

pretreatment VerifyNow P2Y<sub>12</sub> percent inhibition measurements were taken.

\*p-value to compare group variances obtained from an F-test.

Source: Table TABL. 14.54

Reproduced from Sponsor, Table TABL.11.7, page 101 of 1590.

#### 9.2.12.8.7 Thienopyridine Hyporesponsiveness

In the SAP dated July 25, 2007, prespecified endpoints in Phase 1 included

- Thienopyridine hyporesponsiveness defined as IPA to 20  $\mu$ M ADP < 20% or IPA to 5  $\mu$ M ADP < 25% at 2 hours, 6 hours, and 18 to 24 hours following loading dose of study drug. The comparison would be evaluated by Pearson Chi-square test or Fisher exact test as appropriate.

Per the SAP, prespecified endpoints in Phase 2 included

- Thienopyridine hyporesponsiveness defined as IPA to 20  $\mu$ M ADP < 20%, IPA to 5  $\mu$ M ADP < 25%, or less than observed 25<sup>th</sup> percentile of IPA response after 14  $\pm$  2 days of clopidogrel 150 mg daily MD following 14  $\pm$  2 days of study medication. The comparison would be conducted by Prescott's test or exact Prescott's test as appropriate.

The results for these endpoints are displayed in Table 63. Thienopyridine hyporesponsiveness was significantly lower in the prasugrel treatment group at 2 hours, 6 hours, and 18 to 24 hours post loading dose, compared to clopidogrel. However, the number of samples available for the 18 to 24 hour time point was lower than for the other time points. Additionally, at the Day 15 Visit (14  $\pm$  2 days), thienopyridine hyporesponsiveness, defined as IPA with 20  $\mu$ M ADP < 20%, was not statistically significant between treatment groups. However, thienopyridine hyporesponsiveness, defined as IPA with 20  $\mu$ M ADP < 25<sup>th</sup> %IPA was significantly higher in the clopidogrel treatment group, compared to prasugrel. The number of samples at the Day 15 visit was lower when compared to the samples available for the first 6 hours following the loading dose of study drug.

**Table 63. Sponsor's Analysis: Thienopyridine Hyporesponsiveness to 20  $\mu$ M ADP After LD and During MD**

	Prasugrel/Clopidogrel N=99	Clopidogrel/Prasugrel N=98	p-value
<b>30 minutes post LD (N)</b>	70	73	
IPA with 20 $\mu$ M ADP < 20%	30 (42.9%)	64 (87.7%)	<0.0001 <sup>a</sup>
<b>2 hours post LD (N)<sup>†</sup></b>	74	78	
IPA with 20 $\mu$ M ADP < 20%	2 (2.7%)	43 (55.1%)	<0.0001 <sup>a</sup>
<b>6 hours post LD (N)<sup>†</sup></b>	72	77	
IPA with 20 $\mu$ M ADP < 20%	0 (0.0%)	21 (27.3%)	<0.0001 <sup>a</sup>
<b>18 to 24 hours post LD (N)<sup>†</sup></b>	39	46	
IPA with 20 $\mu$ M ADP < 20%	0 (0.0%)	14 (30.4%)	0.0002 <sup>a</sup>
<b>Day 15 Visit (N)<sup>†</sup></b>	40	46	
IPA with 20 $\mu$ M ADP < 20%	1 (2.5%)	7 (15.2%)	0.0629 <sup>b</sup>
IPA with 20 $\mu$ M ADP < 25 <sup>th</sup> %IPA (clopidogrel)	3 (7.5%)	11 (23.9%)	0.0397 <sup>b</sup>
<b>Day 29 visit (N)</b>	40	45	
IPA with 20 $\mu$ M ADP < 20%	4 (10.0%)	1 (2.2%)	0.1827 <sup>b</sup>
IPA with 20 $\mu$ M ADP < 25 <sup>th</sup> %IPA (clopidogrel)	11 (27.5%)	3 (6.7%)	0.0097 <sup>b</sup>
<b>Day 15 visit and Day 29 visit (N)<sup>d</sup></b>	37	43	0.0215 <sup>c</sup>
IPA with 20 $\mu$ M ADP < 20% at Day 15	0 (0.0%)	6 (14.0%)	
IPA with 20 $\mu$ M ADP < 20% at Day 29	4 (10.8%)	1 (2.3%)	

	Prasugrel/Clopidogrel N=99	Clopidogrel/Prasugrel N=98	p-value
IPA with 20 µM ADP < 20% at both Day 15 and Day 29	0 (0.0%)	0 (0.0%)	
IPA with 20 µM ADP < 20% at neither Day 15/Day 29	33 (89.2%)	36 (83.7%)	
IPA with 20 µM ADP < 25 <sup>th</sup> %IPA (clop) at Day 15	1 (2.7%)	8 (18.6%)	0.0017 <sup>c</sup>
IPA with 20 µM ADP < 25 <sup>th</sup> %IPA (clop) at Day 29	9 (24.3%)	1 (2.3%)	
IPA with 20 µM ADP < 25 <sup>th</sup> %IPA (clop) at both Day 15 and Day 29	1 (2.7%)	2 (4.7%)	
IPA with 20 µM ADP < 25 <sup>th</sup> %IPA (clop) at neither Day 15/Day 29	26 (70.3%)	32 (74.4%)	
<p>ADP=adenosine diphosphatase; clop=clopidogrel; IPA=inhibition of platelet aggregation; %IPA (clop)=percentile of IPA response after 14 ± 2 days of clopidogrel daily 150 mg MD; LD=loading dose; MD=maintenance dose; N=number of subjects</p> <p><sup>a</sup>p-value (30 minutes to 18 to 24 hours) is obtained from a Pearson's chi-squared test</p> <p><sup>b</sup>p-value (Day 15 and Day 29) is obtained from a Pearson's chi-squared test when total count ≥ 10 from a Fisher's exact test, otherwise.</p> <p><sup>c</sup>p-value for the combined data is obtained from exact Prescott's test for the comparison of prasugrel versus clopidogrel</p> <p><sup>d</sup>Includes subjects with evaluable samples at both the Day 15 and Day 29 visits</p> <p>Source: Table TABL.14.64 and Table.14.66</p> <p>†Prespecified analyses in the SAP dated July 25, 2007</p>			

9.2.12.8.8 Vasodilator-Stimulated Phosphoprotein (VASP) Phosphorylation Ratio at 2 hours, 6 hours, 18 to 24 hours and 14 ± 2 days Following Loading Dose of Study Drug

VASP results are displayed in Table 64. At all time points, subjects receiving prasugrel had significantly lower VASP platelet reactivity indices, compared to clopidogrel.

Table 64. Sponsor's Analysis: VASP Platelet Reactivity Index (PRI %) Throughout Study

		Prasugrel/ Clopidogrel N=99	Clopidogrel/ Prasugrel N=98	Difference Prasugrel-Clopidogrel (95% CI)	p-value
Pretreatment	N	89	89		
	Mean	88.1	86.4		0.1301 <sup>a</sup>
	SD	7.10	7.48		
	Median	90.0	88.0		
2 hours post LD	N	93	88		
	Mean	21.5	75.0	-54.3 (-61.2, -47.4) <sup>b</sup>	<0.0001 <sup>b</sup>
	SD	27.06	16.91		
	Median	13.0	79.0		
6 hours post LD	N	68	68		
	Mean	7.4	68.4	-60.5 (-67.1, -54.0) <sup>b</sup>	<0.0001 <sup>b</sup>
	SD	16.66	21.18		
	Median	6.5	74.5		
18 to 24 hours post LD	N	48	54		

		Prasugrel/ Clopidogrel N=99	Clopidogrel/ Prasugrel N=98	Difference Prasugrel-Clopidogrel (95% CI)	p-value
	Mean	10.3	64.3	-56.2 (-63.2, -49.2) <sup>b</sup>	<0.0001 <sup>b</sup>
	SD	15.63	18.72		
	Median	8.5	68.0		
Day 15 visit	N	50	52		
	Mean	21.7	39.7	-17.9 (-26.6, -9.1) <sup>b</sup>	0.0001 <sup>b</sup>
	SD	18.97	21.90		
	Median	16.5	40.5		
Day 29 visit	N	51	50		
	Mean	48.0	25.1	-21.7 (-31.0, -12.4) <sup>b</sup>	<0.0001 <sup>b</sup>
	SD	24.06	19.47		
	Median	49.0	24.0		

ANCOVA=analysis of covariance; CI=confidence interval; LD=loading dose; LS=least square; MD=maintenance dose; N=number of subjects; PRI=platelet reactivity index; SD=standard deviation; VASP=vasodilator-stimulated phosphoprotein  
<sup>a</sup>p-value to compare baseline values obtained from a 2 sample t test  
<sup>b</sup>Group means (30minutes to 18 to 24 hours) analyzed using an ANCOVA model with factors for study treatment and laboratory, and a covariate for baseline value, assuming unequal group variances  
<sup>c</sup>This number represents the total number of evaluable samples from subjects that received prasugrel in each MD period (50 from the Day 15 visit and 50 from the Day 29 visit)  
<sup>d</sup>This number represents the total number of evaluable samples from subjects that received clopidogrel in each MD period (52 from the Day 15 visit and 51 from the Day 29 visit)  
<sup>e</sup>Group means for combined Day 15 visit and Day 29 visit data analyzed using an ANCOVA model with factors for study treatment, study phase, treatment order, subject within-treatment order as a random effect and laboratory, and a covariate for baseline value, assuming unequal group variances  
 Source: Table TABL.14.61 and Table TABL.14.62  
 Reproduced from Sponsor, Table TABL. 11.9, page 105 of 1590.

#### 9.2.12.8.9 Additional Platelet Function and Inflammatory Measures

The results are summarized as follows:

- There was no significant difference between treatment groups in sCD40L at 6 and 18 to 24 hours after loading dose of study drug and after 14 ± 2 days of maintenance therapy with study drug
- At 6 hours and 18 to 24 hours, as well as at the Day 15 visit, prasugrel had significantly lower values for monocyte-platelet aggregates and neutrophil-platelet aggregates to 20 μM adenosine diphosphatase
- At 18 to 24 hours post loading dose and at the Day 15 visit, the clopidogrel treatment group had significantly lower mean values of interferon gamma, compared to prasugrel
- At the Day 15 visit, there was a significantly lower mean value of interleukin 13 in the clopidogrel treatment group, compared to prasugrel.
- At 18 to 24 hours post loading dose, there was a significantly lower mean interleukin 15 value in the clopidogrel treatment group, compared to prasugrel.
- At the Day 15 visit, there was a significantly lower mean value of interleukin 18 in the clopidogrel treatment group, compared to prasugrel.
- 6 hours post loading dose, tumor necrosis factor was significantly reduced in the clopidogrel treatment group compared to prasugrel.
- At 6 hours and 18 to 24 hours post loading dose and at the Day 15 visit and Day 29 visit, platelet P-selectin % Positive Platelets to 20 μM adenosine diphosphatase was significantly lower in the prasugrel treatment group, compared to clopidogrel.

- At 6 hours and 18 to 24 hours post loading dose, high-sensitivity C-reactive protein was significantly lower in the clopidogrel treatment group.
- At 6 hours and 18 to 24 hours post loading dose, myeloperoxidase was significantly lower in the prasugrel treatment group

#### 9.2.12.8.10 Myonecrosis Measures

There was no significant correlation between IPA with 20 µM ADP at 6- and 18- to 24-hours post loading dose and CK-MB, except that CK-MB exceeding 1x ULN at 6 hours post LD was negatively correlated in the clopidogrel treatment group (p = 0.0449). However, the number of samples with positive enzymes in this study were small, so no definitive conclusions should be drawn from this analysis.

#### 9.2.12.9 Major Adverse Cardiac Events (MACE)/Other Clinical Endpoints

MACE was a composite of cardiovascular death, myocardial infarction, and stroke during the first 14 ± 2 days of MD therapy in treated subjects who received PCI. Three subjects (2.9%) in the prasugrel/clopidogrel treatment group and one subject (1.0%) in the clopidogrel/prasugrel treatment group experienced the MACE endpoint, as displayed in Table 65. There were no deaths or strokes during the study.

Other clinical endpoints during 14 ± 2 days of maintenance therapy in subjects who were treated and underwent PCI were subacute stent thrombosis, urgent target vessel revascularization, and the individual components of MACE. The results of these clinical endpoints are also displayed in Table 65.

**Table 65. Sponsor's Analysis: Clinical Efficacy Measures Occurring at any Time During the Study (On-Treatment Population) (TABL)**

	Prasugrel/Clopidogrel # Reports	N = 102 # Subjects	Clopidogrel/Prasugrel # Reports	N = 99 # Subjects
MACE endpoint	3	3 (2.9%)	1	1 (1.0%)
Cardiovascular death	0	0 (0.0%)	0	0 (0.0%)
Myocardial infarction	3	3 (2.9%)	1	1 (1.0%)
Stroke	0	0 (0.0%)	0	0 (0.0%)
Subacute stent thrombosis	0	0 (0.0%)	1	1 (1.0%)
Urgent Target Vessel Revascularization	0	0 (0.0%)	1	1 (1.0%)

Reproduced from Sponsor, Table TABL.14.131, page 516 of 1590.  
 Analysis verified by Karen A. Hicks, M.D.. Please note that Subject 301-0032 in the clopidogrel treatment group had subacute stent thrombosis 4 days after index stent placement, requiring urgent target vessel revascularization. This subject was counted under "subacute stent thrombosis" as well as "urgent target vessel revascularization."

9.2.12.10 Exposure

Study drug exposure was similar in each treatment group.

**Table 66. Exposure to Study Medication (On Treatment Population) (TABL)**

		Prasugrel/ Clopidogrel N=102	Clopidogrel/ Prasugrel N=99	Total N=201	p-value*
Received LD		102 (100%)	99 (100%)	201 (100%)	
MD between Day 2 and Day 15					
Took at least 1 MD of study drug		55(53.9%)	55 (55.6%)	110 (54.7%)	
Number of days of study drug	N	54 <sup>a</sup>	55	109	
	Mean	13.9	14.2	14.0	0.1919
	SD	1.17	1.30	1.24	
	Median	14.0	14.0	14.0	
MD between Day 15 and Day 29					
Took at least 1 MD of study drug		53 (52.0%)	55 (55.6%)	108 (53.7%)	
Number of days of study drug	N	53	55	108	
	Mean	13.7	13.8	13.8	0.8563
	SD	2.04	1.61	1.83	
	Median	14.0	14.0	14.0	
N=number of subjects; SD=standard deviation; LD=loading dose; MD=maintenance dose *p-value obtained from a 2-sample t test <sup>a</sup> One subject (prasugrel) did not attend the Day 15 visit. The subject was hospitalized for 21 days after study drug LD. The investigator confirmed that the subject had taken study drug through the Day 15 visit; however, the site did not get quantity of drug returned or number of days' exposure. The subject missed study drug for 4 days. The subject was given 1 dose of open-label clopidogrel on the 4 <sup>th</sup> day of missing study drug and then started study drug (clopidogrel) while in hospital on the following day. Source: Table TABL.14.143 Reproduced from Sponsor, Table TABL.12.1, page 114 of 1590.					

9.2.12.11 Primary Safety Measure

The primary safety measure was non-CABG TIMI significant bleeding defined as the occurrence of TIMI major or minor bleeding in the treated population at the Day 15 visit. There were no TIMI major bleeds in either treatment group up to Day 15.

**Table 67. Sponsor's Analysis: Non-CABG-Related TIMI Clinically Significant Bleeding Events up to Day 15 Visit (Number and Percentage of Subjects) (On-Treatment Population) (TABL)**

	Prasugrel/Clopidogrel (N=102)		Clopidogrel/Prasugrel (N=99)	
	# reports	# subjects	# reports	# subjects
TIMI major or minor bleeding events	2	2 (2.0%)	0	(0.0%)
TIMI major bleeding events	0	0 (0.0%)	0	0 (0.0%)

	Prasugrel/Clopidogrel (N=102)		Clopidogrel/Prasugrel (N=99)	
	# reports	# subjects	# reports	# subjects
TIMI minor bleeding events	2	2 (2.0%)	0	0 (0.0%)

**CABG=coronary artery bypass graft; TIMI=Thrombolysis In Myocardial Infarction.**  
**Note: # reports refers to the number of events that occurred; # subjects refers to the number of subjects who reported at least 1 event and is followed by the percent of total in parenthesis.**  
**Source: TABL.14.147, TABL.14.148, TABL.14.149.**  
**Reproduced from Sponsor, Table TABL.12.3, page 119 of 1590.**  
**Analysis verified by Karen A. Hicks, M.D.**

In the clopidogrel treatment group, there were no adjudicated hemorrhages; however, in the prasugrel treatment group, there were 5 unique hemorrhages, including (2) TIMI minor bleeds (Subjects 102-0003 and 301-0033), and (3) non-CABG related minimal bleeds (Subjects 102-0020, 201-0001, and 301-0026). Additionally, subject 301-0016, randomized to prasugrel experienced a drop in hemoglobin from 13.7 to 8.2 g/dl, but there was no overt bleeding and no reason for the drop in hemoglobin could be identified.

#### 9.2.12.12 Other Prespecified Safety Measures

Other prespecified safety measures included non-CABG related TIMI major bleeding, non-CABG-related TIMI life-threatening bleeding, and non-CABG-related TIMI minor bleeding. The TIMI major or minor bleeding events up to Day 15 are summarized in Table 67. There were no TIMI life-threatening bleeding events. After the Day 15 visit, there were no TIMI major or minor bleeding events.

#### 9.2.12.13 Overview of Adverse Events

There were no deaths during the study. The prasugrel/clopidogrel treatment group had a higher percentage of serious adverse events up to Day 15 and thereafter. One subject in the prasugrel/clopidogrel treatment group discontinued the study due to an adverse event.

In the prasugrel/clopidogrel treatment group, there were 101 reports of nonserious treatment emergent adverse events in 45 (44.1%) subjects occurring at any time during the study. Eighty-seven nonserious treatment emergent adverse events occurred in 40 (39.2%) subjects from randomization to the Day 15 visit, and 14 nonserious treatment emergent adverse events occurred in 12 (22.6%) subjects from the Day 15 Visit to the Day 29 Visit.

In the clopidogrel/prasugrel treatment group, there were 104 reports of nonserious treatment emergent adverse events in 42 (42.4%) subjects occurring at any time during the study. Eighty nonserious treatment emergent adverse events occurred in 40 (40.4%) subjects from randomization to the Day 15 visit, and 24 nonserious treatment emergent adverse events occurred in 16 (29.1%) subjects from the Day 15 Visit to the Day 29 Visit.

An overview of adverse events is displayed in Table 68.

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**Table 68. Sponsor's Analysis: Overview of Adverse Events (Number and Percentage of Subjects) (On-Treatment Population) (TABL)**

	<b>Prasugrel/ Clopidogrel N=102</b>	<b>Clopidogrel/ Prasugrel N=99</b>
Death (entire study duration)	0 (0.0%)	0 (0.0%)
Treatment-Emergent Adverse Events (entire study duration)	45 (44.1%)	42 (42.4%)
<b>Up to Day 15 visit<sup>a</sup></b>		
Number of Subjects	102	99
<b>Non-CABG-related TIMI clinically significant bleeding events<sup>b</sup></b>		
TIMI major bleeding events	0 (0.0%)	0 (0.0%)
TIMI minor bleeding events	2 (2.0%)	0 (0.0%)
Serious adverse events	8 (7.8%)	7 (7.1%)
Discontinuations due to an adverse event	1 (1.0%)	0 (0.0%)
Treatment-emergent adverse events	40 (39.2%)	40 (40.4%)
<b>Post-Day 15 visit<sup>a</sup></b>		
Number of subjects	53	55
<b>Non-CABG-related TIMI clinically significant bleeding events<sup>b</sup></b>		
TIMI major bleeding events	0 (0.0%)	0 (0.0%)
TIMI minor bleeding events	0 (0.0%)	0 (0.0%)
Serious adverse events	3 (5.7%)	1 (1.8%)
Discontinuations due to an adverse event	0 (0.0%)	0 (0.0%)
Treatment-emergent adverse events	12 (22.6%)	16 (29.1%)
<b>CABG=coronary artery bypass graft; N=number of subjects; TIMI=Thrombolysis in Myocardial Infarction</b>		
<b><sup>a</sup>Subjects may be counted in more than 1 category and/or study period for a given category</b>		
<b><sup>b</sup>Non-CABG-related TIMI clinically significant bleeding events include TIMI major and TIMI minor bleeding events.</b>		
<b>Reproduced from Sponsor, Table TABL.12.2, page 115 of 1590.</b>		
<b>TIMI major or minor bleeding events, serious adverse events, and discontinuations due to an adverse event were verified by Karen A. Hicks, M.D.</b>		

9.2.12.14 Serious Adverse Events

Serious adverse events are summarized in Table 69.

**Table 69. Sponsor's Analysis: Serious Adverse Events by System Organ Class and Preferred Term (Number and Percentage of Subjects) (All Randomized Subjects)**

	Prasugrel/Clopidogrel		Clopidogrel/Prasugrel	
	# reports	# subjects	# reports	# subjects
<b>Serious adverse events up to Day 15 visit</b>				
Number of Subjects		102		99
Total Events	8	8 (7.8%)	11	7 (7.1%)
Cardiac disorders	3	3 (2.9%)	3	3 (3.0%)
Atrial fibrillation	1	1 (1.0%)	0	0 (0.0%)
Bradycardia	1	1 (1.0%)	0	0 (0.0%)
Extrasystoles	0	0 (0.0%)	1	1 (1.0%)
Myocardial infarction	0	0 (0.0%)	1	1 (1.0%)
Ventricular fibrillation	1	1 (1.0%)	0	0 (0.0%)
Ventricular tachycardia	0	0 (0.0%)	1	1 (1.0%)
General disorders and administration site conditions	2	2 (2.0%)	3	2 (2.0%)
Chest discomfort	0	0 (0.0%)	1	1 (1.0%)
Chest pain	0	0 (0.0%)	1	1 (1.0%)
Non-cardiac chest pain	0	0 (0.0%)	1	1 (1.0%)
Vessel puncture site haematoma	2	2 (2.0%)	0	0 (0.0%)
Injury, poisoning, and procedural complications	1	1 (1.0%)	1	1 (1.0%)
Fall	0	0 (0.0%)	1	1 (1.0%)
Post-procedural myocardial infarction	1	1 (1.0%)	0	0 (0.0%)
Investigations	1	1 (1.0%)	0	0 (0.0%)
Blood glucose increased	1	1 (1.0%)	0	0 (0.0%)
Nervous system disorders	0	0 (0.0%)	2	1 (1.0%)
Syncope	0	0 (0.0%)	1	1 (1.0%)
Vlth nerve disorder (cranial nerve)	0	0 (0.0%)	1	1 (1.0%)
Respiratory, thoracic, and mediastinal disorders	0	0 (0.0%)	1	1 (1.0%)
Dyspnoea	0	0 (0.0%)	1	1 (1.0%)
Vascular disorders	1	1 (1.0%)	1	1 (1.0%)
Deep vein thrombosis	1	1 (1.0%)	0	0 (0.0%)
Hypotension	0	0 (0.0%)	1	1 (1.0%)
<b>Serious adverse events post-Day 15 visit</b>				
Number of Subjects		53		55
Total Events	4	3 (5.7%)	1	1 (1.8%)
Cardiac disorders	2	2 (3.8%)	0	0 (0.0%)
Acute coronary syndrome	1	1 (1.9%)	0	0 (0.0%)
Tachycardia	1	1 (1.9%)	0	0 (0.0%)
General disorders and administration site conditions	0	0 (0.0%)	1	1 (1.8%)
Non-cardiac chest pain	0	0 (0.0%)	1	1 (1.8%)
Infections and infestations	1	1 (1.9%)	0	0 (0.0%)
Borrelia infection	1	1 (1.9%)	0	0 (0.0%)
Respiratory, thoracic, and mediastinal disorders	1	1 (1.9%)	0	0 (0.0%)
Chronic obstructive pulmonary disease	1	1 (1.9%)	0	0 (0.0%)

Note: # reports refers to the number of events that occurred; # subjects refers to the number of subjects who reported at least 1 event.

Source: Table TABL.14.160 and Table TABL.14.162

(Reproduced from Sponsor, Table TABL.12.6, page 125 of 1590)

### 9.2.13 Summary (TABL)

Based on these study results, prasugrel appears to have a greater inhibitory effect on platelet aggregation than clopidogrel. However, variable reproducibility in light transmission aggregometry measurements and inter-laboratory variability can affect the interpretability of these results. In many cases, there were large standard deviations which were statistically significant between treatment groups, suggesting the results are not as clear. Furthermore, the sponsor has not correlated these results with clinical outcome.

Although the Accumetrics VerifyNow P2Y<sub>12</sub> assay appears to correlate with results from light transmission aggregometry, the device has its own limitations. In 2006, CDRH issued a recall for the Accumetrics VerifyNow P2Y<sub>12</sub> assay device because it could report an erroneous result instead of an error message when a sample was run from a patient with a low hematocrit. TABL was performed during this recall. In the current instructions for use (IFU), the sponsor states assay performance was not affected by hematocrit values between 33-52%, or platelet count values between 119,000-502,000/ $\mu$ l. The IFU also states that there was no assay interference when samples with fibrinogen levels between 171 and 599 mg/dL were tested. However, glycoprotein IIb/IIIa inhibitors, abciximab, eptifibatide, and tirofiban, significantly affect VerifyNow P2Y<sub>12</sub> assay results, and it is recommended that these patients not be tested until platelet function has recovered (approximately 14 days after discontinuation of Abciximab and up to 48 hours for eptifibatide and tirofiban).

In TABL, three subjects undergoing PCI in the prasugrel treatment group and one subject undergoing PCI in the clopidogrel treatment group received glycoprotein IIb/IIIa inhibitors. Additionally, during Period 1 screening, there were 27 clopidogrel subjects with low hematocrits, and two of these subjects had hematocrits < 33%. In the prasugrel treatment group, there were 24 subjects with low hematocrits during Period 1 screening, and one subject with a hematocrit < 32%. However, these few subjects would not have a large impact on the overall findings.

Nevertheless, I believe this science of measuring platelet aggregation is still evolving. Therefore, although these data from TABL are interesting, I consider the results to be exploratory only.