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Quick Pulse

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FDA Cardiovascular and Renal Drugs Advisory Committee Recommends Approval of Lilly/Daiichi Sankyo's Effient (prasugrel)

Silver Spring, MD
February 3, 2009

With a 9 to 0 vote in favor of approval, the CardioRenal panel sent a strong message to the FDA that Lilly/Daiichi Sankyo's Effient (prasugrel) – a new anti-platelet agent – should be approved to treat acute coronary syndrome (ACS) patients. Panel members described prasugrel as a "scientific advance" and a "major advance" and superior to clopidogrel (Sanofi-Aventis's Plavix).

Lilly submitted prasugrel to the FDA on December 26, 2007, and is seeking approval for a 60 mg loading dose and a 10 mg maintenance dose – plus a 5 mg dose for certain subgroups of patients – for "the reduction of atherothrombotic events and the reduction of stent thrombosis in acute coronary syndrome patients with:

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

Lilly is also seeking this wording: "Effient has been shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke, and ***to prevent stent thrombosis***."

Prasugrel is a thienopyridine adenosine diphosphate (ADP) receptor antagonist that irreversibly inhibits the platelet P2Y12 receptor, inhibiting platelet activation and aggregation. It would compete primarily with Sanofi-Aventis/Bristol-Myers Squibb's Plavix (clopidogrel).

Initially, the FDA's Division of Cardiovascular and Renal Products wanted to skip an advisory committee altogether, deciding the efficacy of prasugrel is superior to clopidogrel and "in the interest of public health" did not want to "unnecessarily" delay approval. However, it appears that the safety questions delayed approval and eventually led to the advisory panel meeting.

It was an extremely friendly, positive panel, perhaps surprisingly so. The panel's biostatistician – who can usually be counted on to severely critique a sponsor's data – didn't parse the company's data, and there was no one on the panel who was very critical of the drug or the data. That might be because the night before the meeting the FDA scrubbed one of the panel members, Dr. Sanjay Kaul of Cedars-Sinai Heart Institute in Los Angeles, who is a regular member of the CardioRenal panel.

An FDA official said Dr. Kaul's removal from the panel was due to the "possibility of an appearance issue" – described as "a circumstance where a reasonable person could believe the participant is biased." The official said the Agency did not receive "sufficient information" on the appearance issue "until much later than what we would prefer, very late in the process, and the Agency was unable to go through the review process in sufficient time in order to make a decision on the member's participation in the meeting." Thus, Dr. Kaul was excluded.

The remaining voting members of the panel included 5 regular members: a biostatistician, a consumer rep, a nephrologist, and two cardiologists. There were also 4 temporary voting members: 2 cardiologists from the National Institutes of Health's National Heart, Lung, and Blood Institute (NHLBI) and 2 cardiologists from Tufts University. Missing from the panel were five prominent experts who are regular members of the committee: Dr. Robert Harrington from Duke, Dr. Henry Black from New York University School of Medicine, Dr. A. Michael Lincoff of the Cleveland Clinic, Dr. Darren McGuire of the University of Texas Southwestern Medical Center, and Dr. Jonathan Halperin of Mt. Sinai Medical Center in New York.

None of the usual safety officials from the FDA's Office of Surveillance and Epidemiology were at the panel. An FDA official said that was because the Center for Drug Evaluation and Research (CDER) has sufficient expertise to cover the safety issues itself.

A string of Lilly officials offered a detailed presentation on prasugrel that, with panel questioning, lasted more than four hours. Then, a single FDA official summarized the FDA findings in about an hour. It was almost like watching David and Goliath, but with Goliath winning.

The panel unanimously agreed that prasugrel is superior to placebo and superior to clopidogrel and that it has a favorable risk:benefit profile. The FDA posed a number of other non-voting issues to the panel, which could have led to restrictions on long-term use of prasugrel or for use in elderly patients, low-weight patients, CABG patients, and patients on a glycoprotein IIb/IIIa inhibitor – e.g., Johnson & Johnson's ReoPro (abciximab). The panel rejected all of these proposals, recommending a restriction only on use in patients with a prior stroke or transient ischemic attack (TIA), but agreeing that a dose reduction to 5 mg would be reasonable even without any clinical data to support that in elderly and low-weight (<60 kg) patients. The panel also rejected the idea of labeling the drug differently in STEMI vs. NSTEMI/UA patients.

While the panel agreed that the long-term consequences of a nonfatal hemorrhage are potentially serious – and bleeding is a concern with prasugrel – they determined that the benefits outweighed the risks. Low-weight patients and the elderly should be warned that they are at higher risk of bleeding with prasugrel, but the panel felt the benefit still outweighed the risk, and prasugrel should not be restricted or discouraged in these patients. In patients undergoing CABG, prasugrel should be avoided or discontinued for about seven days prior.

The panel also was not convinced there is a tumor promotion risk with prasugrel, advising the FDA to simply mention the cancer data in the adverse event section of the label, not with a more significant warning.

After the panel meeting, Lilly officials said they are ready to launch Effient (prasugrel) as soon as the FDA approves it, but they added that they expect some more back and forth with the Agency on both labeling and details of the Risk Evaluation and Mitigation Strategy (REMS) program.

THE FDA PERSPECTIVE

Efficacy

The FDA's issue with prasugrel isn't efficacy. That appears undisputed and superior to clopidogrel. On efficacy, the FDA reviewers, in briefing documents prepared for the committee, concluded, "Because TAAL (TRITON-TIMI-38 trial, the pivotal prasugrel trial) demonstrated prasugrel's superiority, not to a placebo but to an active drug (clopidogrel), prasugrel's efficacy seems beyond question."

- **Reduction in key endpoints.** "Prasugrel was associated with an 18% reduction in (a composite of cardiovascular death, nonfatal MI, or nonfatal stroke at 12 months) in a UA/NSTEMI population, a 19% reduction in an all ACS population (p=0.0004), and a 21% reduction in the STEMI population (p=0.019)…The difference (vs. clopidogrel) was evident within the first day and either maintained (STEMI) or widened progressively (NSTEMI/UA) through more than a year of follow-up. Most of the first events were MI (77%), and that is where the difference between the groups was most clear, but CV death (20% of events) trended in favor of prasugrel (as did all-cause mortality)."
- **Benefit is front-loaded and mostly in a reduction in nonfatal MI.** Dr. Ellis Unger, deputy director of the FDA's Division of Cardiovascular and Renal Products, called the front-loading "a bit unusual," but he noted that a landmark analysis found, "Even though the events are front-loaded, the superiority is not due solely to the early benefit."
- **Reduction in stent thrombosis.** In PCI patients, definite/probable stent thrombosis with:
  - Bare metal stents was 1.1% with prasugrel and 1.9% with clopidogrel (40% reduction, p=0.01).
  - Drug-eluting stents was 0.8% with prasugrel and 2.0% with clopidogrel (62% reduction, p<0.001).
- **Advantage begins immediately** for STEMI patients, reaches its maximum at 18 days, and remains unchanged thereafter. "In the NSTEMI/UA population, ~60% of the cumulative treatment advantage occurred within 3 weeks, but the delta continues to increase fairly linearly through

450 days, supporting the concept that prasugrel's treatment advantage persists throughout the entire study."

- **No prevention of stroke was demonstrated.** "In estimating prasugrel's effect on stroke…the evidence of effectiveness is nil."

FDA View of Prasugrel Efficacy in TAAL

Measurement	Prasugrel n=6,813	Clopidogrel n=6,795	p-value
Composite of CV death, nonfatal MI, nonfatal stroke			
Primary endpoint: All ACS patients	9.4%	11.5%	<0.001
UA/NSTEMI patients	9.3%	11.2%	0.002
STEMI patients	9.8%	12.2%	0.019
Patients with prior stroke/TIA	17.9%	13.7%	Nss, 0.15
Definite/probable stent thrombosis by ARC definition in all ACS patients	0.90%	1.87%	<0.001
CV death			
All ACS patients	2.0%	2.2%	Nss, 0.307
UA/NSTEMI patients	1.8%	1.8%	Nss, 0.885
STEMI patients	2.4%	3.3%	Nss, 0.129
Patients with prior stroke/TIA	3.4%	5.9%	Nss, 0.27
Nonfatal MI			
All ACS patients	7.0%	9.1%	<0.001
UA/NSTEMI patients	7.1%	9.2%	<0.001
STEMI patients	6.7%	8.8%	0.016
Patients with prior stroke/TIA	11.1%	9.8%	Nss, 0.61
Nonfatal stroke			
All ACS patients	0.9%	0.9%	Nss, 0.93
UA/NSTEMI patients	0.8%	0.8%	Nss, 0.922
STEMI patients	1.2%	1.1%	Nss, 0.77
Patients with prior stroke/TIA	5.7%	0.8%	0.002

Safety

The three key safety issues with prasugrel, according to the FDA, are cancer, bleeding, and how the drug is affected by a proton pump inhibitor (PPI).

1. Cancer. The question – according to both Lilly and the FDA – is whether prasugrel stimulates tumors, not that it causes them (is carcinogenic). Some FDA officials appear very concerned that long-term use of prasugrel can spur tumor growth.

FDA View of Prasugrel Safety in TAAL

Measurement	Prasugrel	Clopidogrel	p-value
All-cause death	2.76%	2.9%	---
Discontinuations for adverse events	7.2%	6.3%	---
Discontinuations for bleeding	1.6%	0.9%	---
Respiratory failure	0.22%	0.09%	0.050
Hypotension	0.21%	0.06%	0.019
Atrial flutter	0.18%	0.06%	0.046

The FDA accused Lilly of being "dismissive" of any association between prasugrel and cancer, saying Lilly claimed, "There is no evidence that use of prasugrel is associated with a higher risk of cancer."

Two issues have been contentious between Lilly and the FDA on the cancer risk:

a. The role of ascertainment bias in creating the imbalance in malignancies. FDA reviewers rejected Lilly's contention that the imbalance was due to this.

b. Whether or not non-melanomatous skin cancers should be considered in the analyses. FDA reviewers explained, "When all tumors, including non-melanomatous skin cancers are considered, the RR (relative risk) is only 1.2 and not statistically significant…If in fact prasugrel is causally related to the excess cancers, a tumor stimulatory effect is much more likely."

The FDA reviewers determined, "Cancer was somewhat more commonly reported in the prasugrel group than in the clopidogrel group. The strength of association depends largely on whether or not non-melanoma skin cancers are included in the analyses…Although the numbers of events are small, the imbalance in cancer deaths is concerning. The fact that similar proportions of subjects with cancer had a fatal outcome is not reassuring. Moreover, the additional deaths in the prasugrel group argue against the influence of ascertainment bias, given that ascertainment of death should be complete and unbiased."

Dr. Unger told the panel, "There is no evidence that prasugrel causes cancer. Carcinogenesis is not an issue, (but) the time course of discovery of new cancers and

FDA View of Prasugrel Association with Cancer

Cancer	Prasugrel	Clopidogrel	p-value
Colorectal	19 patients	8 patients	RR=2.4
Breast	5 patients	1 patient	RR=5.0
Lung	8 patients	2 patients	RR=4.0
Prostate	16 patients	9 patients	RR=1.8
New non-benign neoplasms	1.82%	1.54%	RR=1.18
New non-benign neoplasms with non-melanomatous skin tumors excluded	1.70%	1.29%	RR=1.31 (p=0.09)

Prasugrel and Cancer: Reassurance vs. Concerns

Reasons to be reassured	Reasons to be concerned
Non-clinical data negative	Excess malignancy deaths are concerning and cannot be explained by bias
No putative mechanism of action	Risk of cancer would seem to be continuous during therapy, whereas benefit is largely front-loaded
Multiplicity of safety analyses – potential for false positive finding	
From mechanistic standpoint, no reason to exclude non-melanomatous skin cancer; signal largely disappears if all skin cancer included	

worsening of existing cancers in TRITON could be consistent with tumor stimulation…One could postulate that there is an effect through platelets, but one would expect to see similar findings with clopidogrel, and (we) looked through the clopidogrel data and didn't really see any effect there in terms of tumors. (And) there is no signal in animal studies. There was a trend in favor of hepatocellular carcinoma, but it was not statistically significant…Originally, the sponsor held strong to the belief that the imbalance was due to ascertainment bias. And on the face of it that made sense…Maybe excess bleeding was leading to more diagnosis of cancer. We looked pretty carefully at this within organ systems…The malignancy deaths blow away the question of ascertainment bias."

2. Bleeding. The FDA found bleeding is "clearly worse on prasugrel" than on clopidogrel, and bleeding with prasugrel "was most frequent around the time of the index PCI, and much more frequent following CABG. All types of bleeding were more frequent on prasugrel than clopidogrel." About one-third of non-CABG bleeding with prasugrel occurred in the first day, and nearly 50% occurred within 10 days. However, the reviewers concluded that excess bleeding "is obviously unwelcome, (but) it does not seem to outweigh prasugrel's benefit…When evaluating the risk:benefit profile for a population, this seems like a reasonable trade."

FDA reviewers found, "The prasugrel-associated bleeding risk was particularly malignant in subjects who underwent CABG …Prasugrel should not be the drug of choice for patients in whom CABG surgery is anticipated. From a practical standpoint, prasugrel is not well-suited for pre-treatment of patients in whom coronary anatomy is unknown." Dr. Unger said, "The bottom line is we don't have enough data to say there is a point in time where it is safe to have CABG (after prasugrel). I would point out that the half-life of the platelet is more important that the half-life of the drug. It is hard to imagine that 10 days after the drug, the drug could be having any effect at all. I doubt it does…It is difficult to say when it is reasonable to have a CABG after the drug."

Bleeding Risk with Prasugrel

Hemorrhages	Prasugrel	Clopidogrel
Fatal bleeding	0.36%	0.09%
Life-threatening bleeding (including fatal)	1.44%	0.94%
TIMI major bleeding (including life-threatening)	2.43%	1.84%

Increased Bleeding Risk with Prasugrel

Type of bleeding	Additional bleeds per 1,000 patients treated with prasugrel
All bleeds	2.4
TIMI life-threatening bleeds	4.3
TIMI major bleeds	5.1
TIMI minor bleeds	5.4
TIMI minimal events	19.4
Total TIMI bleeds of any magnitude	30
TIMI bleeding events associated with a Hg decrease of 3 g/dL	10.5
TIMI bleeding events associated with a Hg decrease of 5 g/dL	5.1

After CABG, the FDA found the major risk factors for major bleeding with prasugrel are:

- **Prior TIA/stroke** (p=0.0016). "Prasugrel patients with a history of stroke/TIA had primary endpoint events nearly twice as often as other prasugrel subjects."
- **Weight <60 kg** (p=0.0027). "Quintile analyses of primary endpoint events reveal a fairly uniform advantage of prasugrel over clopidogrel regardless of weight and suggest no strong relationship between weight and bleeding risk. In contrast, a dichotomous analysis demonstrates a statistically significant increase in bleeding risk for patients <60 kg." Dr. Unger added, "A quarter of the patients (in TAAL) weighed 60 kg. Patient weights were rounded. So, labeling ≤60 will be different from <60. We pointed this out to the company recently, and they are cogitating on it."
- **Treatment with prasugrel** (p=0.0106).
- **Use of GPIIb/IIIa inhibitors** (p=0.0298).
- **Age >75** (p=0.0464). An FDA reviewer wrote, "A reduction in dose might lessen bleeding in patients over 75 years of age, (but) the impact of dose reduction on efficacy is unknown and could be unfavorable. Therefore, the Clinical Pharmacology team opined against a dose reduction for patients over the age of 75." Dr. Unger added, "Older patients have more bleeding. It is not the relative risk of bleeding that is higher but the outcome of bleeds in older patients…It is the result of bleeding, not the relative risk of bleeding."

3. Drug-drug interaction. The prasugrel formulation used in the clinical trials could be affected by a proton pump inhibitor (PPI) – decreasing bioavailability and increasing bleeding – and many patients on an antiplatelet inhibitor use PPIs either chronically or sporadically. However, the prasugrel formulation that will be marketed has a lower ratio of salt to free base than the trial formulation (25% vs. 42%-87%), and the consensus at the FDA was that it would be "shortsighted to delay or deny approval because of the form conversion issue."

FDA reviewers explained that the initial formulation used the free base of the drug substance, but Lilly discovered that the hydrochloride salt form of the drug substance had better bioavailability at higher gastric pH, "Gastric acidity is germane to patients in the ACS setting because a substantial fraction uses PPI or H_2 receptor antagonists to raise gastric pH. Thus, with the concurrence of the (FDA), the sponsor changed the manufacturing process to produce the hydrochloride salt form of the drug substance. Late in development, near the time that TAAL was completed, the sponsor discovered that there was significant in-process form conversion from the salt form to the base form…(The FDA) review team has serious concerns regarding form conversion, in that the

manufacturing process fails to ensure consistent product quality, and approval of a product with significant conversion sets a poor precedent…(And a) prasugrel product with high salt to base conversion is not bioequivalent to product with low or medium conversion. Conversion affects the pharmacokinetics of the product when it is co-administered with a PPI (and, by extension, possibly a H_2 receptor antagonist)…This can be conceptualized as a delay of approximately 20 minutes in achieving maximal inhibition of platelet aggregation. The delay would affect the loading dose but would have no effect on maintenance doses."

Why does the FDA care about salt to base conversion? Dr. Unger told the panel, "The FDA ***may refuse to approve*** an application (if)…The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability."

Dr. Unger's conclusions on salt to base conversions were:

- Bioequivalence in AUC for all levels of product conversion (5%-70%) with or without PPIs.
- In the absence of PPI, bioequivalence in C_{max} for all levels of product conversion, 5%-70%.
- With concomitant PPI use, ***bioinequivalence*** in C_{max} for all levels of product conversion.
- Ramifications:
  - Inequivalence in C_{max} is tantamount to delay in reaching maximal effect, as determined by platelet aggregation.
  - The delay in reaching maximal effect would affect loading dose and could impact peri-procedural events.
  - Delay would not affect daily maintenance therapy.
- In the absence of PPI use:
  - Form conversion in the range of 5%-70% has no effect on bioavailability.
  - ~60% of subjects in TRITON were not using PPIs at any time. Thus, for non-PPI users, safety and efficacy are well-characterized.

Risk:benefit

The bottom line for the FDA is always **risk:benefit**, and the FDA appears to believe that the benefits of prasugrel outweigh the risk. Thus, the question appears to be labeling, not approval. For prasugrel, the FDA concluded prasugrel (vs. clopidogrel) results in a:

- Net reduction of 22 CV events (20 MIs and 2 cardiovascular deaths) per 1,000 ACS patients.
- Net increase of 2 fatal bleeding events, 4 TIMI life-threatening events, and an overall excess of 5 TIMI major bleeding events per 1,000 ACS patients treated.

In summary, the FDA reviewers concluded, "Relative to clopidogrel, prasugrel provides a 25% relative reduction in nonfatal MI without negatively affecting survival or increasing ICH (intracranial hemorrhage). There is much data to indicate that decreasing the frequency of MIs, even silent ones, has a favorable effect on survival, congestive heart failure, etc., although this is difficult to prove vigorously. This probable benefit, however, is weighed against a small excess of bleeding events that were emergent but did not have long-term consequences. An additional point to consider is that the risk:benefit profile might be improved in the future, if patients at higher risk of bleeding and its consequences (patients over 75 and those with prior stroke or TIA) are excluded from treatment."

Dr. Unger told the panel, "For 1,000 patients treated with prasugrel instead of clopidogrel:

- 24 endpoints were prevented (21 nonfatal MIs, 3 CV deaths, no strokes).
- 10 excess TIMI major or minor bleeding events occurred (2 bleeding deaths, 3 nonfatal TIMI major bleeds, 5 TIMI minor bleeds).
- Cancer causality is uncertain but potentially a continuing risk.

Labeling

The FDA found a number of issues that reviewers recommended be addressed in labeling. These included:

- **Asians.** Interestingly, there appears to be an increased prasugrel effect in Asians, which would suggest they need reduced dosing. An FDA reviewer concluded, "Exposure to prasugrel's active metabolite…was approximately 40%-45% higher in Asian vs. Caucasian subjects," even after adjusting for body weight and other covariates, so reviewers recommended that label warn that "prasugrel should be administered with caution in patients of Asian descent."

- **Duration of use.** Given the concern about cancer, as well as increased bleeding risks with prasugrel over time, an FDA reviewer initially recommended "limiting therapy with prasugrel to short-term use (i.e., one week)." A second reviewer recommended "duration of treatment limited to 30 days." The final FDA staff recommendation was against limiting duration because there is no proven switching strategy from prasugrel to clopidogrel.

The final reviewer explained, "It is important to recognize that the population for whom this would be approved, i.e., patients with recent PCI, predominantly with stents, should probably not discontinue their thienopyridine, as this may lead to stent thrombosis, which is associated with poor outcomes. Thus, if the label were to encourage a limited duration of use, it would be critical for patients to switch seamlessly to another approved inhibitor of ADP-induced platelet aggregation, which presents practical problems of its own. Because continued therapy is critical, and because the risk management strategy

of 'switching' has not been tested, this reviewer is not enthusiastic about limiting length of use."

The final reviewer concluded, "There is no clear rationale for selecting a specific length of time. Moreover, mandating or encouraging a limited duration of therapy requires switching to another drug, and this type of risk management strategy has not been tested in the post-PCI setting. By avoiding use of prasugrel in patients at higher risk of bleeding (patients over the age of 75, patients with prior stoke or TIA, and patients who are planned to undergo CABG or other surgery), much of the excess bleeding risk will have been avoided. In terms of cancer risk, lacking definitive data, the strategy of limiting length of use seems ill advised."

- **Hepatic impairment.** The Clinical Pharmacology/Biopharmaceutics review team argued that prasugrel should be contraindicated in patients with severe hepatic impairment due to the potential risk of bleeding.

- **Drug-drug interactions.** A reviewer recommended that "caution should be exercised" when prasugrel is co-administered with aspirin, heparin, and/or warfarin, but no contraindication with a PPI was suggested.

- **5 mg dose.** The FDA found no data to support approval of this dose, and there is concern at the Agency that, though 5 mg might be safer in terms of bleeding, it also could be less effective.

- **Indication.** The reviewers initially recommended that use be restricted to "prevention of MI," but opposition to a claim for prevention of stent thrombosis without another study has been lifted.

- **TIA/Stroke patients.** The FDA reviewers recommended a contraindication for prasugrel in these patients. They found the hazard ratio for the primary endpoint in these patients was "unfavorable for prasugrel, going against the grain of the study as a whole…Specifically, 6.5% of subjects in the prasugrel treatment group experienced a stroke on study (2.3% ICH; 4.2% thrombotic) compared to 1.2% in the clopidogrel treatment group (0% ICH; 1.2% thrombotic), for an HR of 5.64."

- **Age.** The FDA review team concluded that the risk of bleeding is clearly higher with prasugrel, and the label should reflect that the risk of fatal and life-threatening bleeding is higher in patients ≥age 75, but they did not support the 5 mg dose Lilly proposed.

- **CABG patients.** Patients undergoing CABG, or "by extension, probably any surgical procedure," should be warned of the risk of bleeding.

- **Weight ≤60 kg.** Whether there should be labeling relating to weight apparently is still under discussion at the FDA.

- **Cancer warning.** FDA reviewers recommended a warning label about excess cancers and cancer deaths, suggesting that consideration be given to alternative agents in patients with known cancer, and urging a postmarketing study, though acknowledging that an ongoing, ~13,000 patient outcomes study – of 5 mg prasugrel vs. clopidogrel in UA/NSTEMI patients not getting PCI – may suffice.

Risk management

The FDA reviewers are proposing a REMS but not an onerous one. The proposal includes:

- A Medication Guide.
- A Communication Plan to healthcare providers including:
  - Appropriate patient selection, emphasizing that prasugrel should not be used in patients older than 75, or patients with a prior history of TIA or stroke.
  - The risk of bleeding and instructions on management.
  - Information on the potential risk of malignancies and need for monitoring.

Postmarketing requirements

These are also not very severe:

- Possibly a randomized trial looking at cancer rates, though this may be satisfied by an ongoing trial.
- A stent thrombosis registry.

Unsettled FDA issue

The FDA reviewers said there is ongoing discussion at the FDA regarding the need to initiate prasugrel in an inpatient setting.

Criticism of Lilly research

Interestingly, FDA reviewers were critical of Lilly for:

- **Dose selection not clear.** One wrote, "The rationale for dose selection for the Phase III study seems only questionably adequate…The sponsor's decision (to use a 60 mg loading dose and 10 mg maintenance dose) was based on weak trends in the data and a handful of events, rather than statistical certainty. It is possible that a lower prasugrel dose would have resulted in similar efficacy with less risk of bleeding, but the development program does not assess this possibility."

- **Independent angiographic core lab not initially used.** Lilly apparently tried to say that a core lab was not required for stent cases. The FDA guidance said the Agency "strongly recommends" a core lab, which to almost anyone means it is a requirement. Eventually, a selected number of cases were sent to a core lab, and the results "appeared to support the reliability" of the original findings, but the process certainly didn't win friends at the FDA.

- **Cancer analysis inadequate.** The FDA reviewers said, "The sponsor's initial description and analysis of cancer adverse events was difficult to interpret: (1) the distinction between pre-existing neoplasms and treatment-emergent neoplasms was not always clear; (2) there was little attempt to categorize neoplasms as malignant or non-malignant; and (3) there was little emphasis on categorization of cancers by organ or organ system."

THE LILLY PERSPECTIVE

Dr. J. Anthony Ware, vice president, Lilly Research Laboratories, not surprisingly, declared, "We believe this (prasugrel) should be approved." He urged the panel to keep in mind the company's central hypothesis for the prasugrel research program: "A thienopyridine (prasugrel) with a faster, higher, and more consistent (i.e., with fewer poor responders) inhibition of platelet function – any or all of these factors – will produce important clinical benefits for the ACS patient."

Dr. Ware said the company had four key points to make:

1. **Prasugrel addresses an unmet need.** Dr. Eugene Braunwald of Harvard, chairman of the TIMI Study Group at Brigham & Women's Hospital, said 1.24 million UA/NSTEMI patients and 0.33 million STEMI patients are admitted to the hospital in the U.S. each year.
2. **Prasugrel is superior to clopidogrel in preventing CV events, including stent thrombosis.** Dr. Braunwald pointed out that clopidogrel has a "modest antiplatelet effect" with high interpatient variability and a delayed onset of action.
3. **There is no credible evidence that prasugrel is carcinogenic or promotes the growth of tumors.**
4. **The benefit:risk profile is favorable**, and the company has a risk management program "to effectively manage the risk of bleeding in the appropriate patients."

Dose selection. Dr. Jeffrey Riesmeyer from Lilly's Prasugrel Product Team discussed the prasugrel clinical pharmacology and dose selection. He stressed that metabolism is a key difference between prasugrel and clopidogrel, noting that prasugrel, compared to clopidogrel has:

- More efficient and less variable activation.
- No clinically relevant interactions with CYP2C19 variants or inhibitors.
- Higher active metabolite concentrations after the loading dose.
- More effective platelet inhibition.
- Superior response.
- A predictable PK/PD relationship that allows targeted PK.

Risk:benefit. Dr. Elliott Antman of Harvard Medical School reviewed the findings of the pivotal prasugrel trial, TRITON-TIMI-38 (TAAL). He cut to the chase right away, balancing risk and benefit and emphasizing the reduction in MIs and stent thrombosis:

- 24% decrease in the number of MIs with prasugrel vs. clopidogrel ($p<0.0001$).
- 26% decrease in large MIs (≥5xULN) ($p=0.0001$).
- 42% reduction in CV death after MI ($p=0.02$).
- ~50% reduction in stent thrombosis.

Dr. Antman speculated on how prasugrel might be used in clinical practice:

- 80% get 10 mg maintenance dose.
- 16% get reduced maintenance dose (weight <60 kg or age ≥75 years, consider reduced dose).
- 4% avoid prasugrel in patients with prior CVA or TIA.

He also offered two possible ways to reduce the bleeding risk with prasugrel:

- Using the radial vs. femoral access site for PCI.
- Lower the dose in patients ≥age 75 or weight <60 kg.

Risk:Benefit of Prasugrel in TAAL

Measurement	Prasugrel	Clopidogrel	p-value	Hazard ratio	Other
Efficacy					
Primary endpoint: Composite of CV death, stroke, or MI at 450 days in all ACS patients	9.9%	12.1%	0.0004	0.81	NNT=46
TIMI major non-CABG bleeds	2.4%	1.8%	0.03	1.32	NNH=167
MI (fatal and nonfatal) at 3 days	4.3%	5.2%	0.008	0.81	---
MI (fatal and nonfatal) at 450 days	3.4%	4.8%	<0.0001	0.69	---
Safety					
TIMI major bleeds	1.8%	2.4%	0.03	1.2	NNH=167
Life-threatening bleeds	0.9%	1.4%	0.01	1.52	---
Nonfatal bleeds	0.9%	1.1%	Nss, 0.23	---	---
Fatal bleeds	0.1%	0.4%	0.002	--	--
ICH	0.3%	0.3%	Nss, 0.74	---	---
Net benefit endpoints – all favoring prasugrel					
Death/MI/CVA/major bleed	12.2%	13.9%	0.004	0.87	---
Death/MI/CVA	10.7%	12.7%	---	0.83	---
Death/MI/CVA/transfusion	13.5%	14.8%	---	0.90	---
Death/MI/CVA/major or minor bleed	14.0%	15.2%	---	0.91	---

Dr. Antman concluded: "On behalf of patients with ACS and the clinicians who have to care for them, I submit the benefit with prasugrel is real and a significant advance in the management of ACS patients. When we have an effective drug, we can find ways to use it even more safely."

Cancer. Dr. William Macias, a nephrologist and the senior medical director for Cardiovascular and Acute Care at Lilly, stressed that Lilly and the FDA's Division of Oncology Drug Products agree:

- "There are no data in TRITON to support a belief that prasugrel is a (cancer) 'promoter' in humans.
- "Cancers diagnosed in TRITON are likely incidental and the finding is probably spurious.
- "No neoplasm analyses based on TAAL can be conclusive."

Dr. Macias said the FDA and Lilly agree prasugrel is not a carcinogen, noting that:

- Prasugrel was not genotoxic in *in vitro* and *in vivo* tests.
- 2-year toxicology studies in rodents show no increased development of any malignant cell type.
- Benign hepatocellular adenoma was noted in mice, but the FDA admitted, these tumors are common in mice… and not considered relevant to human risk.
- Additional studies requested by the FDA show prasugrel does not stimulate tumor growth.

Dr. Macias argued that non-melanomatous cancers should be included in any analysis of the relationship of prasugrel and cancer because:

- Preclinical data do not support exclusion of any tumor type.
- Exclusion of any tumor type is post hoc and subject to bias.
- Detecting a signal for tumor promotion should assess a wide variety of tumors.
- The biology of skin cancer is similar to other cancers.
- Systemic exposure to some carcinogens results in skin cancers (e.g., arsenical poisoning).
- Skin tumors are sensitive to known tumor promoters and are the most common laboratory model of tumor promotion.

He said Lilly's recommendations for labeling of neoplasms are:

- Should include information that:
  - Reflects the uncertainty of the observation.
  - Is useful to the prescriber.
  - Does not create unfounded alarm for physicians or patients.
  - Does not have equal prominence to the risk of bleeding. Evaluation of GI bleeding should be undertaken because it may unmask previously undiagnosed cancers comparable to warfarin.
- Specific labeling language should:
  - Be included in the adverse event section listing.
  - Not restrict treatment duration.

Elderly and low-weight patients. Dr. Macias also addressed the issue of dose adjustments with prasugrel in patients weighing <60 kg or ≥age 75 from 10 mg to 5 mg, for which there are no clinical data. He said the rationale is:

- Patients <60 kg or ≥75 years had higher exposure to prasugrel active metabolite.
- Increased exposure is associated with increased bleeding during the maintenance phase.
- Reduction in dose would maintain an estimated exposure similar to the general population and a reduced risk of bleeding.
- Reduction in dose would maintain efficacy.

Prasugrel and Cancer

Measurement	Prasugrel	Clopidogrel
Newly diagnosed cancers		
Incidence	1.39% (Nss, 0.30)	1.19%
Malignancy deaths	31.9%	28.8%
Patients with pre-existing non-benign neoplasms		
Malignancy deaths	2.9%	3.3%
Use of anti-neoplastic agents	5.1%	6.1%

TIMI Major Bleeding with Prasugrel by Weight and Age

Measurement	≥age 75	<age 75	Weight ≥60 kg	Weight <60 kg
Non-CABG major bleeding (after 3 days)	4.82%	2.28%	1.21%	3.62%

Lilly Rationale for Prasugrel Dose Adjustments

Measurement	Prasugrel	Clopidogrel	p-value	HR
Patients <age 75, ≥60 kg, and no prior TA/stroke				
CV death, nonfatal MI, or nonfatal stroke	8.3%	11.0%	<0.001	0.75
TIMI major bleeding	2.0%	1.50%	Nss, 0.17	1.24
Patients age ≥75				
CV death, nonfatal MI, or nonfatal stroke	17.2%	18.3%	Nss, 0.596	0.94
TIMI major bleeding	4.2%	3.4%	Nss, 0.24	1.36
Patients age ≥75 with diabetes				
CV death, nonfatal MI, or nonfatal stroke	16.8%	25.0%	---	---

Risk management. The Lilly risk management plan (REMS), as Dr. Macias outlined it, would include:

- Prescriber brochure.
- Extensive pharmacovigilance plan with assessment of spontaneous and clinical trial adverse event reports, automated signal detection in spontaneous report databases, aggregate data reviews and periodic safety reporting to agencies, pharmcoepidemiology studies in the U.S. and Europe, and information from prospective clinical research.
- A letter to healthcare professionals at launch, emphasizing the indicated population, contraindications and warnings, benefit:risk in subpopulations, and management of bleeding risks.
- Patient Medication Guide.
- Package insert.
- Completion of the ongoing randomized TRILOGY trial in >10,000 patients globally, treated for up to 30 months, with 5 mg used in the very elderly and low body weight patients, with collection of neoplasm data.
- A U.S. prospective observational study that should capture patient-level data on effectiveness and safety outcomes and which would link inpatient and outpatient data for up to 18 months.

Concluding the Lilly presentation, Dr. Braunwald said, "I would very much like to be able to offer this to my patients."

Panel Questions for Lilly and FDA Experts

Some panel members – and even FDA officials – were interested in finding out how patients would fare if started on prasugrel and then switched to clopidogrel at 30 days or some other later time point. Panel member Dr. Richard Cannon, a cardiologist from NHLBI asked, "At some time point would it be defensible to switch from prasugrel to clopidogrel?" Dr. Antman discouraged that strategy, citing the results of the ACAPULCO trial, which he said showed that patients given a 900 mg loading dose of clopidogrel and then crossed over to either clopidogrel 150 mg (twice the usual maintenance dose) or 10 mg prasugrel, the platelet inhibition was greater in the prasugrel patients, "We have absolutely no evidence it would be an effective way to treat a patient to switch from prasugrel to clopidogrel. The crossover data (in ACAPULCO) is that there is a risk of losing the benefit…All we would have accomplished is putting the patient at the risk of the events prevented in the beginning but putting them at risk later."

Dr. Robert Temple, director of the FDA's Office of Medical Policy and director of the FDA's Office of Drug Evaluation I, pressed this point, asking if you could use prasugrel for a period and then switch, at least in people you were worried about bleeding, "and still get whatever benefit clopidogrel has." He repeated the question, "If someone switched from prasugrel to clopidogrel, they would do it for less bleeding. Let's say you wanted to do that – I'm not advocating it. Would there be any difficulty in, say, switching on Day 30?" The Lilly experts never answered this directly, emphasizing instead that platelet inhibition would be less with clopidogrel than prasugrel. Dr. Antman said, "There is a rebound that is higher with clopidogrel than with prasugrel…so for some period of time while the crossover is occurring, the patient would be at increased risk of events." Dr. Unger added, "I worry about the logistics of switching."

Asked about the possibility of down titrating at **some** *point in time – perhaps from prasugrel to clopidogrel*, Dr. Antman said, "I don't see the rationale for that…It is an untested strategy to crossover to a less potent inhibition."

Asked whether it would be better to use clopidogrel in patients who can't take 10 mg of prasugrel rather than a 5 mg prasugrel dose, since that dose does not have clinical data, Dr. Antman said the PK/PD modeling have convinced him that the 5 mg prasugrel dose is a better choice, "I would give prasugrel because I would have no way of knowing if you took a higher risk individual and gave clopidogrel if they would fall in a category where I effectively gave them no antiplatelet activity. So, I would prefer to give prasugrel because we have a body of evidence that makes sense to me…Please remember you can take a patient who is an extensive metabolizer to clopidogrel and turn them into a reduced metabolizer of clopidogrel by giving them another drug (e.g., ketoconozole). That is not seen with prasugrel, which is an additional argument to buttress my decision." Lilly's Dr. Macias added, "The reason you can dose adjust down is you have higher exposure in patients over 75, and when you dose adjust down, you stay in the range of what you see in the general population without losing much of the response…(The) data tell us that 5 mg in the elderly should be associated with a relatively low non-responder rate."

Asked for more information on prasugrel in TIA patients, Dr. Macias said, "Certainly, there is more bleeding in those patients, but the real issue is they have more stroke, and the mechanism for that is not known. It is not hemorrhagic stroke; it is ischemic stroke." Dr. Antman added, "We certainly would not want to give prasugrel to an individual with a prior stroke."

How long should a patient wait after stopping prasugrel before having CABG? The panel spent a long time trying to figure this out. The rule of thumb with clopidogrel is 5 days, and, Lilly speakers suggested 7 days would probably be sufficient for prasugrel, and the panel appeared to accept that.

Asked about the cancer deaths (27 prasugrel vs. 19 clopidogrel according to the FDA, and 21 vs. 17 by Lilly's count), a Lilly expert, Dr. Philip Shine of the University of Oxford, said, "The take home message for me is that you'll see a difference in malignancy-related deaths in the database of

13,600 patients. The difference is 21 vs. 17 – four patients out of 13,000 is what we are talking about…And one has to recognize that the presence of pre-existing cancer or risk factors that might lead to cancer were not part of the randomization scheme and were not controlled for. Even so, we are talking about 4 deaths between the 2 arms, and for me that is not a terribly meaningful number." Dr. Macias added, "21 vs. 17 is the end of the randomized period. The additional deaths came during the extended follow-up when we followed the cohort identified as having an event during the trial. That follow-up is beyond the trial." Panel member Dr. James Neaton, a biostatistician from the University of Minnesota School of Public Health, said, "My question is whether I should pay any attention to the follow-up study…and I'm becoming more convinced it (new neoplasms) is less important."

Dr. Shine later added, "The timeframes here are relatively short. How long does it take a cancer to grow and kill? Dr. Richard Peto (famed Oxford statistician) addressed this with the SEAS trial (in which he disputed the finding that Merck/Schering-Plough's ezetimibe causes cancer)...(finding) that it was implausible that a large number of tumors over a broad range of tumors could have emerged and killed within a very finite period of a person's life. I approach it perhaps more biologically. From the initiation of a transforming event to a tumor you might be able to find, there have to be about 30 doublings. And for adult solid tumors the doubling time is about two months. To kill, you need another 10 doublings. The latency period generally recognized for most solid tumors in adults is at least five years. Smoking is much longer…The American Cancer Society guidelines for colorectal screening is 10 years not 10 months."

Asked what advice clinicians should be given if prasugrel is approved, Dr. Antman said, "If I were on the guidelines committee…I think we would have a pretty strong opinion (in favor of) mentioning prasugrel superiority over clopidogrel, and the benefit:risk has to be brought to the attention of clinicians."

Asked how he would deal with the age cutoff, Dr. Macias said, "The major concern we have is the very elderly, not just that they tend to bleed more, but the sequelae of the bleeds is worse. Most of the TIMI major bleeding is not life-threatening hemorrhage except in the elderly."

PUBLIC WITNESSES

Dr. W. Douglas Weaver, president of the American College of Cardiology (ACC), told the panel that "prasugrel offers a strong treatment option when prescribed to the right patient." The ACC's concern is that it be used appropriately and safely in the real-world setting.

Dr. Weaver said there is a "yin and yang" to prasugrel. On the yin side, prasugrel has been shown to be effective, showing clinically meaningful reductions in recurrent nonfatal MI, rehospitalization for ischemia, and stent thrombosis, "On the yang side of the equation…we are concerned about whether the added bleeding risk, particularly fatal bleeding, can be mitigated."

Dr. Weaver said he has two questions:

1. The division of patients into those unlikely to benefit and those at high risk of bleeding was post hoc analysis. "Can we be sure that the same findings would be present in a prospective cohort of patients given the drug?"
2. With direct-to-consumer advertising and detailing of physicians, he is worried that not only cardiologists but also primary care doctors may not get properly educated about appropriate patient selection for prasugrel. "Can we be sure that a product label will be adequate to prevent the prescription of this drug to the subset having these risk factors? Let's be certain that we track the usage so that the appropriate patients receive the appropriate treatments."

Therefore, Dr. Weaver recommended that, if prasugrel is approved, additional postmarketing studies be conducted to ensure its safety and that it is prescribed appropriately. He said the FDA was willing to work with Lilly and the FDA to help conduct such studies and/or a registry.

Dr. Victor Serebruany of Johns Hopkins University, who has a patent related to prasugrel from which he gets royalties from Lilly, was critical of:

- ***The definition of MI used in the TRITON trial.*** He claimed the definition was changed during the trial and that it included peri-procedural MIs, such as chest pain and unstable angina, inflating the clopidogrel event rate. "Not all MIs are born equal," he declared, "What this means is: There is indeed an early benefit (to prasugrel), but the benefit does not expand later, so when we talk of net clinical benefit, we are not talking apples and oranges but watermelons and raspberries."
- ***The cancer signal may be real.*** He suggested that the "huge" prasugrel platelet inhibition could "break the barrier between the tumor and the platelets" that keep it confined, so "silent tumors start to disseminate."

Dr. Serebruany joked, "There is an ATM machine downstairs named TRITON. It is where the money goes."

Panel Consideration of FDA Questions

Question 1. Benefit. The panel recommended unanimously that:

- The primary endpoint in TRITON was reasonable.
- Prasugrel is superior to placebo.
- The data support an overall claim for the ACS patient population.
- The results support a superiority claim for prasugrel over clopidogrel.

FDA officials asked if STEMI and NSTEMI/UA patients should be labeled differently (as separate indications) or if prasugrel should get a broad ACS label. The acting panel chair, Dr. Marvin Konstam, a cardiologist from Tufts University, said the risk:benefit looks like it may be different in the two patient populations, but he did not recommend different indications, just a description of the findings in the label, "The efficacy findings apply to the entire population, and the labeling ought to reflect this was a single trial with efficacy seen in the entire population. I wouldn't draw that line (between STEMI and NSTEMI), (but) I think it would be reasonable to put some information that these two populations differ pathophysiologically, and there may be differences in the risk:benefit ratio in the two populations over time, in the label."

Panel member comments included:

- *Dr. Cannon, NHLBI:* "I think over time that peri-procedural MIs do matter. Lost muscle does mean lost cardiac function and will lead to heart failure over time."
- *Dr. Neaton, a biostatistician:* "I'm reassured that the treatment benefit was present for clinical MIs reported by investigators."
- *Chair:* "It looks like the biggest bang for the buck in STEMI patients is in the beginning, whereas (the benefit) is more continuous for NSTEMI/UA patients, and that is important because it is only in the STEMI population that the CV death signal appears to be evident."

Question 2a. Risk. What are the long-term consequences of nonfatal hemorrhage? Potentially serious.

Panel member comments included:

- *Dr. Jonathan Fox, vice president, Cardiovascular and Gastrointestinal Diseases, AstraZeneca, the panel's industry representative:* "It may not be benign."
- *Dr. James Udelson, a cardiologist from Tufts Medical Center:* "It can be very severe."
- *Chair, Dr. Konstam, a cardiologist:* "I think there has to be something in the label that very clearly provides a warning or caution that proceeding to CABG while receiving prasugrel or soon after discontinuation of prasugrel is associated with a marked increase of peri-operative bleeding…I would, if possible, wait until you know the anatomy (before administering prasugrel)…I think if there is a high likelihood of going on to CABG, you should be dissuaded from using the drug."

FDA officials then wanted to know if prasugrel should be withheld until after coronary angiography was performed, but the panel didn't think that was necessary – or practical. Dr. Konstam suggested distinguishing between STEMI and NSTEMI/UA patients – but not issuing separate indications. Dr. Michael Domanski, chief of the atherothrombosis and coronary artery branch at NHLBI, said, "I can't imagine someone waiting…I would be thoughtful about not getting in a position of telling people not to start something at night."

Question 2b. Can patients likely to require CABG be identified prior to dosing and if so, should prasugrel be withheld in such patients? Perhaps STEMI patients, but not NSTEMI/UA patients, could get prasugrel before coronary angiography.

Panel member comments included:

- *Industry rep:* "Maybe. If it is a relatively stable patient where you think you have time to thoroughly assess the coronary anatomy without crashing…If I thought there was a high probability of CABG, I would withhold it."
- *Dr. John Flack, an epidemiologist from Wayne State University:* "Probably, at least in some settings. And it should be withheld in such patients. But I'm not sure that this doesn't fall under the heading of physician judgment and patient willingness to accept a certain risk…That is an area of physician judgment."
- *Dr. Udelson:* "There is not enough predictive power to know who to withhold therapy from."
- *Dr. Domanski:* "It is hard to predict what procedures will go south…but they rarely do. It is very, very unusual to have to send a patient to emergency surgery…I think prasugrel offers a big advantage here in terms of possible CABG patients."
- *Dr. Cannon:* "I think the labeling has to be consistent with the way the study was performed. For the NSTEMI/UA patients, the drug was not given until the coronary anatomy was known. Because if you give it the afternoon the UA patient comes in, you will give it to people with unsuitable anatomy…With STEMI patients, you know they will have an occluded artery, but the surgeon will be delighted to have you open the artery and cool them off before surgery."

QUESTION 3. Should labeling discourage use of prasugrel in patients:

a. With a history of stroke/TIA or in whom stroke/TIA develop during treatment with prasugrel? YES, unanimously.

b. According to weight? Weight should be mentioned but not contraindicated, with most panel members also favoring allowing a dose reduction to 5 mg.

- *Chair:* "I don't think anything obvious needs to be said (about weight)."
- *Steven Findley MPH of Consumers Union, the panel's consumer rep:* "Yes, and I would agree to a dose reduction to 5 mg."
- *Dr. Udelson, a cardiologist:* "It is worth describing what was seen in the trial and letting clinicians decide."
- *Dr. Domanski, NHLBI:* "Can't we just say that with lesser weight there is more bleeding?"
- *Dr. Flack:* "I wouldn't remain silent. I would say… one reasonable approach may be to lower the dose."
- *Dr. Neaton:* "I wouldn't say anything about body weight except that it is a risk factor for bleeding."

c. According to concomitant GPIIb/IIIa inhibitors? NO.

- *Dr. Mori Krantz, a cardiologist from Denver:* "I might put a precaution that patients shouldn't get extended GPIIb/IIIa therapy."
- *Dr. Neaton, a biostatistician:* "I wouldn't say anything about these."
- *Chair, Dr. Konstam, cardiologist:* "Nothing needs to be said…As the sponsor (Lilly) nicely pointed out, we don't see any subgroup differences on this."
- *Dr. Domanski, NHLBI:* "I wouldn't say anything about that…I can't see how labeling would help."
- *Dr. Udelson:* "I think clinicians will want to know what the data are."
- *Dr. Flack, an epidemiologist:* "I'd say there is an increased risk of bleeding, but you still get efficacy and leave it at that."

d. According to age? A warning but not a restriction.

- *Dr. Cannon, NHLBI:* "I think there should be a warning or statement that there may be less benefit with greater risk (in elderly patients)…but I don't see limiting use – a warning but not a restriction based on age."
- *Dr. Krantz:* "I'm uncertain on dose adjustment."
- *Dr. Emil Paganini, a nephrologist from Chesterland OH:* "I'd cut it in half as you would for pediatrics."
- *Chair, Dr. Konstam:* "Both efficacy and the safety side make you less excited about prasugrel relative to clopidogrel as you get to older age, and I think that has to be attended to. Whether 75 is the key magic age is unknown. That might be a reasonable cut point, but I wouldn't go so far as to not approve it in patients >75, but there should be clear indications that the benefit declines with age…5 mg prasugrel sounds perfectly rational, but the problem is there is not the data."
- *Dr. Domanski:* "You could say that there is increased risk over age 75…but that could be more educational than a fancy warning…Lowering the dose is theoretically reasonable…I would probably be silent on that because we don't have clinical endpoint data with that strategy."
- *Dr. Flack:* "I would not necessarily whack prasugrel on this, but I would essentially say the net benefit is equivalent between the two (prasugrel and clopidogrel in older patients), and it would be reasonable to improve the net benefit by reducing the dose."

QUESTION 4. Does the cancer issue merit a section in Warnings and Precautions, a box warning, or a restriction on use for a limited time? Unanimously NO, the panel recommended it be handled in adverse events.

The FDA's Dr. Temple said no one at the FDA could imagine leaving this out altogether. The question was just where – in adverse events or in one of the more serious categories – it should be discussed. The panel recommended the FDA keep the information in adverse events, not give it more emphasis.

- *Industry rep:* "It merits mention somewhere in the product description but not at the higher levels (of warning.)"
- *Dr. Udelson, a cardiologist:* "In adverse events is most appropriate. The data are not strong but a little suspicious …So, the verdict is it is a low level signal that should be included in some type of low level warning…I wouldn't have a problem giving this drug to a family member… which to me is the litmus test…I'd say we should keep our minds open, that this may not be spurious…We have to revisit this when the TRILOGY trial is done (in a few years)."
- *Dr. Domanski:* "Pending further data, I would make it as inconspicuous as you are willing to do."
- *Dr. Neaton:* "I would say very little about it because whatever you say is probably going to be wrong."
- *Dr. Paganini:* "The verbiage I would use is, 'We need tort reform.' Beyond that, put it in adverse events."
- *Dr. Cannon:* "Adverse events sounds fine with me…but would it be worth adding that the first manifestation of a malignancy may be bleeding?"

QUESTION 5. What, if anything, should labeling say about the formulation issue? No consensus.

QUESTION 6. Risk:benefit. Does the Committee believe that this (prasugrel) represents a favorable benefit-to-risk? Unanimously YES.

QUESTION 7. Does the Committee believe that the following (labeling) restrictions are likely to improve the benefit-to-risk:

- **Avoiding use around CABG or other surgical or invasive procedures? YES, but no specified washout period before CABG, though 7 days was discussed as probably reasonable.**
- **Avoiding use in patients with prior stroke/TIA and discontinuing use in patients who develop a stroke/TIA? YES.**
- **Avoiding use or lowering the dose in low-weight patients? Lowering the dose.**
- **Avoiding use in elderly patients? NO, but issuing a caution.**

Panel member comments included:

- *Dr. Fox, the industry rep:* "The special risks in and around CABG merit mention, and so does stroke. The weight data support a dose adjustment even though there is no direct outcome data, and I still struggle with age."
- *Dr. Flack, an epidemiologist:* "CABG is reasonable, stroke no argument, weight yes. On age, I'm not as negative on the data as others here. The signal is still in favor of this drug vs. clopidogrel, so I would not avoid use in this (age) group."
- *Dr. Udelson:* "CABG yes, it is very clear. On weight and age I wouldn't say avoid use…but (I might) suggest a lower dose."
- *Chair:* "Yes on CABG, TIAs, and age. On weight, the answer is probably yes…I don't see a cut point that suddenly makes prasugrel safe in CABG. I'm troubled by that. I'm not sure what recommendation to give clinicians on how long to wait (after prasugrel before CABG)."
- *Dr. Domanski, NHLBI:* "I would provide enough information in the label to tell people they are probably operating at a somewhat increased risk and then use clinical judgment. On TIA, I would restrict use. I am uncomfortable lowering the dose because we have no clinical data…I think the FDA should give some recommendation, some cut point…I'd recommend 7 days, and you should be okay."
- *Dr. Neaton, a statistician:* "I would use the term 'avoid,' not 'restrict' on TIA/stroke."
- *Dr. Krantz:* "On CABG, I would call out a seven-day period for prasugrel. Yes on TIAs. On weight, a dose reduction might be reasonable. I probably would not recommend a lower dose in the elderly but would issue a general precaution on risk."
- *Dr. Paganini, a nephrologist:* "I would avoid use in TIA/stroke, and caution in CABG. I would use a lower dose with lower weight, and state: 'Cautious with use in elderly.'"
- *Dr. Cannon, NHLBI:* "TIA rises to the level of a black box …A lower dose in lower weight is reasonable…I would just say there is increased risk if a patient is undergoing CABG."

QUESTION 8. Should prasugrel be approved to treat patients with acute coronary syndromes, presenting with either UA/NSTEMI or STEMI? VOTE: Unanimously YES (Yes 9, No 0).

Panel comments included:

- *Chair, Dr. Konstam:* "There was incremental benefit with what was a great antiplatelet benefit but at a cost of increased bleeding risk…Everyone feels it is approvable. I would just say there is a risk:benefit ratio…The community message is ***not*** that all these patients in TRITON should be given prasugrel and not clopidogrel. It is a complicated risk:benefit trade off. There is incremental benefit, but individual decisions need to be made by the clinician on a case-by-case basis."
- *Dr. Neaton:* "It was an extremely well done study. The analyses were quite clear."
- *Dr. Krantz:* "This is a scientific advance. It is nice to see a new (product) rather than add on therapy."
- *Dr. Paganini:* "I enjoyed the quality and quantify of the data…I believe this drug is an advance."
- *Dr. Cannon:* "I do think there was a compelling need for a drug with a more predictable PK and PD than clopidogrel. The issue of clopidogrel resistance is real and matters, and this drug is a major advance in that regard. I hope there will be future research on whether at 30 or 60 days lowering the prasugrel dose may reduce some of the bleeding risk without sacrificing some of the antiplatelet activity…And we need more clarity on treating the elderly. They have the most to lose and potentially the most to gain."

Eliminated questions. Initially, the FDA planned to ask the following questions, but all were eliminated from the final questions presented to the panel.

- Is the Committee concerned about potential bias in the manner of determining stent thrombosis in the TRITON trial?

- Is reduction in stent thrombosis compared to placebo a reasonable claim based on TRITON?
- Is reduction in stent thrombosis compared with clopidogrel a reasonable claim based on TRITON?
- **VOTE:** Should prasugrel be approved to reduce the incidence of stent thrombosis? After the vote, please comment.

LILLY AND DAIICHI SANKYO REACTION TO THE PANEL RECOMMENDATIONS

FDA officials had no comment after the meeting, but Lilly's Dr. Ware said, "We think it is really a great day for patients, and that is what is important…This is a very serious condition. ACS affects 1.5 million people a year, and the number of people (ACS patients) who undergo PCI is 850,000 a year…If all 850,000 PCI patients got prasugrel – which is unrealistic – 23,000 MIs would be saved." Dr. John Alexander, global head of R&D for Daiichi Sankyo added, "We were glad to hear from Dr. Braunwald and a number of panel members that this (prasugrel) represents a 'significant advance.'"

Asked why the stent thrombosis issue was dropped from the FDA questions to the panel, Dr. Ware said, "We've been responding back and forth (with the FDA), and because of that, we've been back to address some of the issues the reviewer had. Because of that, her concerns were taken away, and we have proposed that we get a claim for prevention of stent-associated thrombosis."

Asked if the stent thrombosis claim is likely to be part of the initial indication, Dr. Ware said, "We don't know if stent thrombosis will come with the initial approval."

Asked if the company agrees with the panel recommendations, Dr. Ware said: "Some we have already agreed to. Patients with a history of stroke should not get both prasugrel and aspirin together. For patients ≥75 or patients <60 kg, we recommended a lower maintenance dose of 5 mg, and the panel has some mixed opinions on that. Where the FDA will fall on the label is not clear."

Daiichi Sankyo's Dr. Alexander said, "I think some committee members were unsure, but I think the FDA will recommend dose adjustment in patients with lower body weight."

♦