Table 51. FDA Subgroup Analyses of Primary Endpoint (TAAL)

	Subgroup Analysis of Primary endpoint								
	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Age (yr)									
<65 N	2987	3000	0.75	1201	1134	0.76	4188	4134	0.75
n	224	299	0.63, 0.89	98	121	0.58, 0.99	322	420	0.65, 0.87
%	7.50	9.97	0.0008	6.16	10.67	0.0364	7.69	10.16	<.0001
≥65 N	2057	2030	0.90	568	631	0.88	2625	2661	0.90
n	245	266	0.76, 1.07	76	95	0.65,1.18	321	361	0.77, 1.04
%	11.91	13.10	0.3075	13.38	15.06	0.3445	12.23	13.57	0.1513
≥65 Female N	727	740	0.92	191	219	0.79	918	959	0.89
n	85	93	0.68, 1.23	26	37	0.48, 1.31	111	130	0.69, 1.14
%	11.69	12.57	0.6354	13.61	16.89	0.3562	12.09	13.56	0.3295
≥65 Male N	1330	1290	0.89	377	412	0.93	1707	1702	0.90
n	160	173	0.72, 1.11	50	58	0.64, 1.35	210	231	0.75, 1.09
%	12.03	13.41	0.3571	13.2	14.08	0.6349	12.30	13.57	0.2880
<70 N	3728	3730	0.75	1417	1366	0.79	5145	5096	0.76
n	287	378	0.65, 0.88	121	146	0.62, 1.00	408	524	0.67, 0.87
%	7.70	10.13	0.0002	8.54	10.69	0.0467	7.93	10.29	<.0001
≥70 N	1316	1300	0.96	352	399	0.85	1668	1699	0.93
n	182	187	0.78, 1.17	53	70	0.59, 1.21	235	257	0.78, 1.11
%	13.83	14.38	0.8126	15.06	17.54	0.3365	14.09	15.13	0.444
≥70 Female N	514	17	1.03	135	151	0.75	649	668	0.95
n	67	65	0.73, 1.45	19	28	0.42, 1.34	86	93	0.71, 1.27
%	13.04	12.57	0.6933	14.07	18.54	0.3498	13.25	13.92	0.8253
≥70 Male N	802	783	0.92	217	248	0.91	1019	1031	0.92
n	115	122	0.71, 1.18	34	42	0.58, 1.43	149	164	0.73,1.14
%	14.34	15.58	0.5602	15.67	16.94	0.6138	14.62	9.70	0.4305

Subgroup Analysis of Primary endpoint									
	UA/NSTEMI			**STEMI**			**All ACS**		
	Prasugrel (N=5044)	**Clopidogrel (N=5030)**	**HR 95% CI P-value**	**Prasugrel (N=1769)**	**Clopidogrel (N=1765)**	**HR 95% CI P-value**	**Prasugrel (N=6813)**	**Clopidogrel (N=6795)**	**HR 95% CI P-value**
<75 N	4328	4344	0.78	1584	1543	0.80	5912	5887	0.78
n	356	454	0.68, 0.90	143	173	0.64, 0.99	499	627	0.70, 0.88
%	8.23	10.45	0.0006	9.02	11.21	0.0370	8.44	10.65	<.0001
≥75 N	716	686	0.97	185	222	0.85	901	908	0.94
n	113	111	0.75, 1.26	31	43	0.54, 1.35	144	154	0.75, 1.18
%	15.78	16.18	0.8539	16.76	19.37	0.4478	15.98	16.96	0.5329
≥75 Female N	292	309	0.98	79	96	0.71	371	405	0.91
n	43	46	0.65, 1.49	12	20	0.35, 1.46	55	66	0.63, 1.29
%	14.73	14.89	0.9723	15.19	20.83	0.3637	14.82	16.30	0.5891
≥75 Male N	424	77	0.96	106	126	0.97	530	503	0.96
n	70	65	0.68, 1.34	19	23	0.53, 1.79	89	88	0.72, 1.29
%	16.51	17.24	0.7598	17.92	18.25	0.8197	16.79	17.50	0.6908
Sex									
Female N	1325	1399	0.91	380	419	0.79	1705	1818	0.88
n	137	159	0.72, 1.14	41	56	0.53, 1.19	178	215	0.73,1.07
%	10.34	11.37	0.5150	10.79	13.37	0.2107	10.44	11.83	0.1962
Male N	3719	3631	0.79	1389	1346	0.80	5108	4977	0.79
n	332	406	0.68, 0.91	133	160	0.63, 1.00	465	566	0.7, 0.9
%	8.93	11.18	0.0014	9.58	11.89	0.0503	9.10	11.37	0.0002

Subgroup Analysis of Primary endpoint									
	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Ethnicity									
Caucasian									
N	4575	4569	0.80	1688	1705	0.80	6263	6274	0.80
n	414	511	0.70, 0.91	167	209	0.65, 0.98	581	720	0.72, 0.89
%	9.05	11.18	0.0011	9.89	12.26	0.0242	9.28	11.48	<.0001
African N	177	168	1.03	28	19	0.66	205	187	0.98
n	22	20	0.56, 1.89	3	3	0.13, 3.25	25	23	0.55, 1.72
%	12.43	11.91	0.8896	10.71	15.79	0.5967	12.20	12.30	0.9647
Hispanic									
N	242	237	1.08	27	19	0.70	269	256	1.04
n	33	30	0.66, 1.77	3	3	0.14, 3.46	36	33	0.65, 1.67
%	13.64	12.66	0.7287	11.11	15.79	0.6436	13.38	12.89	0.8737
Asian N	37	42	-	23	22	-	60	64	-
n	0	3	-	1	1	-	1	4	-
%	-	7.14	-	4.35	4.55	-	1.67	6.25	-
Other N	13	14	-	3	0	-	16	14	-
n	0	1	-	0	0	-	0	1	-
%	-	7.14	-			-	-	7.14	-
Prior TIA/stroke									
yes N	213	192	1.53	49	64	0.98	262	256	1.38
n	39	24	0.92, 2.55	8	11	0.39, 2.42	47	35	0.89, 2.13
%	18.31	12.50	0.0677	16.33	17.19	0.9127	17.94	13.67	0.1382
no N	4831	4838	0.79	1720	1701	0.79	6551	6539	0.79
n	430	541	0.69, 0.89	166	205	0.64, 0.97	596	746	0.71, 0.88
%	8.90	11.18	0.0003	9.65	12.05	0.020	9.10	11.41	<.0001

Subgroup Analysis of Primary endpoint									
	UA/NSTEMI-			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Weight (kg)									
<50 N	92	86	1.14	45	39	0.90	137	125	1.05
n	17	15	0.57, 2.29	9	9	0.36, 2.28	26	24	0.60, 1.82
%	18.48	17.44	0.7713			0.9671	18.98	19.2	0.8318
≥50<70 N	844	910	0.86	298	333	0.66	1142	1243	0.79
n	83	103	0.64, 1.14	34	56	0.43, 1.00	117	159	0.62, 1.00
%	9.83	11.32	0.3270			0.0388	10.25	12.79	0.0436
≥70 N	2451	2433	0.84	942	895	0.78	3393	3328	0.83
n	234	275	0.70, 1.00	85	100	0.60, 1.06	319	375	0.71, 0.96
%	9.55	11.30	0.0549			0.1138	9.40	11.27	0.0119
≥70<90 N	1657	1601	0.75	484	498	0.93	2141	2099	0.79
n	135	172	0.60, 0.94	46	51	0.62, 1.38	181	223	0.65, 0.96
%	8.15	10.74	0.0112			0.6796	8.45	10.62	0.0138
<60 N	5044	5030	0.82	1769	1765	0.79	6813	6795	0.81
n	469	565	0.73, 0.93	174	216	0.65, 0.97	643	781	0.73, 0.90
%	9.30	11.23	0.0021	9.84	12.24	0.0192	9.44	11.49	<0.0001
Creatinine Clearance									
<30 N	38	50	0.55	13	4	0.17	51	54	0.47
n	9	19	0.25, 1.21	2	2	0.02, 1.24	11	21	0.22,1.01
%	23.68	38.00	0.3355	15.39	50.00	0.0211	21.57	38.89	0.1272
30-60 N	511	525	1.04	155	195	0.66	666	720	0.93
n	74	73	0.75, 1.43	18	33	0.37, 1.17	92	106	0.70, 1.23
%	14.48	13.90	0.9282	11.61	16.92	0.1664	13.81	14.72	0.5443
>60 N	4422	4379	0.80	1560	1528	0.80	5982	5907	0.80
n	372	457	0.70, 0.92	143	173	0.64, 1.00	515	630	0.71, 0.90
%	8.41	10.44	0.0016	9.17	11.32	0.0388	8.61	10.07	0.0001

Subgroup Analysis of Primary endpoint										
		UA/NSTEMI			STEMI			All ACS		
		Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Use of GPIIb/IIIa inhibitors prior to and during PCI										
Yes	N	1764	1768	0.82	924	953	0.73	2688	2721	0.79
	n	172	208	0.67, 1.01	91	125	0.56, 0.96	263	333	0.67, 0.93
	%	9.75	11.77	0.0939	9.85	13.12	0.018	9.78	12.24	0.0047
No	N	3280	3262	0.82	845	812	0.87	4125	4074	0.83
	n	297	357	0.70, 0.96	83	91	0.65, 1.18	380	448	0.72, 0.95
	%	9.06	10.94	0.0089	9.82	11.21	0.3987	9.21	11.00	0.0058
Female										
Yes	N	433	486	0.88	198	205	0.68	631	691	0.80
	n	41	52	0.58, 1.32	22	32	0.39, 1.17	63	84	0.58, 1.12
	%	9.47	10.70		11.11	15.61		9.98	12.16	0.2178
No	N	892	913	0.92	182	214	0.94	1074	1127	0.92
	n	96	107	0.70, 1.21	19	24	0.52, 1.72	115	131	0.72, 1.18
	%	10.76	11.72		10.44	11.21		10.71	11.62	0.4771
Male										
Yes	N	1331	1282	0.80	726	748	0.75	2057	2030	0.78
	n	131	156	0.64, 1.01	69	93	0.55, 1.03	200	249	0.65, 0.94
	%	9.84	12.17		9.50	12.43		9.72	12.27	0.0108
No	N	2388	2349	0.78	663	598	0.86	3051	2947	0.80
	n	201	250	0.65, 0.94	64	67	0.61, 1.21	265	317	0.68, 0.94
	%	8.42	10.64		9.65	11.20		8.69	10.76	0.0054
Use of GPIIb/IIIa inhibitors up to cath lab										
Yes	N	366	353	0.85	171	199	0.69	537	552	0.80
	n	37	42	0.54, 1.31	14	23	0.36, 0.34	51	65	0.55, 1.15
	%	10.11	11.90	0.5441	8.19	11.56	0.2663	9.50	11.78	0.2769
No	N	4678	4677	0.82	1598	1566	0.80	6276	6243	0.81
	n	435	523	0.72, 0.93	160	193	0.65, 0.99	592	716	0.73, 0.91
	%	9.23	11.18	0.0023	10.01	12.32	0.0348	9.43	11.47	0.0002

Subgroup Analysis of Primary endpoint										
		UA/NSTEMI			STEMI			All ACS		
		Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Female										
Yes	N	84	92	0.13	33	48	0.33	117	140	0.80
	n	10	10	0.47, 2.70	2	8	0.07, 1.57	12	18	0.38, 1.65
	%	11.90	10.87	0.5974	6.06	16.67	0.1476	10.26	12.86	0.6710
No	N	1241	1307	0.89	347	371	0.86	1588	1678	0.88
	n	127	149	0.70, 1.13	39	48	0.56, 1.31	166	197	0.72, 1.09
	%	10.23	11.40	0.4138	11.24	12.94	0.4076	10.45	11.74	0.2214
Male										
Yes	N	282	261	0.77	138	151	0.86	420	412	0.80
	n	27	32	0.46, 1.28	12	15	0.41, 1.85	39	47	0.53, 1.23
	%	9.57	12.26	0.3268	8.70	9.93	0.6897	9.29	11.41	0.3241
No	N	3437	3370	0.79	1251	1195	0.79	4688	4565	0.79
	n	305	374	0.68, 0.92	121	145	0.62, 1.0	426	519	0.70, 0.90
	%	8.87	11.10	0.0022	9.67	12.13	0.0533	9.09	11.37	0.0003
Use of GPIIb/IIIa inhibitors up to cath lab and cath only (no PCI)										
Yes	N							3	9	
	n							0	1	
	%							-	11.11	
No	N							87	83	
	n							7	5	
	%							8.05	6.02	

Subgroup Analysis of Primary endpoint									
	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Timing of Loading Dose									
0-2 hrs prior to PCI	1078 103	1045 117	0.85 0.65, 1.11 0.3212	432 52	440 59	0.90 0.62, 1.30 0.5843	1510 155	1485 176	0.86 0.70, 1.08 0.2340
2-6 hrs prior to PCI	61 4	67 5	0.9191	9 1	7 1	-	70 5	74 6	0.90 0.28, 2.95 0.8927
6-12 hrs prior to PCI	16 3	9 2	0.84 0.14, 5.08 0.8530	4 0	1 1	-	20 3	10 3	0.46 0.09, 2.30 0.3263
≥12 hrs prior to PCI	102 15	84 12	1.01 0.47, 2.16 0.9651	10 1	5 1	-	112 16	89 13	1.01 0.47, 2.16 0.8358
During PCI	3660 329	3671 400	0.82 0.71, 0.95 0.0081	1221 110	1213 143	0.75 0.59, 0.97 0.0209	4881 439	4884 543	0.80 0.71, 0.91 0. 0005
Post PCI	48 5	47 14	0.30 0.11, 0.84 0.0145	15 2	21 2	-	63 7	68 16	0.43 0.18, 1.04 0.0391
Use of any statin									
Yes N n %	4859 446 9.18	4878 543 11.13	0.82 0.72, 0.93 0.002	1717 164 9.55	1698 194 11.43	0.83 0.67, 1.02 0.0653	6576 610 9.28	6576 737 11.21	0.82 0.74, 0.91 0.0002
No N n %	185 23 12.43	152 22 14.47	0.88 0.49, 1.57 0.7254	52 10 19.23	67 22 32.84	0.54 0.26, 1.14 0.0787	237 33 13.92	219 44 20.09	0.69 0.44, 1.08 0.1124

Subgroup Analysis of Primary endpoint										
		UA/NSTEMI			STEMI			All ACS		
		Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Use of proton pump inhibitor										
Yes	N	2474	2463	0.83	916	882	0.80	3390	3345	0.82
	n	262	310	0.70, 0.98	103	122	0.62, 1.05	365	432	0.72, 0.95
	%	10.59	12.59	0.0319	11.24	13.83	0.0857	10.77	12.91	0.0056
No	N	2570	2567	0.81	853	883	0.77	3423	3450	0.80
	n	207	255	0.67, 0.97	71	94	0.57, 1.05	278	349	0.68, 0.93
	%	8.05	9.93	0.0248	8.32	10.65	0.0986	8.12	10.12	0.0046
Diabetes										
Yes	N	1246	1226	0.70	330	344	0.71	1576	1570	0.70
	n	135	184	0.56, 0.88	45	64	0.49, 1.04	180	248	0.58, 0.85
	%	10.84	15.01	0.0018	13.64	18.61	0.0610	11.42	15.80	0.0002
No	N	3798	3804	0.87	1439	1421	0.83	5237	5225	0.86
	n	334	381	0.76, 1.01	129	152	0.66, 1.05	463	533	0.76, 0.98
	%	8.79	10.02	0.0856	8.96	10.70	0.1174	8.84	10.20	0.0193
Analysis by Ouquan Liu, M.D., M.S., Biometrics, FDA										

9.2 Study H7T-MC-TABL(Clinical Study Report: "PRasugrel IN Comparison to Clopidogrel for Inhibition of Platelet Activation and AggrEgation (PRINCIPLE) – TIMI 44") (Study Dates: August 24, 2006 – June 20, 2007) (Date of Report: October 1, 2007)

9.2.1 Protocol, Amendment, and Post Hoc Changes

The study description was based on the original protocol dated February 28, 2006 and Protocol Amendment (a) dated May 11, 2006. Protocol Amendment (a) was completed prior to enrollment of subjects in the study and included the following changes:

1. The 15 minute sampling times were excluded for the following Phase 1 Platelet Function Measures:
    a. IPA to 20 μM ADP
    b. IPA to 5 μM ADP
    c. Maximum platelet aggregation to 20 μM ADP
    d. Maximum platelet aggregation to 5 μM ADP
    e. Final extent of platelet aggregation (at 6 minutes after ADP addition) to 5 or 20 μM ADP

2. Under "Myonecrosis Measures," troponin I was changed to troponin.

9.2.2 Study Design

This was a multicenter, randomized, parallel, double-blind, double-dummy, cross-over, active comparator-controlled study in subjects undergoing elective cardiac catheterization with planned percutaneous coronary intervention (PCI) with coronary stenting. The study had two phases. Phase 1 included study drug loading dose, cardiac catheterization, PCI (if indicated), and daily maintenance dose for 14 ± 2 days in subjects undergoing PCI. In Phase 2, subjects were crossed over to the alternative daily maintenance dose for an additional 14 ± 2 days.

9.2.3 Study Population

The study population included subjects undergoing cardiac catheterization with planned elective PCI with coronary stenting.

9.2.4 Objectives

Primary Objectives:
The primary objectives of the study were

- to compare the inhibition of platelet aggregation (IPA) to 20 μM adenosine disphosphate (ADP) measured at 6 hours (± 30 minutes) after prasugrel 60 mg loading dose versus clopidogrel 600 mg loading dose (LD) in subjects in the "on treatment population" who did not receive a GPIIb/IIIa inhibitor
- to compare the IPA to 20 μM ADP measured after 14 ± 2 days of prasugrel 10 mg daily maintenance dose versus the IPA after 14 ± 2 days of clopidogrel 150 mg daily maintenance dose (MD) in the "on treatment population" who have received PCI (this includes subjects receiving clopidogrel and prasugrel in either order during the crossover phase)

Secondary Objectives:
The secondary objectives of the study were

- to measure the inhibition of platelet aggregation to 20 μM ADP measured at approximately 2 hours after prasugrel 60 mg loading dose versus clopidogrel 600 mg loading dose in subjects in the "on treatment population" who did not receive a GPIIb/IIIa inhibitor
- to compare overall safety and tolerability of prasugrel 60 mg LD and 10 mg daily MD versus clopidogrel 600 mg LD and 150 mg daily MD after 14 ± 2 days in treated subjects who have received PCI. Safety measures

include, but are not limited to, the following: non-CABG-associated TIMI Major Bleeding, non-CABG related TIMI life-threatening bleeding, and non-CABG-related TIMI Minor Bleeding.

- to compare overall safety and tolerability of the following dosing regimens: prasugrel 60 mg LD and 10 mg daily MD for 14 ± 2 days with crossover to clopidogrel 150 mg daily MD for 14 ± 2 days versus clopidogrel 600 mg LD and 150 mg daily MD for 14 ± 2 days in treated subjects who have received PCI. Safety measures include but are not limited to the following: Non-CABG-associated TIMI Major Bleeding, non-CABG-related TIMI life-threatening bleeding, and non-CABG-related TIMI Minor Bleeding.
- to compare prasugrel (60 mg LD, 10 mg MD) versus clopidogrel (600 mg LD, 150 mg MD) in the occurrence of Major Adverse Cardiac Events (MACE) after 14 ± 2 days in treated subjects who have received PCI.
- to compare prasugrel versus clopidogrel on additional measures of platelet inhibition including, but not limited to, thienopyridine hyporesponsiveness, vasodilator-stimulated phosphoprotein (VASP), biomarkers of inflammation, and biomarkers of platelet activation
- to compare prasugrel (60 mg LD, 10 mg MD) versus clopidogrel (600 mg LD, 150 mg MD) in measures of myonecrosis [creatine kinase-MB isoforms (CK-MB), troponin)

9.2.5 Inclusion/Exclusion Criteria

Inclusion Criteria (Reproduced from Sponsor, page 879)
Subjects are eligible to be entered in the study if they meet the following criteria only:

1. Subjects ≥ 18 years of age undergoing cardiac catheterization with planned percutaneous coronary intervention (if coronary anatomy is suitable) for an indication of chest pain +/or anginal equivalent felt by the treating physician to be related to coronary ischemia
2. At least one of the following (a through c)
    a. Functional study (exercise, or pharmacologic) within the past 8 weeks consistent with ischemia as manifested by at least one of the following:
        i. a reversible defect on nuclear imaging
        ii. a reversible wall-motion abnormality by echocardiography
        iii. horizontal or down-sloping ST-depressions > 1 mm on electrocardiogram (ECG) (if no imaging performed
    b. Prior coronary revascularization (PCI or coronary artery bypass grafting (CABG))
    c. A cardiac catheterization with at least one coronary artery lesion amenable to PCI (not yet performed) within 14 days prior to enrollment

Exclusion Criteria (Reproduced from Sponsor, page 879)
Subjects cannot be entered and will be excluded from the study if they meet **any** of the following criteria:

Cardiovascular Exclusion Criteria

1. Known creatine kinase-myocardial bands (CK-MB) or cardiac troponin greater than the upper limit of normal (ULN) at the time of screening
2. Have a planned PCI procedure as initial treatment for an acute myocardial infarction (MI) (STEMI or NSTEMI), or a planned PCI within 48 hours of fibrinolytic therapy for STEMI
3. Have cardiogenic shock at the time of screening (systolic blood pressure < 90 mm Hg associated with clinical evidence of end-organ hypoperfusion, or subjects requiring vasopressors to maintain systolic blood pressure over 90 mm Hg and associated with clinical evidence of end-organ hypoperfusion)
4. Have refractory ventricular arrhythmias
5. Have New York Heart Association (NYHA) Class IV congestive heart failure (CHF)

Bleeding Risk Exclusion Criteria

6. Have active internal bleeding or history of bleeding diathesis
7. Have clinical findings, in the judgment of the investigator, associated with an increased risk of bleeding