1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval of prasugrel for the reduction of atherothrombotic events in patients with acute coronary syndromes (ACS) as follows:

- patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) who are managed with percutaneous coronary intervention (PCI)
- patients with ST-segment elevation myocardial infarction (STEMI) who are managed with primary or delayed PCI.

In TAAL, prasugrel significantly reduced the rate of the combined primary endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the UA/NSTEMI, All ACS, and STEMI populations at a median follow-up of 12 months, compared to clopidogrel. Subjects appeared to receive most of the treatment benefit from prasugrel within the first several days of therapy.

In the prasugrel treatment group, however, there was a 36% increased risk of overall bleeding and a 46% increased risk of serious bleeding, compared to clopidogrel. Although the rates of intracranial hemorrhage were similar between the two treatment groups, the fatality rate associated with this event was two-fold higher with prasugrel. Additionally, the risk of bleeding events with prasugrel appeared to increase over time.

Furthermore, preliminary analyses from TAAL suggest there may be an increased rate of new malignancies in the prasugrel treatment group, compared to clopidogrel ($p= 0.006$), with a divergence in the incidence of these malignancies at 4 months.

Based on these preliminary analyses as well as increased bleeding risks with prasugrel over time, I recommend limiting therapy with prasugrel to short-term use (i.e., one week), so that patients may receive the benefits of this therapy while avoiding some of the possible risks.

I do not recommend approval of prasugrel for the reduction of stent thrombosis because the sponsor has not met the scientific rigor required for such a claim and has selectively used the standardized definitions for stent thrombosis developed in 2007 by the Academic Research Consortium (ARC) and our CDRH colleagues. For such a claim to be considered, angiographic confirmation of stent thrombosis would be necessary, generally determined by an angiographic core laboratory, or pathological confirmation with evidence of recent thrombus within the stent determined at autopsy or via 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. The CEC made the determination of stent thrombosis by clinical adjudication and review of cardiac catheterization and percutaneous coronary intervention reports. The CEC did not review angiograms and did not review all suspected events of stent thrombosis. In some cases, there was evidence of poor 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.

1.2 Recommendation on Postmarketing Actions

The sponsor plans to perform TABY, a study comparing prasugrel to clopidogrel in UA/NSTEMI patients (n > 13,000) who are medically managed. In this study, the sponsor proposes lowering the loading dose to 30 mg for patients needing a loading dose and lowering the maintenance dose from 10 mg to 5 mg in patients ≥ 75 years of age or weighing < 60 kg.

Based on our preliminary analysis which suggests there may be an increased rate of malignancy in the prasugrel treatment group, the sponsor will need to carefully collect all information related to neoplasia and bleeding. Perhaps cancer screening can be incorporated into the trial following the index hospitalization. Additionally, the sponsor will need to clearly distinguish neoplasia as past medical history from a new diagnosis in the clinical trial. Patients with worsening of their underlying malignancy should also be followed closely.

1.2.1 Risk Management Activity

The sponsor has proposed a risk management plan for prasugrel. Important identified risks include intracranial hemorrhage, gastrointestinal hemorrhage, intraocular hemorrhage, epistaxis, percutaneous coronary intervention-related hemorrhage, CABG-related hemorrhage, other procedure-related hemorrhage, and anemia. The sponsor has also identified important potential risks to include phototoxicity (skin or ocular), drug-induced hepatic injury, allergic reactions, thrombocytopenia, thrombotic thrombocytopenic purpura, and neutropenia. To date, neoplasia has not been identified as an important risk but needs to be incorporated into the sponsor's risk management plan.

Elements of the risk management plan include routine pharmacovigilance of adverse events with prasugrel, targeted surveillance activities with specific follow-up forms for the important identified risks and potential risks, and active surveillance in the ongoing clinical trials with prasugrel.

1.2.2 Required Phase 4 Commitments

The sponsor has already established a registry to follow stent thrombosis. The sponsor should also establish a registry to follow patients for the development of neoplasms or worsening of a previously diagnosed neoplasm.

[redacted] b(4)

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The prasugrel clinical development program consisted of 50 pharmacokinetic, pharmacodynamic, and clinical studies including TAAL (n=13,608), TABL (n=201), and TAAH (n=904). TAAL was a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study in subjects with acute coronary syndrome and was the predominant study submitted for consideration of the efficacy claim. In TAAL, subjects were randomized to prasugrel (60 mg loading dose, 10 mg maintenance dose) or clopidogrel (300 mg loading dose, 75 mg

maintenance dose). The primary endpoint was the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at a median follow-up of 12 months. TABL was a multicenter, randomized, parallel, double-blind, double-dummy, cross-over, active comparator-controlled study in subjects undergoing elective cardiac catheterization with planned PCI. In TABL, subjects were randomized to prasugrel (60 mg loading dose; 10 mg maintenance dose x 14 ± 2 days) or clopidogrel (600 mg loading dose; 150 mg maintenance dose x 14 ± 2 days) and subsequently crossed over to the alternative regimen for an additional 14 days. The primary endpoints included the inhibition of platelet aggregation after the loading dose or after 14 ± 2 days of maintenance dosing. Lastly, TAAH was a multicenter, randomized, parallel, double-blind, double-dummy, active comparator-controlled trial in subjects undergoing elective or urgent PCI with coronary stenting. In TAAH, subjects were randomized to clopidogrel (300 mg loading dose, 75 mg maintenance dose x 30-35 days) or three different regimens of prasugrel (40 mg loading dose/7.5 mg maintenance dose; 60 mg loading dose/10 mg maintenance dose; or 60 mg loading dose/15 mg maintenance dose). The primary safety measure was a comparison between treatment groups of the development of significant non-CABG-associated bleeding complications through 30 to 35 days after PCI.

1.3.2 Efficacy

In TAAL, prasugrel significantly reduced the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke using the original and expanded definitions of peri-procedural myocardial infarction, as displayed in Table 1 and Table 2, respectively. The original definition of peri-procedural myocardial infarction required an elevation of creatine kinase-myocardial band (CK-MB) to > 3x upper limit of normal (ULN) on a minimum of two samples within 48 hours of PCI. The modified definition, specified in Protocol Amendment (a) dated January 10, 2006, maintained the original definition but extended periprocedural myocardial infarctions to a CK-MB > 5x ULN on one sample if it was the last available sample and was drawn ≥ 12 hours after PCI.

Table 1. Sponsor's Analysis: Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI or Nonfatal Stroke Using the Definition of Peri-Procedural Myocardial Infarction Prior to Protocol Amendment (CEC Adjudicated) (All Randomized Subjects) (TAAL)

	Prasugrel			Clopidogrel			Total					
Subject Population	N	n	(%)[a]	N	n	(%)[a]	N	n	(%)[a]	HR	(95% CI)[b]	p-value[c]
UA/NSTEMI	5044	443	(8.78)	5030	536	(10.66)	10074	979	(9.72)	0.817	(0.720, 0.926)	0.002
STEMI	1769	162	(9.16)	1765	201	(11.39)	3534	363	(10.27)	0.793	(0.645, 0.976)	0.024
All ACS	6813	605	(8.88)	6795	737	(10.85)	13608	1342	(9.86)	0.810	(0.727, 0.902)	<0.001

CI=confidence interval, CV=cardiovascular, HR=hazard ratio, N=number treated, n=number of subjects reaching primary endpoint.
[a]% is percentage of randomized subjects reaching the primary endpoint.
[b]HR and two-sided 95% CI derived using Cox proportional hazards model.
[c]Two-sided p-values are based on Gehan-Wilcoxon 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.
(Reproduced from Sponsor, Table TAAL.14.20, page 1407 of 27,024)
Analysis verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

Table 2. Sponsor's Analysis: Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke Using the Expanded Definition (CEC Adjudicated) (All Randomized Subjects) (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total					
	N	n	(%)[a]	N	n	(%)[a]	N	n	(%)[a]	HR	(95% CI)[b]	p-value[c]
UA/NSTEMI	5044	469	(9.30)	5030	565	(11.23)	10074	1034	(10.26)	0.820	(0.726, 0.927)	0.002
STEMI	1769	174	(9.84)	1765	216	(12.24)	3534	390	(11.04)	0.793	(0.649, 0.968)	0.019
All ACS	6813	643	(9.44)	6795	781	(11.49)	13608	1424	(10.46)	0.812	(0.732, 0.902)	<0.001

CI=confidence interval, HR=hazard ratio, N=number treated, n=number of subjects reaching primary endpoint.
[a]% is percentage of randomized subjects reaching the primary endpoint.
[b]HR and two-sided 95% CI used as an estimate of overall relative risk, Prasugrel versus Clopidogrel, over the course of the study.
[c]Two-sided p-values are based on Gehan-Wilcoxon 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.
(Reproduced from Sponsor, Table TAAL.11.5, page 202 of 27,024).
Analysis verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

1.3.3 Safety

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 3.

Table 3. 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.

In the UA/NSTEMI, STEMI, and All ACS populations, prasugrel also significantly increased CABG-related TIMI major bleeding, as shown in Table 4. Bleeding analyses from TAAL suggest that prasugrel should be discontinued at least 7 days prior to CABG, if possible.

Table 4. Sponsor's Analysis: CEC-Adjudicated CABG-Related Bleeding Events Through Study End (Overall) (TAAL)

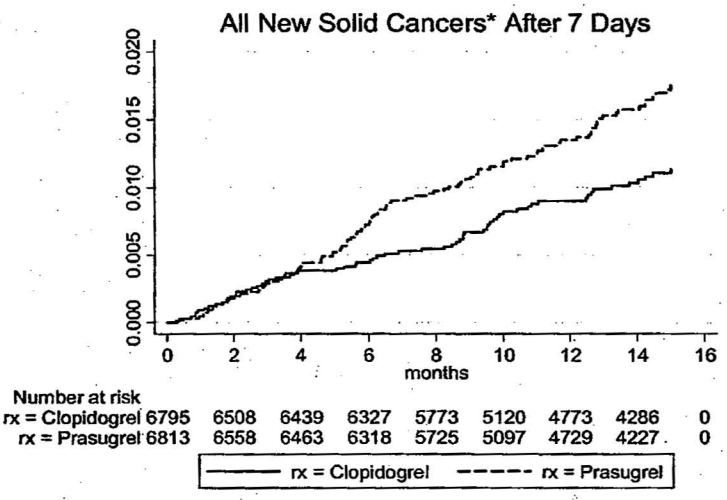
Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI)[b]	p-value[c]
	N	n	(%)[a]	N	n	(%)[a]	N	n	(%)[a]			
TIMI Major												
UA/NSTEMI	138	12	(8.70)	141	4	(2.84)	279	16	(5.73)	3.262	(1.025, 10.38)	0.035
STEMI	75	12	(16.00)	83	4	(4.82)	158	16	(10.13)	3.762	(1.157. 12.23)	0.020
All ACS	213	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.

In TAAL, an unexpected safety finding in the prasugrel treatment group was the increased rate of all cancers, particularly the solid tumors (e.g. breast, colorectal, esophageal, lung) ($p = 0.006$). Since tumor findings were sometimes noted at screening but not further evaluated until after enrollment, initial FDA analyses excluded cancers diagnosed during Days 0 to 7. While these results are preliminary, the Kaplan-Meier incidence plot by treatment for all new first cancers (excluding skin and brain tumors) demonstrates a divergence in incidence between the

prasugrel and clopidogrel treatment groups at 4 months with continuing divergence through the duration of the study, as shown in Figure 1.

Figure 1. Kaplan-Meier (K-M) Incidence Plot for All New Solid Cancers Diagnosed After 7 Days in TRITON



***excluding non-melanoma skin cancers and brain tumors; p = 0.006 by log rank**

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

Consultants from the Division of Oncology Products agreed that when the incidences of "all cancers" between the two Triton study arms were compared, a p-value of < 0.05 was obtained; however, they were not certain of the statistical or clinical significance of this finding. The consult states, "given the absence of a well-defined cancer screening at Triton study entry and short drug exposure to the study drugs (6 to 15 months), the cancers diagnosed in this study are more likely to be incidental." Recommendations included consultation with the Office of Surveillance and Epidemiology, incorporation of these neoplasia findings in labeling, and establishment of a registry by the sponsor to track the incidence of cancer on prasugrel, all of which we are doing.

We requested additional data from the sponsor on neoplasms from TAAL which are pending at the time of this review. Final recommendations on the approvability of prasugrel will depend on a thorough analysis of these data.

1.3.4 Dosing Regimen and Administration

The sponsor recommends oral dosing to include a single 60-mg loading dose followed by 10-mg once daily maintenance dosing.

For patients weighing < 60 kg (132 pounds), the sponsor recommends a single 60-mg loading dose followed by a 5-mg once daily maintenance dose.

For patients ≥ 75 years of age, the sponsor recommends a single 60-mg loading dose with consideration given to a 5-mg once daily maintenance dose as an alternative to a 10-mg once daily maintenance dose.

1.3.5 Drug-Drug Interactions

In Study TACS, high (70%), intermediate (58%), and low conversion tablets (5%) of prasugrel were found to be bio-inequivalent in healthy subjects pre-treated with lansoprazole (30 mg). The difference in plasma levels translated into differences in platelet aggregation which could be clinically relevant.[1]

Inhibitors of CYP3A decreased the C_{max} of the active metabolite, R-138727, by 46% but had no effect on the AUC and T_{max}. Rifampicin (600 mg daily), a potent inducer of CYP3A and CYP2B6 and an inducer of CYP2C9, CYP2C19, and CYP2C8, did not significantly affect the pharmacokinetics of prasugrel.

There appears to be a potential for drug-drug interaction with atorvastatin. One healthy subject in Study TAAV (Subject 11) experienced acute hepatic failure after coadministration of high-dose atorvastatin and prasugrel. Liver function abnormalities resolved after the discontinuation of both medications.

1.3.6 Special Populations

1.3.6.1 Age ≥ 75 years

Subjects ≥ 75 years of age appeared to receive less benefit from prasugrel, compared to clopidogrel, as shown in Table 5.

Table 5. FDA Subgroup Analysis: Composite of Cardiovascular Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke at a Median of 12 Months of Follow-Up by Age (TAAL)

	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 years									
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	**<0.0001**
≥ 75 years									
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**
Analysis by Ququan Liu, M.D., M.S., Division of Biometrics, FDA.									

In both treatment groups, subjects ≥ 75 years of age had a higher incidence of Non-CABG-related TIMI Major or Minor bleeding events (8.98% prasugrel, 6.94% clopidogrel for subjects ≥ 75 years; 3.81% prasugrel, 2.90% clopidogrel for subjects < 75 years).[2] Additionally, subjects ≥ 75 years of age had a higher risk of Non-CABG-related TIMI Major Life-Threatening bleeding events, including fatal bleeds and symptomatic intracranial hemorrhage for both treatment groups (fatal bleeding: 1.01% prasugrel, 0.11% clopidogrel; symptomatic intracranial hemorrhage: 0.79% prasugrel, 0.34% clopidogrel).[3]

Based on these data, prasugrel should probably not be the treatment of choice in patients ≥ 75 years of age. Even with a maintenance dose reduction from 10 mg to 5 mg daily in this population, efficacy is unclear and the risk of bleeding is higher. If prasugrel is approved for all age groups, physicians will need to carefully balance the risks versus benefits when prescribing prasugrel in patients ≥ 75 years of age.

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[1]Analysis by Patrick Marroum, Ph.D., Biopharmaceutics Review, Division of Clinical Pharmacology, FDA.
[2]Sponsor, Risk Management Plan, page 21 of 97.
[3]Sponsor, Risk Management Plan, page 21 of 97 and TAAL Clinical Study Report, Table TAAL.12.15, page 601.

1.3.6.2 Patients with a Prior History of Transient Ischemic Attack (TIA)/Cerebrovascular Accident (CVA)

Prasugrel appeared to have less benefit in patients with a prior history of TIA/CVA, as shown in Table 6.

Table 6. FDA Subgroup Analysis: Composite of Cardiovascular Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke at a Median of 12 Months of Follow-up in Patients With and Without a Prior History of Transient Ischemic Attack/Cerebrovascular Accident (TAAL)

	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
Prior History of TIA/CVA									
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 Prior History of TIA/CVA									
N	5831	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	**<0.0001**

ACS=acute coronary syndrome; CVA=cerebrovascular accident; NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; TIA=transient ischemic attack; UA=unstable angina
Analysis by Ququan Liu, M.D., M.S., Division of Biometrics, FDA.

Additionally, in patients with a prior history of TIA/CVA, the incidence of stroke was 6.5% (2.3% intracranial hemorrhage(ICH)) in the prasugrel treatment group, compared to 1.2% (0% ICH) in the clopidogrel treatment group (p-value < 0.001 for interaction).[4] In patients without a prior history of TIA/CVA, 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.

In subjects ≥ 75 years of age, there was a significantly higher incidence of stroke in the prasugrel treatment group compared to clopidogrel (2.89% versus 1.43%, p=.024) and a similar incidence between treatment groups in subjects < 75 years of age (0.83% versus 0.99%, not significant).[5]

Based on these data, I recommend prasugrel is contraindicated in patients with a prior history of TIA/CVA.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

CS-747 (prasugrel) is a new molecular entity that inhibits platelet activation and aggregation. Prasugrel is a prodrug that undergoes deacetylation by esterases to form a thiolactone (inactive), which is converted to the active moiety, R-138727, via the cytochrome P450 system. Similar to clopidogrel, the active metabolites of prasugrel irreversibly inhibit the $P2Y_{12}$ ADP receptor for the entire lifespan of the platelet.

2.2 Currently Available Treatment for Indications

Ticlopidine hydrochloride and clopidogrel bisulfate are FDA-approved adenosine diphosphate (ADP) receptor antagonists of the thienopyridine class that inhibit platelet activation and aggregation.

[4]**TAAL Clinical Study Report, Table TAAL.11.36, Number and Percentage of Subjects Reaching Primary, Secondary, and Other Efficacy Endpoints (CEC Adjudicated) (Subgroup Analysis by Prior TIA or Stroke), page 448.**
[5]**Sponsor, Risk Management Plan, page 22 of 97.**