Table 19. Sponsor's Analysis: Number and Percentage of Subjects Reaching the Secondary Composite Endpoints--CEC Adjudicated (All Randomized Subjects) (TAAL)

Analyzed Endpoint	Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI)	p-value
		N	n	(%)[a]	N	n	(%)[a]	N	n	(%)[a]			
CV Death, Nonfatal MI, or Nonfatal Stroke Through 90 Days													
	UA/NSTEMI	5044	333	(6.60)	5030	395	(7.85)	10074	728	(7.23)	0.835	(0.721, 0.966)	0.015
	STEMI	1769	129	(7.29)	1765	178	(10.08)	3534	307	(8.69)	0.715	(0.570, 0.897)	0.004
	All ACS	6813	462	(6.78)	6795	573	(8.43)	13608	1035	(7.61)	0.797	(0.705, 0.901)	<0.001
CV Death, Nonfatal MI, or Nonfatal Stroke Through 30 Days													
	UA/NSTEMI	5044	274	(5.43)	5030	336	(6.68)	10074	610	(6.06)	0.808	(0.689, 0.948)	0.009
	STEMI	1769	115	(6.50)	1765	166	(9.41)	3534	281	(7.95)	0.684	(0.540, 0.868)	0.002
	All ACS	6813	389	(5.71)	6795	502	(7.39)	13608	891	(6.55)	0.767	(0.672, 0.876)	<0.001
CV Death, Nonfatal MI, or UTVR Through 90 Days													
	UA/NSTEMI	5044	345	(6.84)	5030	420	(8.35)	10074	765	(7.59)	0.812	(0.704, 0.937)	0.004
	STEMI	1769	127	(7.18)	1765	168	(9.52)	3534	295	(8.35)	0.748	(0.594, 0.942)	0.013
	All ACS	6813	472	(6.93)	6795	588	(8.65)	13608	1060	(7.79)	0.794	(0.703, 0.896)	<0.001
CV Death, Nonfatal MI or UTVR Through 30 Days													
	UA/NSTEMI	5044	281	(5.57)	5030	349	(6.94)	10074	630	(6.25)	0.798	(0.682, 0.933)	0.005
	STEMI	1769	118	(6.67)	1765	155	(8.78)	3534	273	(7.72)	0.754	(0.594, 0.958)	0.020
	All ACS	6813	399	(5.86)	6795	504	(7.42)	13608	903	(6.64)	0.784	(0.688, 0.894)	<0.001
All Cause Death, Nonfatal MI, or Nonfatal Stroke Through Study End													
	UA/NSTEMI	5044	504	(9.99)	5030	590	(11.73)	10074	1094	(10.86)	0.844	(0.749, 0.950)	0.005
	STEMI	1769	188	(10.63)	1765	232	(13.14)	3534	420	(11.88)	0.797	(0.657, 0.966)	0.020
	All ACS	6813	692	(10.16)	6795	822	(12.10)	13608	1514	(11.13)	0.831	(0.751, 0.919)	<0.001
CV Death, Nonfatal MI, Nonfatal Stroke, or Rehospitalization for CIE Through Study End													
	UA/NSTEMI	5044	598	(11.86)	5030	688	(13.68)	10074	1286	(12.77)	0.858	(0.769, 0.958)	0.006
	STEMI	1769	199	(11.25)	1765	250	(14.16)	3534	449	(12.71)	0.781	(0.648, 0.941)	0.009
	All ACS	6813	797	(11.70)	6795	938	(13.80)	13608	1735	(12.75)	0.838	(0.762, 0.921)	<0.001
Definite or Probable Stent Thrombosis through Study End[d†]													
	UA/NSTEMI	4798	39	(0.81)	4789	78	(1.63)	9587	117	(1.22)	0.48	(0.33, 0.70)	<0.0001
	STEMI	1624	19	(1.17)	1633	38	(2.33)	3257	57	(1.75)	0.49	(0.28, 0.84)	0.0074
	All ACS	6422	58	(0.90)	6422	116	(1.81)	12844	174	(1.35)	0.48	(0.35, 0.66)	<0.0001

CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction; N=number treated; n=number of subjects reaching the endpoint; NE=not evaluated due to insufficient data.
[a]% is percentage of randomized subjects reaching the endpoint.
[b]HR and two-sided 95% CI derived using Cox proportional hazards model. Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification

factor in analysis involving All ACS subjects.
[c]Two-sided p-values are based on a log-rank test comparing event free survival distributions of prasugrel and clopidogrel within the subgroup. Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving all ACS subjects.
[d]Denominator consists of subjects who had a stent placed during their index procedure.
†FDA Analysis. Initial analysis by sponsor included 4 additional patients in the clopidogrel treatment arm (n=120), but these four events of stent thrombosis occurred outside of the efficacy window. In the clopidogrel treatment group, the number of events of stent thrombosis within the efficacy window should be 116. This analysis does not include 4 clopidogrel and 2 prasugrel patients who were thought to have stent thrombosis but whose cases were not referred to the CEC for adjudication (Subjects TAAL-010050-13384, 010355-13961, 390691-14674, 970989-13056, 490607-14838, and 550855-22276)
Reproduced from Sponsor, Clinical Study Report, Table TAAL.11.7, pages 233-234.
Analyses verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

Table 20. Sponsor's Analysis: Number and Percentage of Subjects Reaching Secondary and Other Efficacy Endpoints--CEC Adjudicated (All Randomized Subjects) (TAAL)

Analyzed Endpoint	Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI)	p-value
		N	n	(%)[a]	N	n	(%)[a]	N	n	(%)[a]			
CV Death or Nonfatal MI													
	UA/NSTEMI	5044	436	(8.64)	5030	527	(10.48)	10074	963	(9.56)	0.818	(0.720, 0.929)	0.002
	STEMI	1769	153	(8.65)	1765	201	(11.39)	3534	354	(10.02)	0.750	(0.608, 0.926)	0.007
	All ACS	6813	589	(8.65)	6795	728	(10.71)	13608	1317	(9.68)	0.799	(0.717, 0.890)	<0.001
CV Death													
	UA/NSTEMI	5044	90	(1.78)	5030	92	(1.83)	10074	182	(1.81)	0.979	(0.732, 1.309)	0.885
	STEMI	1769	43	(2.43)	1765	58	(3.29)	3534	101	(2.86)	0.738	(0.497, 1.094)	0.129
	All ACS	6813	133	(1.95)	6795	150	(2.21)	13608	283	2.08)	0.886	(0.701, 1.118)	0.307
All Cause Death													
	UA/NSTEMI	5044	130	(2.58)	5030	121	(2.41)	10074	251	(2.49)	1.076	(0.840, 1.378)	0.563
	STEMI	1769	58	(3.28)	1765	76	(4.31)	3534	134	(3.79)	0.759	(0.539, 1.068)	0.113
	All ACS	6813	188	(2.76)	6795	197	(2.90)	13608	385	(2.83)	0.953	(0.781, 1.164)	0.639
Nonfatal MI													
	UA/NSTEMI	5044	357	(7.08)	5030	464	(9.22)	10074	821	(8.15)	0.761	(0.663, 0.873)	<0.001
	STEMI	1769	118	(6.67)	1765	156	(8.84)	3534	274	(7.75)	0.746	(0.588, 0.948)	0.016
	All ACS	6813	475	(6.97)	6795	620	(9.12)	13608	1095	(8.05)	0.757	(0.672, 0.853)	<0.001
All MI													
	UA/NSTEMI	5044	366	(7.26)	5030	476	(9.46)	10074	842	(8.36)	0.760	(0.663, 0.871)	<0.001
	STEMI	1769	119	(6.73)	1765	157	(8.90)	3534	276	(7.81)	0.748	(0.589, 0.949)	0.016
	All ACS	6813	485	(7.12)	6795	633	(9.32)	13608	1118	(8.22)	0.757	(0.673, 0.852)	<0.001
Nonfatal Stroke													
	UA/NSTEMI	5044	40	(0.79)	5030	41	(0.82)	10074	81	(0.80)	0.979	(0.633, 1.513)	0.922
	STEMI	1769	21	(1.19)	1765	19	(1.08)	3534	40	(1.13)	1.097	((0.590, 2.040)	0.770
	All ACS	6813	61	(0.90)	6795	60	(0.88)	13608	121	(0.89)	1.016	(0.712, 1.451)	0.930
All Stroke													
	UA/NSTEMI	5044	49	(0.97)	5030	46	(0.91)	10074	95	(0.94)	1.068	(0.714, 1.597)	0.748
	STEMI	1769	26	(1.47)	1765	25	(1.42)	3534	51	(1.44)	1.032	(0.596, 1.787)	0.911
	All ACS	6813	75	(1.10)	6795	71	(1.04)	13608	146	(1.07)	1.055	(0.763, 1.460)	0.745
Rehospitalization Due to Ischemic Event													
	UA/NSTEMI	5044	153	(3.03)	5030	161	(3.20)	10074	314	(3.12)	0.950	(0.761, 1.185)	0.648
	STEMI	1769	31	(1.75)	1765	42	(2.38)	3534	73	(2.07)	0.731	(0.460, 1.163)	0.184
	All ACS	6813	184	(2.70)	6795	203	(2.99)	13608	387	(2.84)	0.904	(0.741, 1.104)	0.323

Analyzed Endpoint	Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI)	p-value
		N	n	(%)[a]	N	n	(%)[a]	N	n	(%)[a]			
Urgent Target Vessel Revascularization													
	UA/NSTEMI	5044	118	(2.34)	5030	179	(3.56)	10074	297	(2.95)	0.654	(0.518, 0.825)	<0.001
	STEMI	1769	38	(2.15)	1765	54	(3.06)	3534	92	(2.60)	0.697	(0.460, 1.056)	0.087
	All ACS	6813	156	(2.29)	6795	233	(3.43)	13608	389	(2.86)	0.664	(0.542, 0.813)	<0.001

CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction; N=number treated; n=number of subjects reaching the specified endpoint; NE=not evaluated due to insufficient data.
[a]% is percentage of randomized subjects reaching the specified endpoint.
[b]HR and two-sided 95% CI derived using Cox proportional hazards model.
[c]Two-sided p-values are based on a log-rank test comparing event free survival distributions of prasugrel and clopidogrel. Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving all ACS subjects.
[d]Denominator consists of subjects who had a stent placed during their index procedure.
Reproduced from Sponsor, Clinical Study Report, Table TAAL.11.7, pages 235-236.
Analyses verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

6.1.5 Clinical Microbiology N/A

6.1.6 Efficacy Conclusions (Study TAAL)

In patients with acute coronary syndromes, prasugrel significantly reduced the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at a median of 12 months of follow-up in the UA/NSTEMI, All ACS, and STEMI populations, compared to clopidogrel.

With regard to the major secondary endpoints in the UA/NSTEMI, STEMI, and all ACS populations, prasugrel, compared to clopidogrel,

- significantly reduced CV death, nonfatal MI or nonfatal stroke through 90 days
- significantly reduced CV death, nonfatal MI or nonfatal stroke through 30 days
- significantly reduced CV death, nonfatal MI, or urgent target vessel revascularization through 90 days
- significantly reduced CV death, nonfatal MI, or urgent target vessel revascularization through 30 days
- significantly reduced all cause death, nonfatal MI, or nonfatal stroke through study end
- significantly reduced CV death, nonfatal MI, nonfatal stroke or rehospitalization for cardiac ischemic events through study end

Finally, although prasugrel appeared to reduce ARC definite or probable stent thrombosis through study end in all three of these populations, in my opinion, the sponsor did not adhere to the scientific rigor required for such a claim. The determination of stent thrombosis was made by clinical adjudication, without the use of an angiographic core laboratory and without pathological confirmation. The CEC did not review any angiograms and did not review all cases of presumed stent thrombosis. In some cases, there was evidence of suboptimal adjudication by the CEC. Furthermore, there was no prospective attempt in TAAL to gather pathological evidence of stent thrombosis. Although two autopsies were subsequently obtained and demonstrated stent thrombosis, this limited amount of pathological confirmation for a trial of this size is not adequate. Since the results of clinical adjudication can be different from outside angiographic and pathologic review, which is currently required by our CDRH colleagues, I consider the results from TAAL to be promising but exploratory. Therefore, I recommend the sponsor participate in a randomized, prospective clinical trial to further evaluate these preliminary findings.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The prasugrel safety database included primary, secondary, and tertiary safety databases, in addition to 5 individually reported studies.

Study TAAL served as the primary safety database and included 13,457 subjects (6741 prasugrel, 6716 clopidogrel) with ACS who were to be managed by PCI. Within TAAL, there were 707 prasugrel subjects and 769 clopidogrel subjects with abnormal renal function, defined as a creatinine clearance $\leq$ 60 mL/min as estimated by the Cockcroft-Gault equation. Additionally, there were 32 prasugrel subjects and 37 clopidogrel subjects with hepatic impairment based on pre-existing conditions, including ALT > 3 x upper limit of normal and total bilirubin > 1.5 x ULN. Severe hepatic dysfunction was an exclusion criterion for TAAL.

The secondary safety database included all subjects enrolled in TAAD TAAH, TABL, and TABR with either ACS or other different clinical manifestations of atherosclerosis that may not have required PCI (940 prasugrel, 484 clopidogrel).

The tertiary safety database included integrated clinical pharmacology study data of 839 healthy subjects, 22 subjects with hepatic impairment, and 37 subjects with renal impairment (898 subjects total). The 5 completed clinical pharmacology studies in healthy subjects conducted in Japan (non-investigational new drug studies with a different formulation of prasugrel) were not integrated with the clinical pharmacology studies, as these studies were considered supportive studies.

7.1.1 Deaths

In TAAL, there was no significant difference in all cause death or cardiovascular death between treatment groups.

By CEC adjudication in TAAL, there were a total of 188 (2.76%) all cause deaths in the prasugrel treatment group and 197 (2.90%) all cause deaths in the clopidogrel treatment group in the All ACS population. In the UA/NSTEMI population, there were 130 (2.58%) deaths in the prasugrel treatment group and 121 (2.41%) deaths in the clopidogrel treatment group. In the STEMI population, there were 58 (3.28%) deaths in the prasugrel treatment group and 76 (4.31%) deaths in the clopidogrel treatment group.

With respect to cardiovascular deaths in the All ACS population, there were 133 events in the prasugrel treatment group and 150 events in the clopidogrel treatment group. In both treatment groups, most of the cardiovascular deaths were sudden or unwitnessed. The fatality rate for intracranial hemorrhages was twice as high in the prasugrel treatment group compared to the clopidogrel treatment group. A summary of CEC adjudicated deaths is displayed in Table 21.

In the All But TAAL (ABT) studies included in the secondary safety database, there were 3 deaths. These three subjects from Study TAAH were treated with prasugrel and died due to non-hemorrhagic cardiovascular adverse events including sudden death, circulatory collapse, and decreased cardiac output. There were no deaths in Studies TAAD, TABR, and TABL.

In the tertiary safety database, there were no deaths.

Table 21. Sponsor's Analysis: Summary of CEC-Adjudicated Deaths (All Randomized Subjects) (TAAL)

	UA/NSTEMI					STEMI					All ACS				
	Prasugrel (N=5044)		Clopidogrel (N=5030)		p-value[b]	Prasugrel (N=1769)		Clopidogrel (N=1765)		p-value[b]	Prasugrel (N=6813)		Clopidogrel (N=6795)		p-value[b]
Variable	**n**	**(%)[a]**	**n**	**(%)[a]**		**n**	**(%)[a]**	**n**	**(%)[a]**		**n**	**(%)[a]**	**n**	**(%)[a]**	
All Cause Death	**130**	**(2.58)**	**121**	**(2.41)**	**0.563**	**58**	**(3.28)**	**76**	**(4.31)**	**0.113**	**188**	**(2.76)**	**197**	**(2.90)**	**0.639**
Cardiovascular	**90**	**(1.78)**	**92**	**(1.83)**	**0.885**	**43**	**(2.43)**	**58**	**(3.29)**	**0.129**	**133**	**(1.95)**	**150**	**(2.21)**	**0.307**
Atherosclerotic Vascular Disease (Excluding Coronary)	0		3	(0.06)		0		0			0		3	(0.04)	
Congestive Heart Failure/Cardiogenic Shock	17	(0.34)	15	(0.30)		14	(0.79)	15	(0.85)		31	(0.46)	30	(0.44)	
Directly Related to Revascularization (CABG or PCI)	12	(0.24)	11	(0.22)		3	(0.17)	5	(0.28)		15	(0.22)	16	(0.24)	
Dysrhythmia	2	(0.04)	5	(0.10)		2	(0.11)	2	(0.11)		4	(0.06)	7	(0.10)	
Pulmonary Embolism	3	(0.06)	0			0		0			3	(0.04)	0		
Myocardial Infarction	14	(0.28)	21	(0.42)		10	(0.57)	15	(0.85)		24	(0.35)	36	(0.53)	
Sudden or Unwitnessed	30	(0.59)	29	(0.58)		6	(0.34)	13	(0.74)		36	(0.53)	42	(0.62)	
Intracranial Hemorrhage	6	(0.12)	3	(0.06)		3	(0.17)	2	(0.11)		9	(0.13)	5	(0.07)	
Non-Hemorrhagic Stroke	3	(0.06)	2	(0.04)		2	(0.11)	4	(0.23)		5	(0.07)	6	(0.09)	
Other Cardiovascular	3	(0.06)	3	(0.06)		3	(0.17)	2	(0.11)		6	(0.09)	5	(0.07)	
Non-Cardiovascular	**40**	**(0.79)**	**29**	**(0.58)**	**0.181**	**15**	**(0.85)**	**18**	**(1.02)**	**0.589**	**55**	**(0.81)**	**47**	**(0.69)**	**0.428**
Accidental/Trauma	3	(0.06)	3	(0.06)		1	(0.06)	1	(0.06)	0.589	4	(0.06)	4	(0.06)	
Hemorrhage, nonintracranial	6	(0.12)	0			3	(0.17)	1	(0.06)		9	(0.13)	1	(0.01)	
Infection	9	(0.18)	7	(0.14)		2	(0.11)	3	(0.17)		11	(0.16)	10	(0.15)	
Malignancy	16	(0.32)	11	(0.22)		5	(0.28)	6	(0.34)		21	(0.31)	17	(0.25)	
Suicide	2	(0.04)	1	(0.02)		1	(0.06)	1	(0.06)		3	(0.04)	2	(0.03)	
Other Non-Cardiovascular	4	(0.08)	7	(0.14)		3	(0.17)	6	(0.34)		7	(0.10)	13	(0.19)	

N=randomized subjects, n=number of deaths, NE=not evaluated due to insufficient data.
[a]% is percentage of randomized subjects
[b]Two-sided p-values are based on a log-rank test comparing event free survival distributions of Prasugrel and Clopidogrel. Clinical presentation, UA/NSTEMI vs. STEMI, used as a stratification factor in analysis involving all ACS subjects.
Reproduced from Sponsor, ISS, Table APP.2.7.4.71, pages 267-268.

7.1.2 Other Serious Adverse Events

7.1.2.1 Bleeding

Safety endpoints for Study TAAL included:

- Non-CABG-related TIMI major bleeding
- Non-CABG-related TIMI life-threatening bleeding
- Non-CABG-related TIMI minor bleeding
- Non-CABG-related fatal bleeding
- CABG related bleeding

7.1.2.1.1 Non-CABG-Related Bleeding

In the UA/NSTEMI and all ACS populations, prasugrel significantly increased non-CABG related TIMI major, TIMI life-threatening, TIMI fatal, and TIMI minor bleeding, compared to clopidogrel, as shown in Table 22.

Table 22. Sponsor's Analysis: CEC Adjudicated Non-CABG-Related Bleeding (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI)[b]	p-value[c]
	N	n	(%)	N	n	(%)	N	n	(%)			
TIMI Major[a]												
UA/NSTEMI	5001	108	(2.16)	4980	77	(1.55)	9981	185	(1.85)	1.404	(1.048, 1.881)	0.022
STEMI	1740	38	(2.18)	1736	34	(1.96)	3476	72	(2.07)	1.115	(0.702, 1.770)	0.645
All ACS	6741	146	(2.17)	6716	111	(1.65)	13457	257	(1.91)	1.315	(1.028, 1.683)	0.029
TIMI Life-Threatening[a]												
UA/NSTEMI	5001	65	(1.30)	4980	38	(0.76)	9981	103	(1.03)	1.711	(1.146, 2.553)	0.008
STEMI	1740	20	(1.15)	1736	18	(1.04)	3476	38	(1.09)	1.109	(0.587, 2.096)	0.750
All ACS	6741	85	(1.26)	6716	56	(0.83)	13457	141	(1.05)	1.517	(1.083, 2.126)	0.015
TIMI Fatal												
UA/NSTEMI	5001	14	(0.28)	4980	3	(0.06)	9981	17	(0.17)	4.664	(1.341, 16.230)	0.008
STEMI	1740	7	(0.40)	1736	2	(0.12)	3476	9	(0.26)			NE
All ACS	6741	21	(0.31)	6716	5	(0.07)	13457	26	(0.19)	4.191	(1.580, 11.113)	0.002
TIMI Minor[a]												
UA/NSTEMI	5001	117	(2.34	4980	80	(1.61)	9981	197	(1.97)	1.466	(1.103, 1.948)	0.008
STEMI	1740	47	(2.70)	1736	45	(2.59)	3476	92	(2.65)	1.041	(0.691, 1.566)	0.848
All ACS	6741	164	(2.43)	6716	125	(1.86)	13457	289	(2.15)	1.313	(1.040, 1.656)	0.022

CI=confidence interval; HR=hazard ratio; N=number of subjects; n=number of subjects with event; NE=not evaluated due to insufficient data..

[a]Subjects experiencing multiple bleeding events may be included in more than one category

[b]HR and two-sided 95% CI derived using Cox proportional hazards model

[c]Two-sided log-rank p-value based on time to first event analysis compares the event free survival distributions for Prasugrel and Clopidogrel. Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analyses of All ACS subjects.

Reproduced from Sponsor, Table TAAL.12.3, page 511 and Table 12.4, pages 517-520. Analysis verified by Karen A. Hicks, M.D.

7.1.2.1.2 CABG-Related Bleeding

In the UA/NSTEMI, STEMI, and All ACS populations, CABG-related TIMI major bleeding was 3 to 3.5-fold higher with prasugrel compared to clopidogrel, as shown in Table 23.

Table 23. Sponsor's Analysis: CEC-Adjudicated CABG-Related Bleeding Events Through Study End (Overall) (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI)[b]	p-value[c]
	N	n	(%)[a]	N	n	(%)[a]	N	n	(%)[a]			
TIMI Major												
UA/NSTEMI	138	12	(8.70)	141	4	(2.84)	279	16	(5.73)	3.262	(1.025, 10.38)	0.035
STEMI	75	12	(16.00)	83	4	(4.82)	158	16	(10.13)	3.762	(1.157. 12.23)	0.020
All ACS	213	24	(11.27)	224	8	(3.57)	437	32	(7.32)	3.496	(1.531, 7.986)	0.002
TIMI Fatal												
UA/NSTEMI	138	0		141	0		279	0				NE
STEMI	75	2	(2.67)	83	0		158	2	(1.27)			NE
All ACS	213	2	(0.94)	224	0		437	2	(0.46)			NE

CI=confidence interval; HR=hazard ratio; N=number of subjects; n=number of subjects with event; NE=not evaluated due to insufficient data..
[a]% is percentage of N
[b]Odds ratio (OR) is based on the frequency procedure
[c]Two-sided p-values based on Pearson chi-square in UA/NSTEMI and STEMI, CMH general association test with clinical presentation as a blocking factor in All ACS.
Reproduced from Sponsor, Table TAAL.12.42, page 763-770. Analysis verified by Karen A. Hicks, M.D.

If a subject required CABG, the percentage of subjects having CABG-related TIMI major bleeding events was always higher on prasugrel, compared to clopidogrel. The highest percentage of bleeding was seen in STEMI subjects whose last dose of prasugrel was 0-2 days prior to CABG (prasugrel: 4/19 (21.05%) versus clopidogrel: 1/17 (5.88%)). The percentage of subjects on prasugrel experiencing CABG-related TIMI major bleeding events was lowest when the prasugrel was discontinued > 7 days prior to surgery, as seen in Table 24. These data suggest prasugrel should be discontinued at least 7 days prior to undergoing CABG, if possible.

Table 24. Sponsor's Analysis: Number and Percentage of Subjects with CABG-Related TIMI Major Bleeding Events Through Study End (CEC-Adjudicated) (All Treated Subjects)

	Prasugrel			Clopidogrel			Total			OR	(95% CI)[c]	p-value
	N	n	(%)[b]	N	n	(%)[b]	N	n	(%)[b]			
Days from Most Recent Dose to CABG												
UA/NSTEMI												
0-2 Days	39	3	(7.69)	48	2	(4.17)	87	5	(5.75)			NE
3-5 Days	16	2	(12.50)	24	2	(8.33)	40	4	(10.00)			NE
> 5 Days	83	7	(8.43)	69	0		152	7	(4.61)			NE
> 7 Days	53	4	(7.55)	43	0		96	4	(4.17)			NE
STEMI												
0-2 Days	19	4	**(21.05)**	17	1	(5.88)	36	5	(13.89)			NE
3-5 Days	14	2	(14.29)	17	1	(5.88)	31	3	(9.68)			NE
> 5 Days	42	6	(14.29)	49	2	(4.08)	91	8	(8.79)			NE
> 7 Days	26	3	(11.54)	26	2	(7.69)	52	5	(9.62)			NE
All ACS												
0-2 Days	58	7	(12.07)	65	3	(4.62)	123	10	(8.13)	2.704	(0.758, 11.11)	0.161
3-5 Days	30	4	(13.33)	41	3	(7.32)	71	7	(9.86)			NE
> 5 Days	125	13	(10.40)	118	2	(1.69)	243	15	(6.17)	7.933	(1.646, 38.22)	0.003
> 7 Days	79	7	(8.86)	69	2	(2.90)	148	9	(6.08)			NE

N=number of treated subjects undergoing CABG; n=number of treated subjects undergoing CABG with CABG-related bleeding events; OR=Odds Ratio; NE=not evaluated due to insufficient data
[a]Subject undergoing multiple CABG may be included in more than 1 category
[b]% is percentage of N
[c]Odds ratio (OR) is based on the frequency procedure.
[d]Two-sided p-values based on Pearson chi-square in UA/NSTEMI and STEMI, CMH general association test with clinical presentation as a blocking factor in All ACS.
Reproduced from Sponsor, Table TAAL.12.42, page 769.
Analysis verified by Karen A. Hicks, M.D.