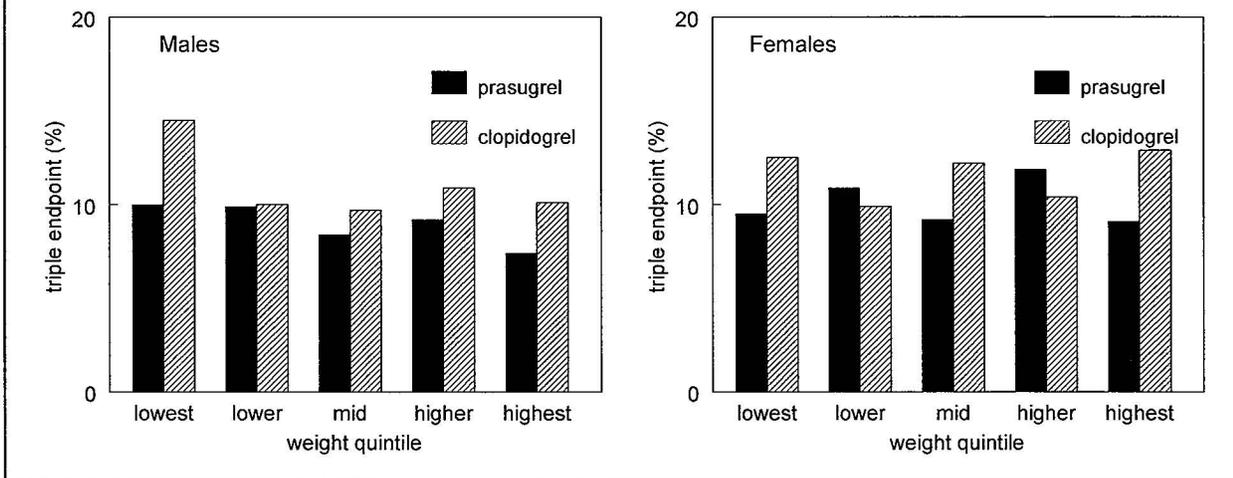
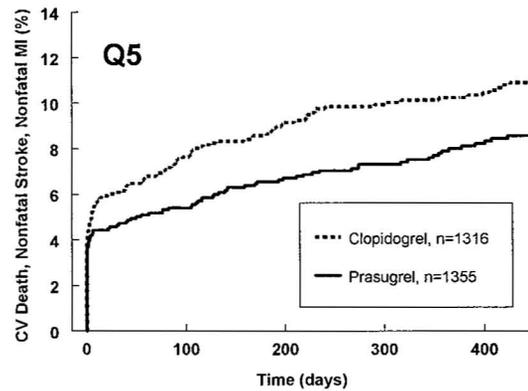
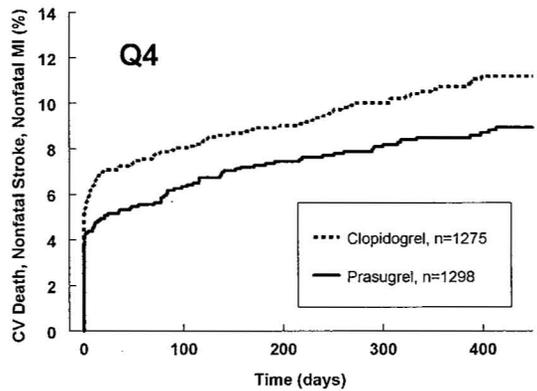
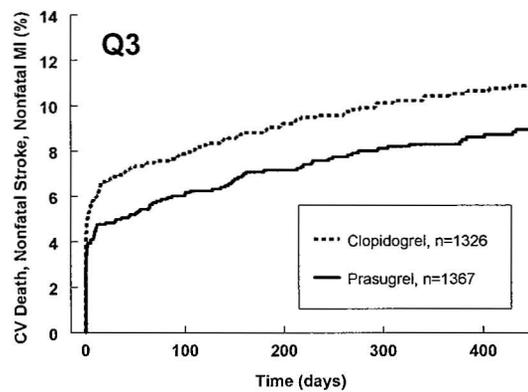
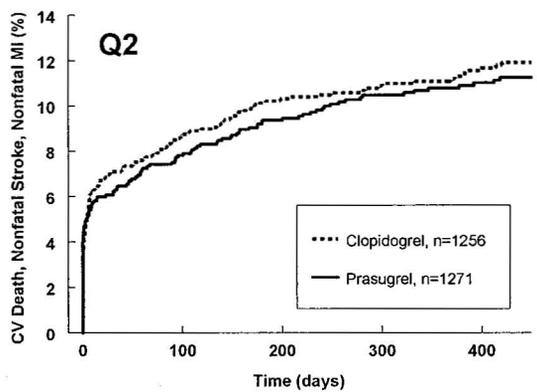
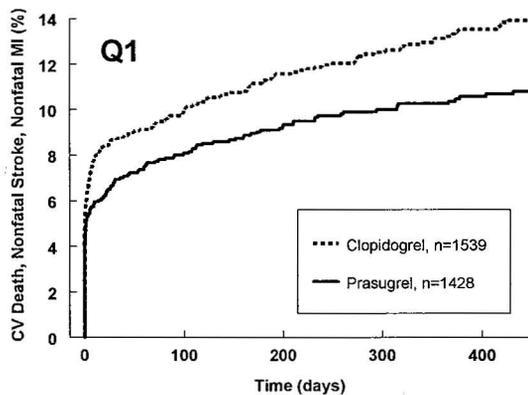
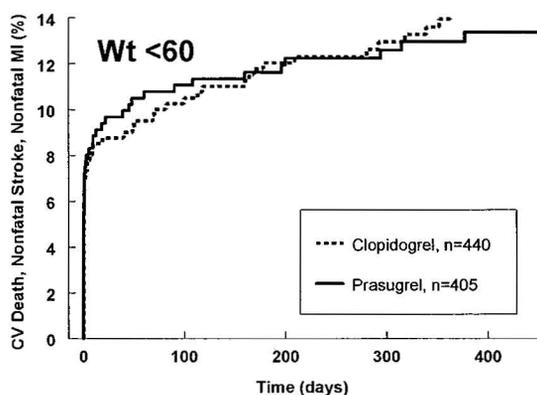


Figure 11: Triple Efficacy Endpoint by Weight Quintiles and Sex



In short, prasugrel appears effective over the range of weights studied. For the small subgroup of subjects weighing <60 kg, prasugrel appears similar, and not superior, to the comparator on the 1° efficacy endpoint.

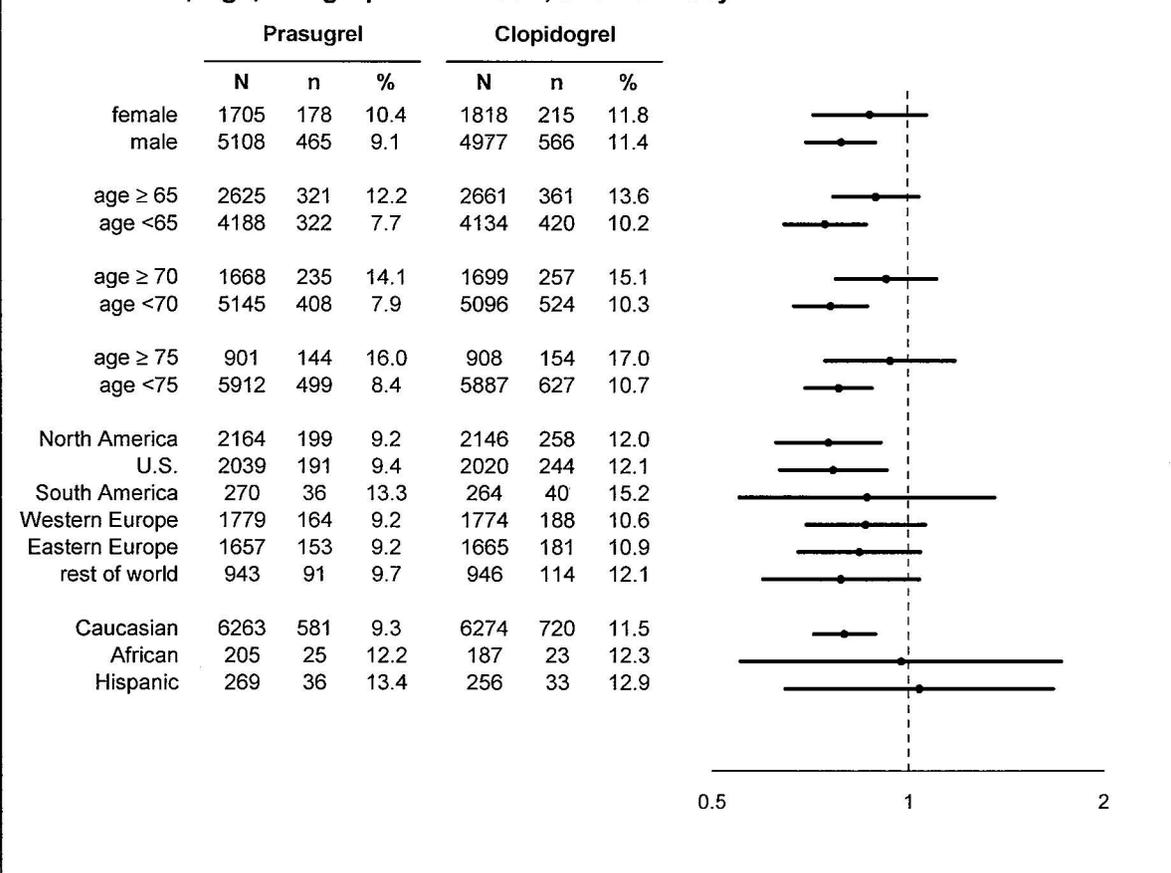
Figure 12: Primary Triple Composite Endpoint by Weight



Subgroups on Sex, Age, and Geographic Location:

Hazard ratios and 95% confidence intervals are shown for the 1° efficacy endpoint for the overall All ACS population across subgroups of sex, age, and geographic location (Figure 13). The treatment benefit of prasugrel tended to be greater in younger versus older populations. Event rates in subjects of African descent tended to be higher than those in Caucasians and the effect of prasugrel was essentially neutral compared to clopidogrel in this population, although the strength of this conclusion is limited given the small number of subjects of African descent studied (less than 3% of the total study population). The numbers of subjects of Asian descent, and numbers of events, were small, and are not shown (1/60 in the prasugrel group; 4/64 in the clopidogrel group). Exposure may be higher in patients of Asian descent (see section 5.2.5).

Figure 13: Results for Triple Composite Endpoint – All ACS Population – Subgroups of Sex, Age, Geographic Location, and Ethnicity



Event rates were fairly similar across geographic regions, except for South America, where event rates were higher. There, too, the odds ratio trended favorable for prasugrel.

Figure 14 shows the results for subgroups of prior (known) vascular disease, metabolic syndrome, diabetes, creatinine clearance (Ccr), prior MI, prior PCI, prior CABG, and history of stroke or TIA. The results trend consistently in favor of prasugrel, with the exception of subjects with a prior history of TIA or stroke.

5.64. In patients with no prior history of TIA or non-hemorrhagic stroke, the incidence of stroke was 0.9% (0.2% ICH) in the prasugrel treatment group and 1.0% (0.3%) in the clopidogrel treatment group.

It is striking that more than one-quarter of the non-fatal strokes in the prasugrel treatment group (17 of 61) occurred in the sub-population of subjects with a history of prior TIA or non-hemorrhagic stroke, a sub-population encompassing only 3.8% of the total subject population. Moreover, it should be re-emphasized that subjects with a history of ischemic stroke within 3 months of randomization, as well as subjects with a history of hemorrhagic stroke at any time, were excluded from the study. (It is possible that such patients would have fared even worse.)

Based on these concerns, the clinical reviewer recommended a contraindication for prasugrel in patients with a prior history of TIA or stroke. This reviewer supports that recommendation.

Table 8: Cardiovascular Death, Nonfatal MI, Nonfatal Stroke, and All Stroke in Subjects With and Without a Prior History of Stroke or TIA

Endpoint	Prior TIA or Stroke?	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%		
Triple Composite	Yes	262	47	17.9	256	35	13.7	1.38 (0.89, 2.13)	0.15
	No	6551	596	9.1	6539	746	11.4	0.79 (0.71, 0.88)	<0.001
CV Death	Yes	262	9	3.4	256	15	5.9	0.63 (0.28, 1.44)	0.27
	No	6551	124	1.9	6539	135	2.1	0.92 (0.72, 1.17)	0.48
Nonfatal MI	Yes	262	29	11.1	256	25	9.8	1.15 (0.67, 1.97)	0.61
	No	6551	446	6.8	6539	595	9.1	0.74 (0.66, 0.84)	<0.001
Nonfatal Stroke	Yes	262	15	5.7	256	2	0.8	7.39 (1.69, 32.3)	0.002
	No	6551	46	0.7	6539	58	0.9	0.79 (0.54, 1.17)	0.23
All Stroke	Yes	262	17	6.5	256	3	1.2	5.64 (1.65, 19.3)	0.002
	No	6551	58	0.9	6539	68	1.0	0.85 (0.60, 1.21)	0.36

Concomitant Therapies:

- Stents

In the All ACS population, the hazard ratio for prasugrel compared to clopidogrel was essentially the same in subjects receiving any stent (0.81), no stent (0.82), any drug-eluting stent (0.79), and any bare metal stent (0.80).

- GPIIb/IIIa Inhibitors

In the All ACS population, the hazard ratio for prasugrel compared to clopidogrel was similar in subjects receiving a GPIIb/IIIa inhibitor during the index procedure (0.79) compared to subjects not receiving a GPIIb/IIIa inhibitor during the index procedure (0.83). A similar pattern was observed for the UA/NSTEMI and STEMI populations.

- Statins

For the overall ACS population, the hazard ratio in favor of prasugrel was similar in subjects treated and not treated with a statin, 0.81 and 0.83, respectively. Hazard ratios were similar for the UA/NSTEMI and STEMI populations.

- Aspirin

According to the sponsor's analyses, the relative risk reduction with prasugrel compared to clopidogrel in the all ACS population was not influenced by the maximum aspirin dose (>0 to <100, 100 to 200, >200-mg/day) administered through 3 days after randomization and more than 3 days from randomization. These observations were similar for the UA/NSTEMI and STEMI populations.

- Proton Pump Inhibitors

If PPI had importantly diminished prasugrel's pharmacodynamic effects in the setting of salt-to-base conversion, one would expect diminished efficacy in subjects who were receiving PPI. Approximately 40% of the subjects in each treatment group reported use of PPI as a concomitant medication. The Cox proportional hazard ratio favored prasugrel over clopidogrel in subsets of subjects who received and did not receive PPI, and was virtually the same in both subsets. Hazard ratios were 0.82 and 0.80 in subjects who reported and did not report use of PPI, respectively.

- CABG

In the All ACS population undergoing CABG, the hazard ratio was favorable for prasugrel (0.71).

Time from First Symptom to Randomization:

For the UA/NSTEMI population, the hazard ratios were favorable for prasugrel in subjects randomized ≤24 hours and >24 hours after symptom onset (hazard ratios 0.75 and 0.87, respectively).

For the STEMI population, the hazard ratios were favorable for prasugrel in subjects randomized >12 hours after symptom onset and ≤12 hours after symptom onset (hazard ratios 0.65 and 0.87, respectively).

Time from Loading Dose to PCI:

Dr. Raj Madabushi explored the relation between the triple-endpoint outcome and the time interval between LD and start of PCI. He divided subjects in octiles based on time between LD and start of PCI, and computed the proportion of triple endpoint events for each octile, by treatment arm. Within each octile, there were fewer numbers of events in prasugrel-treated subjects, demonstrating a consistent advantage of prasugrel over clopidogrel, irrespective of the timing of the LD relative to PCI.

Interestingly, in both treatment arms, the lowest numbers of endpoint events were observed when the loading dose was administered at the start of PCI or within 30 minutes thereof. With increasing time between the LD and start of PCI (earlier or later), the proportion of endpoint events increased. Dr. Madabushi concluded that the LD (for either prasugrel or clopidogrel) should be administered within 30 minutes of the start of PCI.

This conclusion is subject to interpretation. The finding of an association between outcome and timing of the LD relative to PCI does not prove causality. For example, administration of the LD >1 hour after leaving the catheterization laboratory was a protocol violation, and could be related to a subject's medical instability. Prolonged intervals between administration of the LD and subsequent PCI were interpreted as "early" administration of the LD, but may in fact represent delayed PCI, due to difficult vascular access, complex anatomy, clinical instability, etc., which might be associated with worse outcomes. Thus, although these analyses are

interesting and merit consideration, this secondary reviewer is not convinced that the association should be used to provide advice to practitioners in labeling.

7.3.3. Secondary Endpoints

Results from the 2° endpoints are shown in Table 9. The triple composite endpoint was statistically significant in favor of prasugrel at Days 30 and 90. (Although these were denoted as 2° endpoints, they are, in fact, sensitivity analyses on the 1° endpoint.)

The other 2° endpoints were statistically significantly in favor of prasugrel for the All ACS population, and to lesser extents, for the UA/NSTEMI and STEMI populations individually.

The stent thrombosis endpoint is robust (0.49 RR in favor of prasugrel, 95% CI 0.36, 0.68, for the overall ACS population, $p < 0.001$). Initially, the clinical reviewer (Dr. Karen Hicks) raised concerns regarding the validity of the stent thrombosis endpoint, because the CEC review did not meet the diagnostic standards for stent thrombosis developed recently by the Academic Research Consortium (2007). These standards require angiographic confirmation of stent thrombosis, generally determined by an angiographic core laboratory or pathological confirmation: evidence of recent thrombus within the stent or direct examination of tissue retrieved following thrombectomy. In TAAL, there was no review of angiograms by an angiographic core laboratory, and there was limited pathological confirmation; only reports of coronary angiograms and other clinical reports were used to make determinations of stent

Table 9: TAAL – Secondary Endpoints

endpoint	Patient population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%	N	n	%		
Composite of CV death, nonfatal MI, or UTVR at Day 30												
	UA/NSTEMI	5044	281	5.57	5030	349	6.94	10074	630	6.25	0.80 (0.68, 0.93)	0.005
	STEMI	1769	118	6.67	1765	155	8.78	3534	273	7.72	0.75 (0.59, 0.96)	0.02
	All ACS	6813	399	5.86	6795	504	7.42	13608	903	6.64	0.78 (0.69, 0.89)	<0.001
Composite triple endpoint at Day 30												
	UA/NSTEMI	5044	274	5.43	5030	336	6.68	10074	610	6.06	0.81 (0.69, 0.95)	0.009
	STEMI	1769	115	6.50	1765	166	9.41	3534	281	7.95	0.68 (0.54, 0.87)	0.002
	All ACS	6813	389	5.71	6795	502	7.39	13608	891	6.55	0.77 (0.67, 0.88)	<0.001
Composite of CV death, nonfatal MI, or UTVR at Day 90												
	UA/NSTEMI	5044	345	6.84	5030	420	8.35	10074	765	7.59	0.81 (0.70, 0.94)	0.004
	STEMI	1769	127	7.18	1765	168	9.52	3534	295	8.35	0.75 (0.59, 0.94)	0.013
	All ACS	6813	472	6.93	6795	588	8.65	13608	1060	7.79	0.79 (0.70, 0.90)	<0.001
Composite triple endpoint at Day 90												
	UA/NSTEMI	5044	333	6.60	5030	395	7.85	10074	728	7.23	0.83 (0.72, 0.97)	0.015
	STEMI	1769	129	7.29	1765	178	10.08	3534	307	8.69	0.72 (0.57, 0.90)	0.004
	All ACS	6813	462	6.78	6795	573	8.43	13608	1035	7.61	0.80 (0.71, 0.90)	<0.001
Composite triple endpoint or re-hospitalization for cardiac ischemic events												
	UA/NSTEMI	5044	598	11.86	5030	688	13.68	10074	1286	12.77	0.86 (0.77, 0.96)	0.006
	STEMI	1769	199	11.25	1765	250	14.16	3534	449	12.71	0.78 (0.65, 0.94)	0.009
	All ACS	6813	797	11.70	6795	938	13.80	13608	1735	12.75	0.84 (0.76, 0.92)	<0.001
Composite of all-cause mortality, nonfatal MI, or nonfatal stroke												
	UA/NSTEMI	5044	504	9.99	5030	590	11.73	10074	1094	10.86	0.84 (0.75, 0.95)	0.005
	STEMI	1769	188	10.63	1765	232	13.14	3534	420	11.88	0.80 (0.66, 0.97)	0.02
	All ACS	6813	692	10.16	6795	822	12.10	13608	1514	11.13	0.83 (0.75, 0.92)	<0.001
Definite or probable stent thrombosis per Academic Research Consortium (ARC) definition at study end												
	UA/NSTEMI	4798	39	0.81	4789	80	1.67	9587	119	1.24	0.49 (0.34, 0.72)	<0.001
	STEMI	1624	19	1.17	1633	40	2.45	3257	59	1.81	0.50 (0.29, 0.87)	0.011
	All ACS	6422	58	0.90	6422	120	1.87	12844	178	1.39	0.49 (0.36, 0.68)	<0.001

thrombosis.

The sponsor argued (regulatory response of August 22, 2008) that according to FDA draft guidance, an angiographic core laboratory is not *required*: "FDA strongly recommends that interpretation of data from tests such as angiograms, IVUS, and ECGs be performed by independent core labs and that blinded adjudication of clinical events be conducted by a clinical events committee (CEC Clinical adjudication committees should be independent of core lab analysis centers to avoid potential bias)."³

Ultimately, Dr. Hicks selected a number of cases for review by an independent core laboratory, and requested details regarding the adjudication process. The independent review appeared to support the reliability of the original results.

7.3.4. Efficacy Conclusions

Treatment with prasugrel was associated with a statistically significant reduction in the composite triple endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke. These findings were statistically persuasive across the UA/NSTEMI population, the STEMI population, and the overall ACS population, and robust to exploration. The effect of prasugrel on the 1^o endpoint was evident across the spectrum of subject weight, age, and sex, and in the presence and absence of concomitant diseases and medications that are common in the ACS population. Results were similar whether or not subjects received a stent, and irrespective of whether a bare metal stent or drug-eluting stent was deployed.

Efficacy was driven by a reduction in non-fatal MI, which was statistically significant in both the STEMI and UA/NSTEMI populations. There was a positive trend in mortality in favor of prasugrel in the STEMI population, but not in the larger UA/NSTEMI population. Stroke was similar in the two groups. In exploratory analyses, variability in salt to base conversion had no demonstrable effect on prasugrel's efficacy.

The following weaknesses and concerns have been identified:

1) Prevention of stroke: Importantly, the efficacy of clopidogrel was established in CURE, where clopidogrel was compared to placebo on a background of aspirin in subjects presenting with UA/NSTEMI. The study utilized a triple composite endpoint similar to that used in TAAL. In CURE, clopidogrel was associated with a 20% relative risk reduction on the triple endpoint, but was essentially neutral on the stroke component of the endpoint. Specifically, rates of stroke were 1.2% and 1.4% for the clopidogrel and placebo groups, respectively, for a non-statistically significant relative risk reduction of 14% (95% C.I. -17.7% to 36.6%). In TAAL, prasugrel's effect on stroke was neutral with respect to clopidogrel (hazard ratio 1.02 in favor of clopidogrel, 95% C.I. 0.71 to 1.45). Therefore, in estimating what prasugrel's effect on stroke would have been relative to placebo, the neutral effects in CURE and TAAL are chained, and the evidence of effectiveness is nil.

2) For subjects with a prior history of TIA or stroke, the overall effect of prasugrel was negative, driven by a striking *increase* in strokes (hazard ratio of 5.64, 95% C.I. 1.65 to 19.3). (Of note, subjects with a history of hemorrhagic stroke were excluded from participation, and it is possible that inclusion of such patients might have driven the risk of recurrent stroke even higher.) *Presently, the evidence that prasugrel causes stroke in patients with a prior TIA or*

³ Guidance for Industry: "Coronary Drug-Eluting Stents-Nonclinical and Clinical Studies," draft, March 2008. <http://www.fda.gov/cdrh/ode/guidance/6255.html>

stroke seems more persuasive than the evidence that prasugrel prevents stroke in those without such a history. As such, it would not be appropriate to give prasugrel an indication for stroke, based on extant data. On the contrary, risk management should include a contraindication for patients with a prior history of TIA or stroke.

3) Subjects of African descent: Subjects of African descent accounted for less than 3% of the subject population in TAAL. At this point, there is no reason to believe that results from Caucasians can not be extrapolated to patients of African descent, but the size of the subgroup was too limited to be very informative in its own right.

7.4. Safety

7.4.1. Exposure

TALL included 6741 subjects in the prasugrel treated population and 6716 subjects in the clopidogrel treated population (13,457 in total). Taking into consideration temporary drug discontinuations, median exposure was 442 days in the prasugrel group and 444 days in the clopidogrel group. Over 4200 subjects in each treatment group were exposed for greater than one year.

Although TAAL was a large cardiovascular outcome study, it was by no means a large “simple” trial. Subjects were evaluated at hospital discharge, Days 30, 90, 180, 270, 360, and 450 (or last visit) for adverse events and concomitant medications. In addition, vital signs, ECG, complete blood count, platelet count, and clinical chemistries were performed at each visit. Thus, the safety database is quite robust.

Because 98.8% of randomized subjects received the study agent, the safety population is not importantly different from the ITT efficacy population. As such, the reader is referred back to Table 2 and Table 3 for a breakdown of demographic and historical characteristics, respectively.

The following weaknesses are identifiable in terms of exposure: the database included few subjects with hepatic and renal impairment. Approximately 0.5% of subjects in each group had pre-existing hepatic impairment; approximately 0.8% had severe renal impairment (calculated creatinine clearance < 30 mL/min). Approximately 10% of subjects had calculated creatinine clearance between 30-60 mL/min. Thus, experience is extremely limited in subjects with severe hepatic and renal dysfunction, and this should be pointed out in labeling.

7.4.2. All-Cause Mortality

Table 10 displays the sponsor’s summary breakdown of deaths in TAAL, adapted from Table TAAL.11.10 of the TAAL study report. The right-most column provides point estimates for the numbers of events that prasugrel would be expected to prevent (if >0) or cause (if <0), relative to clopidogrel, per 1000 patients treated.

There was no significant difference in all-cause death between treatment groups; the frequencies of CEC-adjudicated all-cause mortality were 2.76% and 2.90% in the prasugrel and clopidogrel treatment groups, respectively (p=0.64, Table 10). Differences in mortality in the various categories are not statistically significant, but the most favorable trends for prasugrel (fewer deaths) are in those classified as related to acute MI and sudden/unwitnessed. The most unfavorable trends for prasugrel are in deaths classified as hemorrhagic/non-ICH, ICH, and malignancy.