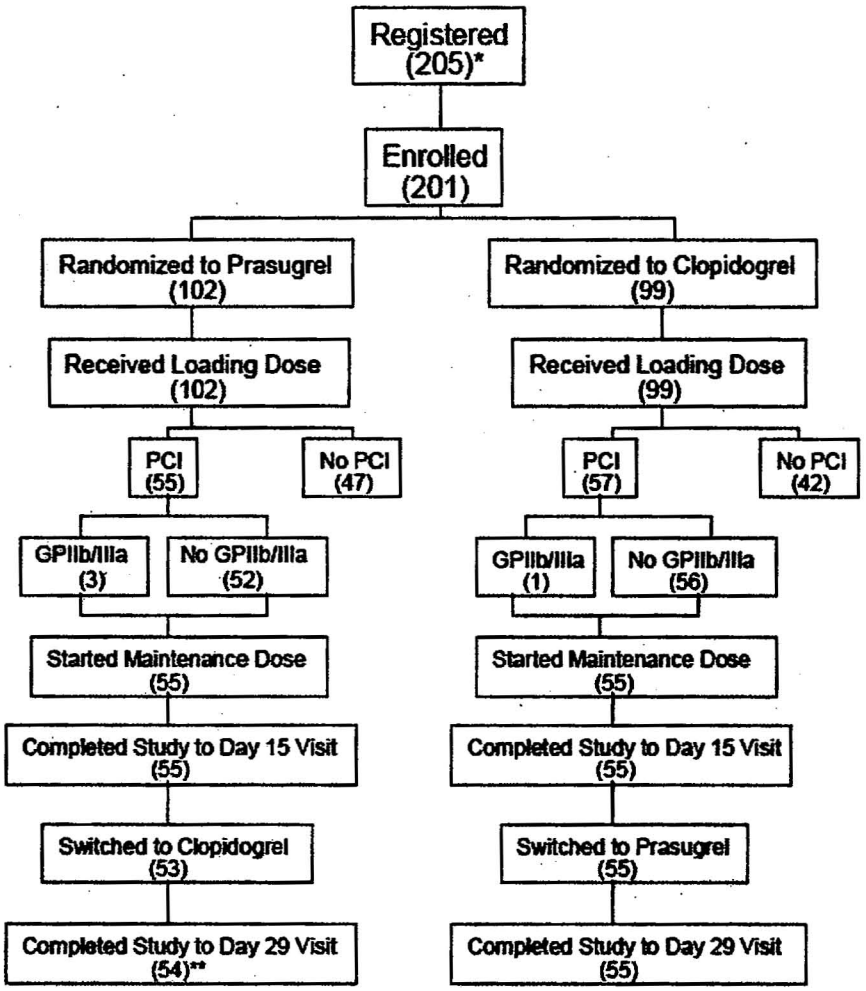
Figure 30. Subject Disposition (TABL)



Abbreviations: GPIIb/IIIa = glycoprotein IIb/IIIa; PCI = Percutaneous Coronary Intervention

*Four subjects were registered via the Interactive Voice Response System (IVRS), but withdrew from the study prior to administration of the allocated study drug loading dose (LD; see Section 10.1). No further data were collected from these subjects and they were not considered to have been enrolled into the study.

**One subject ceased study drug on Day 10 on the advice of The Thrombolysis in Myocardial Infarction (TIMI) Study Group medical hotline and did not provide any further efficacy data. The subject did not take clopidogrel during the second maintenance dose (MD) period; however, all other study data was complete and the subject was considered to have completed the study.

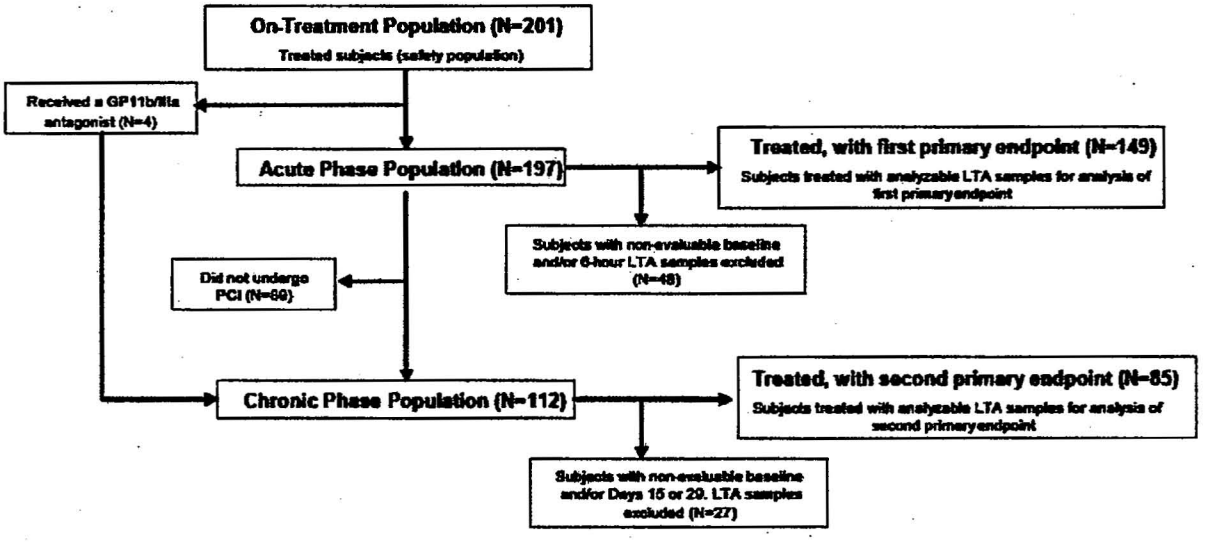
(Reproduced from Sponsor, Figure TABL.10.1, Subject Disposition, page 79 of 1590)

Fours subjects (2%) received GP IIb/IIIa inhibitors, including three subjects (2.9%) in the prasugrel/clopidogrel treatment group and one subject (1.0%) in the clopidogrel/prasugrel treatment group. Therefore, a total of 197 subjects were in the acute phase population, including 99 subjects in the prasugrel/clopidogrel group and 98 subjects in the clopidogrel/prasugrel group. Of the 99 subjects in the prasugrel/clopidogrel group, 52 subjects underwent PCI. Of the 98 subjects in the clopidogrel/prasugrel group, 56 subjects underwent PCI.

The "chronic phase population," defined as all subjects in the on-treatment population who underwent PCI, regardless of the use of a GPIIb/IIIa antagonist, was comprised of 112 subjects, including 55 (53.9%) in the prasugrel/clopidogrel group and 57 (57.6% in the clopidogrel/prasugrel group). Of the 55 subjects in the prasugrel/clopidogrel group, all subjects started their first MD period (Day 2 through Day 15 visits), 53 started the crossover MD period, and 54 completed the study. On the advice of the Thrombolysis in Myocardial Infarction (TIMI) medical hotline, one subject discontinued study drug on Day 10. Although the subject did not take clopidogrel during the second maintenance dose (MD) period, the sponsor considered the subject to have completed the study because all other study data was complete.

The study populations, including the "on treatment population," "acute phase population,", and "chronic phase population" are summarized in Figure 31.

Figure 31. Study Populations (TABL)



Abbreviations: GP11b/111a = glycoprotein 11b/111a; IVRS = Interactive Voice Response System; LD = loading dose; LTA = light transmission aggregometry; N = number of subjects; PCI = percutaneous coronary intervention

(Reproduced from Sponsor, Figure TABL.11.1, Study Populations, page 85 of 1590)

9.2.12.3.1 Premature Discontinuations

In addition to the four subjects who discontinued from the study prior to LD, three subjects (1.5%) prematurely discontinued from the study, including one subject in the prasugrel treatment group (1.0%) and two subjects in the clopidogrel treatment group (2.0%). All subjects withdrew consent to follow-up.

Of the 112 subjects who underwent PCI, five subjects (4.5%) prematurely discontinued study drug but completed the study visits. In the prasugrel treatment group, two (3.6%) of the 55 subjects prematurely discontinued study drug, compared to three (5.3%) of the 57 subjects in the clopidogrel treatment group. In the prasugrel treatment group, one subject experienced the adverse event of deep venous thrombosis during the first maintenance dose

period, leading to study drug discontinuation on the recommendation of the TIMI Study Group. Additionally, one subject did not want to continue to take study drug when crossed over to clopidogrel.

Of the 3 clopidogrel/prasugrel subjects who underwent PCI but prematurely discontinued study drug, two subjects did not receive a MD of study drug (one failed to meet the entry criteria and one elected to discontinue study drug) and one subject who elected to stop taking study drug the second (prasugrel) MD period.

9.2.12.4 Demographics and Baseline Characteristics

With the exception of subjects randomized to prasugrel loading dose having lower weights and heights, the baseline characteristics seemed to be balanced between treatment groups. The demographic data are summarized in Table 55.

Table 55. Demographic and Baseline Characteristics (TABL)

Characteristics		Prasugrel/Clopidogrel (N= 102)	Clopidogrel/Prasugrel (N=99)	Total (N=201)
Sex	Male	73 (71.6%)	77 (77.8%)	51 (25.4%)
Age (years)	N	102	99	201
	Mean	64.0	63.8	63.9
	SD	10.73	9.38	10.06
	≥ 75 years	16 (15.7%)	13 (13.1%)	29 (14.4%)
Race	Caucasian	97 (95.1%)	94 (94.9%)	191 (95.0%)
Weight (kg)	N	102	98	200
	Mean	82.73	88.12	85.37
	SD	16.91	19.66	18.46
Height (cm)	N	102	97	199
	Mean	169.8	172.9	171.3
	SD	8.48	8.95	8.83
Prior MI		31 (30.4%)	28 (28.3%)	59 (29.4%)
Prior PCI		42 (41.2%)	37 (37.4%)	79 (39.3%)
Prior CABG		17 (16.7%)	22 (22.2%)	39 (19.4%)
Hypertension		87 (85.3%)	77 (77.8%)	164 (81.6%)
Congestive Heart Failure		36 (35.3%)	35 (35.4%)	71 (35.3%)
Peripheral Arterial Disease		9 (8.8%)	8 (8.1%)	17 (8.5%)
Cerebrovascular Disease (any)		8 (7.8%)	7 (7.1%)	15 (7.5%)
Dyslipidemia		92 (90.2%)	86 (86.9%)	178 (88.6%)
Diabetes Mellitus		33 (32.4%)	29 (29.3%)	62 (30.8%)

Characteristics		Prasugrel/Clopidogrel (N= 102)	Clopidogrel/Prasugrel (N=99)	Total (N=201)
Family h/o premature CAD		38 (38.2%)	35 (35.4%)	74 (36.8%)
Smoking	Current	18 (17.6%)	16 (16.2%)	34 (16.9%)
	Former	32 (31.4%)	35 (35.4%)	67 (33.3%)
	Never	52 (51.0%)	48 (48.5%)	100 (49.8%)
Reproduced from Sponsor, Table TABL.11.2, page 89 of 1590)				

9.2.12.5 Compliance

There were no instances of poor compliance during the LD period; however, one subject taking prasugrel and three subjects taking clopidogrel were poorly compliant (percentage compliance < 80% or > 120%) during the MD period.

9.2.12.6 Sampling

During the study, each subject contributed 1 blood sample for each time point. There were 149 non-evaluable samples from 79 subjects for maximal platelet aggregation (MPA) to 20 μM adenosine disphosphate, including 94 from the prasugrel/clopidogrel group (44 subjects) and 55 from the clopidogrel/prasugrel group (35 subjects). However, the percentages of evaluable samples for IPA and MPA were not significantly different between prasugrel and clopidogrel at each LTA time point.

9.2.12.7 Primary Efficacy Endpoint

9.2.12.7.1 IPA with 20 μM ADP by LTA at 6 hours (± 30 minutes) after LD of study drug.

As shown in Table 56, prasugrel significantly inhibited platelet aggregation at 6 hours post loading dose compared to clopidogrel ($p < 0.0001$). However, the standard deviation between treatment groups was also statistically significant ($p < 0.0001$).

Table 56. Sponsor's Analysis: IPA by LTA with 20 μM ADP 6 Hours post LD (Acute Phase Population) (TABL)

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference Prasugrel – Clopidogrel (95% CI)	p-value
6 hours post LD	N	72	77		
	Mean	74.81	31.77	43.21 (38.04, 48.38)[a]	<0.0001[a]
	SD	13.01	21.07		<0.0001*
	Median	77.03	31.43		
ANCOVA=analysis of covariance; CI=confidence interval; LD=loading dose.					
[a]Group means for data analyzed using an ANCOVA model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances.					
***p-value to compare group variance obtained from an F-test.**					
Reproduced from Sponsor, Table TABL.11.5, page 95 of 1590.					

9.2.12.7.2 IPA to 20 μM ADP at 14 ± 2 days

As shown in Table 57, the prasugrel treatment group had significantly higher inhibition of platelet aggregation and significantly higher least-squares mean inhibition of platelet aggregation over the 14 ± 2 days. The sponsor found no carry-over effect (p = 0.9675).

Table 57. Sponsor's Analysis: IPA to 20 μM ADP at 14 ± 2 days (Chronic Phase Population) (TABL)

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference Prasugrel – Clopidogrel (95% CI)	p-value
Day 15 visit (14 ± 2 days)	N	40	46		
	Mean	61.94	45.40	15.72 (9.24, 22.20)[a]	< 0.0001[a]
	SD	17.91	19.89		0.5054*
	Median	63.45	49.68		
Maintenance Dose (14 ± 2 days)	N	85[b]	86[c]		
	LS Mean	55.48	40.55	14.93 (10.60, 19.26)[d]	<0.0001[d]
Treatment order					0.9675[d]

ANCOVA=analysis of covariance; CI=confidence interval; LSM=least-squares mean
[a]Group means for data analyzed using an ANCOVA model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances.
[b]This number represents the total number of evaluable samples from subjects that received prasugrel in each MD period (40 from the Day 15 visit and 45 from the Day 29 visit)
[c]This number represents the total number of evaluable samples from subjects that received clopidogrel in each MD period (46 from the Day 15 visit and 40 from the Day 29 visit)
[d]Group means for combined Day 15 and Day 29 data analyzed using an ANCOVA model with factors for pooled study site, and a covariate for baseline MPA, assuming unequal group variances
***p-value to compare group variance obtained from an F-test.**
Reproduced from Sponsor, Table TABL.11.5, page 95 of 1590.

9.2.12.8 Additional Efficacy Measures

9.2.12.8.1 IPA to 20 μM ADP at 30 min, 2 hours, 18 to 24 hours Following Loading Dose of Study Drug

Subjects in the prasugrel treatment group had significantly greater inhibition of platelet aggregation to 20 μM ADP at 30 minutes, 2 hours, and 18 to 24 hours post loading dose, compared to the clopidogrel treatment group. However, the standard deviations between treatment groups were significant at all time points.

Table 58. Sponsor's Analysis: IPA to 20 μM ADP at 30 min, 2 hours, 18 to 24 hours Following Loading Dose of Study Drug

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference Prasugrel – Clopidogrel (95% CI)	p-value
30 minutes post LD	N	70	73		
	Mean	30.79	4.92	26.04 (18.91, 33.16)[a]	<0.0001[a]
	SD	29.02	13.19		<0.0001*
	Median	32.24	6.74		

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference Prasugrel – Clopidogrel (95% CI)	p-value
2 hours post-LD	N	74	78		
	Mean	64.54	20.32	44.75 (38.35, 51.15)[a]	< 0.0001[a]
	SD	20.43	20.22		0.9294*
	Median	70.06	18.39		
6 hours post-LD	N	72	77		
	Mean	74.81	31.77	43.21 (38.04, 48.38)[a]	< 0.0001[a]
	SD	13.01	21.07		<0.0001*
	Median	77.03	31.43		
18 to 24 hours post-LD	N	39	46		
	Mean	69.25	32.62	36.40 (29.04, 43.76)[a]	< 0.0001[a]
	SD	13.97	19.85		0.0284*
	Median	71.62	32.39		

ANCOVA=analysis of covariance; CI=confidence interval; LD=loading dose; N=number of subjects; SD=standard deviation.
[a]Group means for data analyzed using an ANCOVA model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances.
***p-value to compare group variance obtained from an F test.**
Reproduced from Sponsor, Table TABL.11.5, page 95 of 1590.

9.2.12.8.2 IPA to 5 μM ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours Following Loading Dose of Study Drug

As shown in Table 59, there was a significantly higher mean IPA for prasugrel compared to clopidogrel at all time points. However, the standard deviations between treatment groups were statistically significant for all time points except 2 hours post loading dose.

Table 59. Sponsor's Analysis: Inhibition of Platelet Aggregation with 5 μM Adenosine Diphosphate (Acute Phase Population) (TABL)

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value*
30 minutes post LD	N	68	72		
	Mean	34.70	4.32	29.68 (22.10, 37.27)	<0.0001
	SD	28.21	18.067		0.003
	Median	37.87	5.57		
2 hours post-LD	N	74	75		
	Mean	66.19	23.95	42.61 (35.80, 49.43)	<0.001
	SD	20.82	21.97		0.6461
	Median	72.81	24.42		
6 hours post-LD	N	71	76		
	Mean	76.21	36.80	39.38 (33.49, 45.28)	<0.0001
	SD	13.11	23.17		<0.0001
	Median	77.78	37.14		

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value*
18 to 24 hours post-LD	N	39	48		
	Mean	70.97	34.48	36.36 (28.67, 44.05)	< 0.0001
	SD	12.58	21.85		0.0007
	Median	72.84	33.79		

ANCOVA=analysis of covariance; CI=confidence interval; LD=loading dose; N=number of subjects; SD=standard deviation.
***Group means analyzed using an Analysis of Covariance model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances.**
p-value to compare group variances obtained from an F-test
Reproduced from Sponsor, Table TABL.14.44, pages 279-280 of 1590.

9.2.12.8.3 Maximum Platelet Aggregation to 20 μM ADP at 30 min, 2 hours, 6 hours, and 18 to 24 hours Following Loading Dose of Study Drug

Maximum platelet aggregation was significantly lower in the prasugrel treatment group, compared to clopidogrel, at 30 minutes, 2 hours, 6 hours, and 18 to 24 hours following the loading dose. However, standard deviations for most time points were significant, and the confidence interval for the difference between the prasugrel-clopidogrel treatment groups was large at Day 15, making these results less certain.

Table 60. Sponsor's Analysis: Maximum Platelet Aggregation to 20 μM ADP at 30 minutes, 2 hours, 6 hours and 18 to 24 hours following Loading Dose of Study Drug (Acute Phase Population) (TABL)

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value
Pre-treatment	N	84	84		
	Mean	75.86	76.95		0.5140*
	SD	11.87	9.727		
	Median	74.50	76.00		
30 minutes post LD	N	70	74		
	Mean	52.40	72.51	-20.26 (-25.72, -14.79)[a]	<0.001[a]
	SD	21.72	9.96		<0.0001**
	Median	51.00	73.00		
2 hours post-LD	N	74	79		
	Mean	26.76	60.70	-33.95 (-38.71, -29.20)[a]	<0.0001[a]
	SD	15.36	14.53		0.6289**
	Median	20.00	60.00		
6 hours post-LD[c]	N	72	77		
	Mean	18.86	52.05	-33.11 (-37.05, -29.16)[a]	<0.0001[a]
	SD	9.49	16.06		0.0326**
	Median	17.50	50.00		

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value
18 to 24 hours post-LD	N	39	47		
	Mean	23.21	51.09	-27.37 (-32.87, -21.87)[a]	<0.0001[a]
	SD	10.22	14.39		0.0326**
	Median	21.00	54.00		
Day 15 visit[c]	N	40	47		
	Mean	28.50	41.53	-12.13 (-1618, -7.44)[a]	0.0001[a]
	SD	12.88	14.12		0.5578**
	Median	26.50	40.00		

ANCOVA=analysis of covariance; CI=confidence interval; LD=loading dose; MPA=maximum platelet aggregation; N=number of subjects; SD=standard deviation.
[a]Group means for data analyzed using an ANCOVA model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances
[b]This number represents the total number of evaluable samples from subjects that received prasugrel in each MD period (40 from theDay 15
[c]Key secondary endpoint per SAP dated July 25, 2007 (but not prespecified in the Protocol or Protocol Amendment)
***p-value obtained from 2-sample t test**
****p-value to compare group variance obtained from an F-test**
Source: TABL 14.47 and TABL 14.49
Reproduced from Sponsor, Table TABL.11.6, page 99 of 1590.

9.2.12.8.4 Maximum Platelet Aggregation to 5 μM ADP at 30 minutes, 2 hours, 6 hours, and 18 to 24 hours Following Loading Dose of Study Drug

The results for the MPA to 5 μM ADP, as seen in Table 61, were consistent with the 20 μM results.

Table 61. Sponsor's Analysis: Maximal Platelet Aggregation to 5 μM Adenosine Disphosphate (Acute Phase Population) (TABL)

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value*
Pre-treatment	N	81	83		
	Mean	68.65	67.88		0.6803
	SD	12.94	11.05		
	Median	68.00	70.00		
30 minutes post LD	N	69	73		
	Mean	44.71	64.67	-20.58 (-25.73, -15.44)	<0.0001*
	SD	19.17	12.65		0.0006*
	Median	42.00	65.00		
2 hours post-LD	N	75	76		
	Mean	23.00	51.12	-28.87 (-33.24, -24.51)	<0.0001
	SD	13.57	14.47		0.5838
	Median	18.00	51.00		

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value*
6 hours post-LD	N	71	77		
	Mean	16.38	42.61	-26.44 (-30.36, -22.52)	<0.0001*
	SD	9.27	15.53		<0.0001*
	Median	15.00	44.00		
18 to 24 hours post-LD	N	39	48		
	Mean	19.74	43.13	-23.69 (-28.67, -18.71)	<0.0001*
	SD	9.20	14.05		0.0084*
	Median	19.00	45.50		

***p-value to compare baseline values obtained from a 2 sample t-test**
Group means analyzed using an Analysis of Covariance model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances.
p-value to compare group variances obtained from an F-test.

9.2.12.8.5 Final Extent of Platelet Aggregation (at 6 minutes after ADP addition) to 5 or 20 μM ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours Following Loading Dose of Study Drug

All results were reviewed.

9.2.12.8.6 Mean VerifyNow™ P2Y12 Percent Inhibition Data at 6 Hours and at the Day 15 Visit

Although this endpoint was not initially prespecified in the Protocol or Protocol Amendment, the endpoint was considered to be a key secondary endpoint in the SAP dated July 25, 2007. Interpretability of these results is limited, given the lack of baseline values in both treatment groups.

Table 62. Sponsor's Analysis: VerifyNow™ $P2Y_{12}$ Percent Inhibition Data

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value*
30 minutes post LD	N	77	88		
	Mean	45.6	11.0	34.6 (26.7, 42.5)[a]	<0.0001[a]
	SD	34.7	8.5		<0.0001[a]
	Median	37.0	12.0		
6 hours post-LD	N	83	90		
	Mean	89.5	38.4	51.4 (45.5, 57.4)[a]	<0.0001[a]
	SD	10.5	26.1		<0.0001[a]
	Median	95.0	30.5		
Day 15 Visit	N	50	53		
	Mean	83.3	65.1	18.9 (11.7, 26.1)[a]	<0.0001[a]
	SD	16.0	23.1		0.0115*
	Median	90.5	67.0		

ANCOVA=Analysis of Covariance; CI=confidence interval; LD=loading dose; N=Number of subjects; SD=standard deviation
aGroup means analyzed using an ANCOVA model with factors for study treatment and pooled study site, assuming unequal group variances. Note that the model did not contain a covariate for baseline value, as no