CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 22433 Ticagrelor (Brilinta) for reduction of cardiovascular events in patients with ACS.

Sponsor: Astra Zeneca

Review date: 8 July 2011

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22433
HFD-110/Monteleone/Marciniak

This memo conveys the Division's recommendation to approve this application.

This review covers matters arising from the sponsor's response to the FDA Complete Response action of 15 December 2010. I refer here to applicable reviews: pre-clinical (Hausner 25 April 2011), statistical (Zhang, 28 April 2011), and clinical (Blank, 6 May 2011; Marciniak, 14 May 2011).

As shown below, effects were heterogeneous with respect to region with the US results being the main driver of the North American anomaly. Substantial efforts have been made by the sponsor and the review team to investigate the cause of the discrepancy in results in the US vs. the rest of the world.

As shown in the table below (Table 1 in the statistical review of 31 August), in the US, ticagrelor fared worse with respect to each of the components of the primary end point.

	Characteristic	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Hazard ratio (95% CI)
Non-US	Composite of CV Death/MI (excl. silent MI)/Stroke	780	947	0.82 (0.74,0.90)
	CV death	329	423	0.77 (0.67, 0.89)
	MI (excl. silent MI)	440	546	0.80 (0.70, 0.90)
	Stroke	118	102	1.15 (0.88, 1.50)
US	Composite of CV Death/MI (excl. silent MI)/Stroke	84	67	1.27 (0.92,1.75)
	CV death	24	19	1.26 (0.69, 2.30)
	MI (excl. silent MI)	64	47	1.38 (0.94, 2.01)
	Stroke	7	4	1.73 (0.51, 5.92)

In the US the point estimate of the hazard ratio was about 1.27. The point estimates for the hazard ratios in placebo-controlled studies of clopidogrel are in the ballpark of 1/1.27, so, by the most generous of non-inferiority calculations, based solely on point estimates, the US results are entirely consistent with there being no effect whatsoever of ticagrelor in the US.

No single or combination of baseline covariates was found to explain the US-foreign differences in outcome. However, post-randomization dose of aspirin does appear to account for regional differences, at least in the statistical sense.

The Agency issued a Complete Response letter on 16 December 2011. I interpret the Agency's position with regard to approval to have been critically dependent upon the persuasiveness of the aspirin hypothesis. Had the Agency been ready to accept the

regional disparity in results as a chance finding, it would have approved Brilinta in the first cycle, even if it were unclear how to advise patients to dose concomitant aspirin. Thus, the letter requested the sponsor to conduct a series of variations on the aspirin hypothesis, intended to show that it was robust to different ways of calculating the relevant "aspirin dose" used in the analyses, given the post hoc nature of the determination of dose and the moderate quality of source data upon which to compute a representative dose.

The sponsor's complete response was received on 20 January 2011. In addition to the requested analyses of clinical data, the sponsor provided what non-clinical support it had for aspirin interaction, and I will summarize those non-clinical findings before describing the clinical analyses and other analyses performed by the review team.

In human platelets in vitro, low-dose aspirin blocks COX-1, decreasing thromboxane A2 and reducing the platelet aggregation in response to collagen. High-dose aspirin (corresponding to a dose of 325 mg) produces no greater effect. In the dog femoral artery, high-dose aspirin blocks endothelial cell COX-2, decreasing prostacyclin and causing vasoconstriction.

High levels of ticagrelor or the prasugrel active metabolite produce near complete inhibition of P2Y12 receptor and also appear to block[1] partially the COX-1-thromboxane A2 pathway, such that aspirin contributes no further platelet inhibition. Lesser levels of P2Y12 antagonists do not block aspirin's COX-1-mediated effects.

In a dog femoral artery, high-dose aspirin produces similar and small[2] increases in vascular resistance in the presence of either clopidogrel or ticagrelor. Further addition of iloprost, a prostacyclin analog and agonist, would be expected to reverse such an increase in resistance, but it had no effect in the group treated with clopidogrel and caused a further increase[3] in vascular resistance in the group on ticagrelor, a result that makes sense to no one.

In summary, the non-clinical work is consistent with there being no further benefit of aspirin used with complete P2Y12 receptor blockade, but it provides little support for the hypothesis that high-dose aspirin leads to "harm" of increased vascular resistance in the presence of P2Y12 blockade.

I next address matters specifically cited in the Agency's Complete Response letter.

Dr. Zhang reports[4] the p-value for the US-OUS comparison in PLATO to be <0.01 (the pre-specified 4-region comparison has a somewhat higher p-value). She notes that the chance of the US result being ≥1.27 when the overall HR is 0.84 also has p-value <0.01. The sponsor's analysis of the effect of aspirin has a p-value in the same ballpark—0.003—but Dr. Zhang gives several reasons to question this analysis: (1) It is based on a post-randomization factor. While it may be possible to discuss multiplicity correction for a finite set of baseline factors, it is much more difficult to adjust once one enters the universe of post-randomization factors. (2) The reported aspirin model is sensitive to the disposition of a relatively small number of OUS subjects on high-dose aspirin, and generally on who is included in the analyses—subjects with missing data on aspirin dose, those discontinuing aspirin after a single dose, or those never receiving aspirin.

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[1] Whether this is a downstream effect of P2Y12 blockade or an "off-target" effect of P2Y12 inhibitors is not clear. The sponsor's tests found not much affinity of ticagrelor, clopidogrel, or prasugrel active metabolite on either COX-1 or COX-2 receptors.

[2] The effect is about 5%, of dubious clinical significance.

[3] About 10%.

[4] First cycle review.

There are two parts to the aspirin analyses. One was using the medication records to assign a day-by-day dose of aspirin per subject. Because of the spotty nature of the source data, this is mostly an exercise in imputation. The sponsor described what it did (6 variations), and Dr. Zhang found what the sponsor did reasonable and verified the results. The second part is the one dose assigned to a subject in an analysis[5]. Per the Agency's recommendations, the sponsor crafted 13 variations on the determination of a representative aspirin dose for analysis. These variations (a) used different metrics (mean, median, last, or maximum), (b) included or not the initial aspirin loading dose, (c) incorporated various times leading up to a censoring event (within 5, 10, or 30 days), and (d) incorporate all follow-up or only the first 30 days.

I have adapted Dr. Zhang's table illustrating the degree of accord by incorporating a description of the imputation methods and how a representative aspirin dose was obtained. The columns are the various alternatives for imputing a dose on a subject with incomplete data. The rows are the 13 analyses involving assignment of a single aspirin dose for the subject. The shaded cells are the ones for which the treatment-aspirin interaction has $p<0.05$ in a Cox proportional hazard model with terms only for treatment, region, aspirin, and interactions of treatment with either aspirin or region.

[5] *So far as I can tell, no one performed analyses incorporating time-varying aspirin dose.*

Imputations											
If a subject has...	...some data, impute...	Zero	X	X			X	
		Previous value			X	X		X
	...no data, impute...	Zero		X		X		
		Country median	X		X			
		Worst case					X	X

Analyses	Metric	For analyses of events...					M1	M2	M3	M4	M5	M6
		...on days 1-30, start with later of...		...on days >30, start with later of								
		...Day	... or days before censoring	...Day	... or days before censoring							
	Mean	1	5	1	5	**A1**	■			■		■
	Mean	1	10	1	10	**A2**	■	■		■		■
	Mean	1	30	1	30	**A3**	■	■		■		
	Median	1	5	1	5	**A4**	■	■	■	■		
	Median	1	10	1	10	**A5**	■	■	■	■		
	Median	1	30	1	30	**A6**	■	■	■	■		
	Last	1	30	1	30	**A7**	■	■	■	■		
	Mean	1	30	1	Any	**A8**						
	Median	1	30	1	Any	**A9**	■					
	Maximum	1	30	1	Any	**A10**						
	Median	1	30	31	Any	**A11**	■	■	■	■		
	Median	1	30	2	Any	**A12**	■	■	■	■		
	Last	1	30	1	Any	**A13**						

Imputation methods M5 (significant interactions with aspirin dose in 0/13 analyses) and M6 (significant interactions with aspirin in 2/13 analyses) both impute a low dose to ticagrelor subjects with missing aspirin data before an event and a high dose to ticagrelor subjects with missing aspirin data before censoring without an event, and then treats clopidogrel the opposite way. This is analogous to an oft-performed analysis of mortality assuming subjects on control are alive and subjects on study drug die when lost to follow-up. These are highly and unreasonably conservative analyses, and failure to show an effect persists with them is not informative.

Analyses A8-A13 all handle the representative aspirin dose differently for censoring or events in the first 30 days and for censoring or events after Day 30. While all events are included in these analyses, the representative aspirin dose is often affected by days many platelet lifetimes from either censoring or the event. It is therefore not surprising that the result is somewhat less powerful than when the representative aspirin dose in restricted to a window more proximal to the censoring or event. However, you might expect this wide inclusion window to have had much impact on A13, which uses the last known aspirin dose, but p-values for the aspirin-treatment interaction ranged from 0.11 to 0.46 in A13 (M1-M4), while the p-values for region-treatment interaction in these analyses ranged from 0.02 to 0.05.

For analyses I consider possibly able to give useful insight[6], I tallied how often the interaction of treatment with aspirin had a lower p-value than did the interaction of treatment with region. These cases are shown with an X in the table below.

	M1	**M2**	**M3**	**M4**		**M1**	**M2**	**M3**	**M4**
A1	X			X	**A6**	X	X	X	X
A2	X			X	**A7**	X	X	X	X
A3	X	X		X	**A11**			X	X
A4	X		X	X	**A12**	X		X	
A5	X	X	X	X	**A13**				

I and the statistical review team rate the aspirin hypothesis in PLATO as being not highly dependent on the analysis performed, but also only moderately robust. At least some of the p-values for the interaction with aspirin are smaller than the p-value for the interaction by region.

Dr. Blank explored interactions of aspirin with treatment for bleeding. However, the risk of bleeding does not increase in going from low-dose (<90 mg) to high-dose aspirin in either treatment group, and the relative risk of bleeding on ticagrelor vs. clopidogrel appears to be independent of aspirin dose[7].

If aspirin dose interacts with ticagrelor because of its high inhibition of P2Y12, then one would expect prasugrel to have shown a similar interaction in TRITON. For these analyses, Dr. Zhang used an estimated median dose over the observation period for events (with start times of randomization or the next day and follow-up for 30 days or the full period of observation). This dose was dichotomized as low or high, corresponding to a median below or above 100 mg. In the various analyses, the hazard ratio for primary end point events (prasugrel/clopidogrel) 0.59 to 0.89 on low-dose aspirin and 0.56-0.85 on high-dose aspirin. For the 4 analyses that included at least half of the end point events, the corresponding ranges are 0.76-0.79 (low) and 0.78-0.85 (high). She does a similar set of analyses on non-CABG TIMI Major bleeding, but there are many fewer events in these analyses. By these analyses, aspirin does not appear to interact with prasugrel.

I next present comments specific to Dr. Marciniak's "Review of Complete Response" document dated 14 May 2011.

There are six areas in which the decisions that Dr. Marciniak makes in his review lack a persuasive rationale and often lack documentation as to their implications. I describe these six issues first, and then I tabulate the many analyses in his review along with the applicability of each issue.

Issue 1: Time frame. The primary analysis, the one in the statistical analysis plan, included follow-up through the close-out procedures. While it is of some interest that the treatment early effect of ticagrelor in PLATO was not much like the early time course for prasugrel in TRITON, the full time course—like other aspects of the pre-specified

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[6] I.e., not M5 or M6 and not A8, A9, or A10.

[7] Dr. Blank does a similar analysis of dyspnea. The data for aspirin dose <90 mg are not shown, but the relative risk of dyspnea on ticagrelor vs. clopidogrel increases somewhat with higher dose of aspirin. She considers this further evidence that aspirin and ticagrelor do not interfere with one another, but the dyspnea effect is clearly off-target; i.e., it has nothing to do with P2Y12.

primary analysis—still has to be respected for being the one analysis for which the corresponding p-value has any easily understood meaning.

Issue 2: Primary end point. The primary end point in PLATO was time to first event of cardiovascular death, myocardial infarction, or stroke. Dr. Marciniak refers to this as "AZ's PEP". Dr. Marciniak analyzes an end point "MACE", in which he has (a) excluded some, but not all, hemorrhagic deaths, (b) excluded some, but not all, deaths of unknown cause, (c) included some, but not all, multi-organ failure deaths, and (d) included all deaths following withdrawal of consent. All of these steps are at variance to the pre-specified analysis plan. While Dr. Marciniak crafts an alternative end point that appears to be reasonable, if post hoc, he describes nothing of the implications of any of these adjustments.

Issue 3: Data errors. In the course of reviewing CRFs and SAS datasets, Dr. Marciniak identified a number of places where the datasets contain unequivocal errors. He uses his corrected data. However, if the hunt for such errors were biased, and I cannot tell from the review whether it was or not, the result of the correction could introduce bias. Either the error rate should have been considered too high to use the data—as we did when we refused to file another application recently—or the original data with its errors should have been used.

Issue 4: Adjudication. Dr. Marciniak reviewed adjudication packages for 617 subjects. He describes disagreements as being rare, but employed his adjudications. The edited adjudications have the same problem as correction of data errors. Despite generally agreeing with the adjudications by the blinded committee, Dr. Marciniak also reports analyses using unadjudicated events reported by the sites. The rationale for using unadjudicated data is unclear. He notes that missing data can be a problem, but there is no reason to believe that missingness was biased.

Issue 5: Censoring time. Dr. Marciniak describes the sponsor's censoring rule as follows: "AZ, for its time-to-event analyses, used censoring data for patients without the event of interest based on the last study visit date for the 'completers' but projected based on either a future planned visit date plus 30 days for withdrawals or upon the last dispense date plus 90 days for patients who continued on study medication after a 'last' visit." Dr. Marciniak uses either the "last good CV follow-up" or the end of study day. Although he states that this makes little difference in his analyses, the results are not shown.

Issue 6: Modeling. The pre-specified analysis incorporated no co-factors. The sponsor's exploratory analysis of the effects of aspirin and region used those factors, treatment, and their interaction. Dr. Marciniak infers this is "cherry-picking", and, noting the heterogeneous inclusion criteria (STEMI vs. NSTEMI, invasive vs. non-invasive management, and early vs. no early clopidogrel, argues for a "full model", with co-factors "based on availability for PLATO, clinical knowledge regarding risk predictors in other ACS and CHD trials, and significant results in PLATO regression with the following exceptions: body weight and histories of MI, stroke, heart failure, peripheral vascular disease, and renal impairment", "to simplify the regression", asserting that the exclusions are inconsequential (not shown). Then, he retains age ("always one of the most significant factors for CV risk") and baseline creatinine clearance ("both a risk factor and a surrogate for body size and drug clearance"). He uses one dichotomous categorization of aspirin dosage and one set of rules to determine dose, reasonable, but only one of many reasonable choices. Then he "included interaction terms that have been identified as of interest … and others that are significant (or close to significant) in some analyses". None of these decisions is inherently unreasonable, but neither are they secure from bias.

In addition, generally the implications of the many decisions behind the models are not explored. The aspirin hypothesis has some credibility only to the extent to which it is not highly sensitive to various alternatives to how the analysis was conducted, including such things as what the relevant aspirin dose was considered to be. Assessment of the robustness of his various analyses is not much in evidence in Dr. Marciniak's review, and it is all the more critical there, because of the large number of additional assumptions and decisions that Dr. Marciniak makes in these analyses.

The table below lists analyses reported by Dr. Marciniak in his review of May 14, with my notations regarding which of the above 6 issues apply and render difficult the interpretation of the corresponding analysis. For example, all 6 of the above issues are relevant to the 30-day MACE analysis in Table 2 of Dr. Marciniak's review.

	Location	**Timing**	**End point**	**Data errors**	**Adjudication**	**Censoring**	**Modeling**
30-day MACE	Table 2	×	×	×	×	×	×
30-day mortality	Table 3	×		×		×	×
30-day CV mortality	Table 4	×	×	×	×	×	×
30-day "primary"	Table 5	×		×	×	×	×
Mortality by region and ASA	Table 6			×	×	×	
Mortality with AZ monitoring[8]	Table 7			×	×	×	×
Mortality	Table 8			×	×	×	×
CV mortality	Table 9		×	×	×	×	×
Simplified mortality	Table 10			×	×	×	×
Mortality with early PCI	Table 11	×		×	×	×	×
Mortality by PCI and region	Table 12	×		×	×	×	×
CV mortality by PCI and region	Table 13	×	×	×	×	×	×
Thromboembolism and ischemia	Table 14		×			×	
Non-thrombic AEs[9]	Table 15		×			×	
Non-CABG minor bleeding[10]	Table 16	×	×			×	×
Non-CABG major bleeding	Table 17	×	×			×	×
Non-CABG major bleeding through day 30	Table 18	×	×			×	×
Non-CABG, non-PCI bleeding	Table 19	×	×			×	×
End point timing relative to visits[11]	Figure 1		×	×	×	×	
MACE	Table 22		×	×	×	×	×
MACE plus post-randomization factors[12]	Table 23						

[8] The rationale for this unusual exploratory analysis is never provided.

[9] The table shows non-thrombotic adverse events "differing between ticagrelor and clopidogrel". Dr. Marciniak comments that bradycardia is a "unique" adverse event to ticagrelor, but the table shows the rates of bradycardia to be 4.04% on clopidogrel and 4.36% on ticagrelor, maybe "differing" (by maybe as many as 4 subjects), but hardly "unique" to ticagrelor. AV block and sinus arrests are also described in the text as unique to ticagrelor, although they are not in the table and not rare in the study population.

[10] Dr. Marciniak introduces another variation in calculating aspirin dosage, presumably applying it to all three analyses of bleeding events.

[11] Dr. Marciniak calls these "unusual distributions", but there is no analysis that shows them to be different from one another.

[12] Dr. Marciniak is making a humorous point here.

MACE plus ASA	Table 24	×	×	×	×	×	×

While bias is a risk in analyses such as that that Dr. Marciniak performed, there simply is not sufficient information in the review to know whether his decisions were biased. One can, however, say that the language he employs displays bias. He refers to the sponsor's aspirin analyses as "cherry-picking" and based upon "post hoc, wildly post-randomization, and erratically defined ASA dosages", and he refers to "censoring abominations", but decisions behind his own analyses appear often post hoc and arbitrary. The sponsor "alleges" and "claims" various things (even when they have faithfully relayed information obtained from investigators), while Dr. Marciniak "asserts", "judges", "finds" and states opinion. Such rhetorical devices do not make his opinions any more compelling.

Despite my reservations about some of the methodology, I am nevertheless anxious to avoid missing some important insight from Dr. Marciniak's work, but that is certainly a risk. Here are areas I thought merited further consideration.

Data quality issues. Dr. Marciniak cites some actual errors, examples of missing data, and his dissatisfaction with the sponsor's adjudication to "conclude that there are sufficient problems with PLATO data quality such that, at best, the US results are representative of ticagrelor's efficacy". How poor data quality leads to an assertion that the true effect of treatment is at least as adverse as the US results is not clear, but at least one needs to consider whether data quality issues undermine our ability to interpret anything from PLATO.

Dr. Marciniak's review contains anecdotes for cases he considers problematic. These amount to about one case per 1000 subjects enrolled, but without subject IDs some of the descriptions may refer to the same subject. Importantly, Dr. Marciniak's review gives little insight into how cases came under his scrutiny, so the possibility exists for the inadvertent introduction of bias in case selection. Thus, one has to decide whether the total number of problems identified by Dr. Marciniak is enough to call for re-evaluation or a new study, but I do not believe that one can make reliable inferences from the distribution of cases Dr. Marciniak identified by treatment groups.

Although Dr. Marciniak seems suspicious, neither he nor DSI found evidence of sponsor misbehavior. Considering the effort Dr. Marciniak expended on review of individual cases, he found relatively few problems of any kind. As far as I can tell, the data quality issues are not of great concern. Were we to rely upon non-inferiority results, the matter might be a closer call, but nothing that added noise here would do anything other than make the two groups more similar and reduce the apparent treatment difference. This includes frank errors, censoring times for which I or Dr. Marciniak might have made different choices, and accuracy and completeness of data provided for adjudication. If anything, these problems result in an underestimate of the treatment effect, not a skew towards a more favorable effect.

If the error rate were deemed too high, then no one should have used any part of these data in further analyses. Clearly, no one thought these errors to be that problematic. If the error rate was deemed acceptable, the original data should have been used in the analyses, not a dataset with spotty corrections. In my view, the sponsor properly "refused to correct" these errors, because the process of uncovering errors was susceptible to bias, and stood by analyses as the data were blindly curated.

Censoring. One methodological problem in the study was declaring the censoring time for a composite end point based on non-visit follow-up for mortality only. However, Dr.

Marciniak found that this made little difference in the analyses that he performed[13]. I conclude that this was not a serious flaw in the study.

Aspirin and diabetes. Dr. Marciniak finds an interaction between aspirin and diabetes in some analyses and he cites external information on the reduced responsiveness of diabetics to aspirin's anti-platelet effects. If ticagrelor is approved with some recommendation regarding dose of aspirin, that advice ought to take into consideration the external information, but the findings with respect to an interaction in PLATO are not particularly compelling, as the interaction is only positive in Dr. Marciniak's analyses of MACE and 30-day all-cause and CV mortality, and apparently not in various other analyses closer to the study's actual primary end point or using the full study's data.

Early PCI. Dr. Marciniak finds a significant interaction term for treatment by early PCI (a post-randomization variable[14]) in some analyses. "Early" (timing for which is arbitrary) PCI, Dr. Marcinaik notes, is inseparable from other cofactors, including aspirin dose (because high dose is often used post-PCI) and region (because PCI was more common as a treatment strategy in the US).

Summary and recommendations. The main PLATO results are shown below:

	Clop	**Ticag**	**HR**	**P**
CV death, MI, stroke	11.7%	9.8%	0.84	0.0003
CV death	5.1%	4.0%	0.79	
MI	6.9%	5.8%	0.84	
Stroke	1.3%	1.5%	1.2	

Secondary end points were analyzed sequentially as follows:

[13] *Nonetheless, he is "concerned about the validity of any conclusions" when the number of subjects with missing terminal follow-up exceeds the difference in end point events. I cannot imagine very many end point trials surviving such a worst-case analysis, particularly one with composite end points.*

[14] *Unlike aspirin as a cofactor, Dr. Marciniak does not consider "early PCI" to be "wildly" post-randomization. He does not consider the PCI analyses to be post hoc, because he "proposed analyzing them to the primary efficacy reviewer prior to the NDA receipt". Dr. Marciniak does not say what all was proposed nor what detail was pre-specified. Note, too, that Dr. Marciniak* chooses *to analyze post-randomization actual PCI, rather than the available pre-randomization "intent to manage with PCI"; his explanation for this choice is on page 16 of his review.*

	Clop	**Ticag**	**HR**	**P**
CV death, MI, stroke invasive management	10.0	8.5	0.84	0.0025
All-cause mortality, MI, stroke	11.5	9.7	0.84	0.0001
CV death, MI[15], stroke, recurrent ischemia, TIA, or other arterial thrombotic events	15.7	13.8	0.88	0.0006
MI	6.4	5.4	0.84	0.0045
CV death	4.8	3.8	0.79	0.0013
Stroke	1.1	1.3	1.17	0.22
All-cause mortality	5.4	4.3	0.78	0.0003

Up to the secondary end point of stroke alone, all pre-specified analyses were highly statistically significant, particularly impressive considering these are comparisons to an active agent[16]. Not only do these data support approval, they support a claim of superiority to clopidogrel, on the basis of a single study. Further, the p-values for the primary end point and the secondaries through stroke have a particular interpretation—they say how likely it is that a finding as extreme as this one could have occurred by chance if the two treatments were, in fact, the same.

There are many more p-values cited in reviews of this application, but, while they give some indication of how likely the result is through chance, they cannot be interpreted the same way as ones that were part of the prospective statistical analysis plan. As many of these analyses involve many assumptions, generally made with data available, that makes interpretation of the corresponding p-values the more ambiguous.

So then what is one to make of a planned analysis that suggests a regional heterogeneity? I believe that the answer depends first upon whether it tempts you to discount the overall study findings. That is rarely the case, but it is clearly relevant in this case, because the finding suggests that the overall result might not apply to the US—and, in fact, appears to be adverse. In such a case, I believe that part of due diligence, on the part of the review team and the sponsor, is to evaluate such a finding to see how credible it is. Is there some aspect of US (or North American) subjects or their care that distinguishes them from subjects and care in the rest of the world?

Contributing to the credibility of this finding is that it appears to apply to the primary end point and its major components, but I do not make a lot of that, since the major components, cardiovascular mortality and myocardial infarction are surely correlated.

Many hundreds of person-hours have been expended by the sponsor and the review team to address this question by looking for co-factors that singly or in combination "explain" the discrepant US results. In this effort, all parties have had a rich set of baseline and post-randomization factors from which to choose. The most likely identified factor distinguishing US and non-US subjects is aspirin dose. Of note, aspirin appears to affect treatment responses for the primary end point and its major components, as region did, adding as much the credibility of the aspirin hypothesis as to the regional differences. However, the aspirin hypothesis (that aspirin

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[15] *Including asymptomatic*

[16] *The primary end point meets a two-trial-equivalent standard of p<0.00125. All results are highly persuasive of effectiveness if not superiority to clopidogrel.*

dose accounts for regional differences in outcome) is not highly persuasive—by mechanism or analyses as a factor in the study outcomes, and no version of it predicts adverse effects of high-dose aspirin. (I will return to this later when I discuss implications for labeling.)

If the regional difference is, in fact attributable to dose of aspirin, then the problem is resolved by advising use with low-dose aspirin, in most patients[17], and if this is wrong, then there does not appear any harm in advising use with low-dose aspirin. Unless one can identify a factor intrinsic to US patients or their care that explains the regional disparity in outcomes and then cannot circumvent the effect of that factor, then, despite residual doubts, one is forced to conclude that the evidence favoring true regional differences is far less compelling than is the overall study result.

If neither regional differences nor the aspirin hypothesis are highly compelling, how should they be represented in labeling?

Labeling always incorporates observations obtained outside of a formal statistical framework. These include non-clinical, clinical pharmacology, and clinical data, relating to both safety and effectiveness. We believe that what is in these sections is likely to be reproducible if the study were replicated, and thus expect these findings to apply in practice, but we would not accord most of them the same degree of surety that we do the findings obtained under a formal analysis plan, nor do we assert equivalent confidence in all such findings that we report.

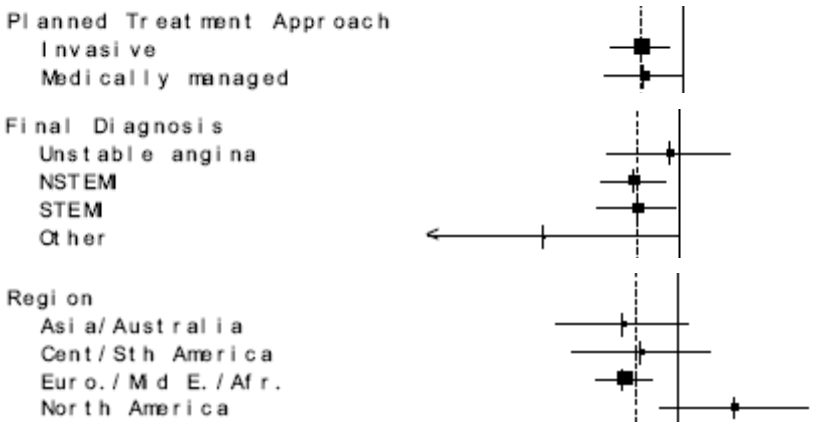
Where we are concerned that describing such observations could lead to over-interpretation, we insert precautionary language. Doing so is part of our responsibility in providing the most reasonable possible interpretation of the data.

Thus, I would insert the pre-specified region analysis in the forest plot. The accompanying text should have the generic disclaimer, but also should say that the factor best accounting for the regional effect is subsequent aspirin dose. That association, in my view, is not sufficiently compelling to warrant elevation to a contraindication against use with high-dose aspirin or a mandated communications plan on the part of the sponsor, but, in my view, should be *briefly* described under Warnings and Precautions.

There is a claim made for reduction of stent thrombosis. While not reachable through the planned hierarchical analysis, I would have considered it a valid claim, robust whether one looks at ARC-definite only, definite plus probable, or definite through possible stent thromboses. One need only believe clopidogrel not worse than placebo. We reached a similar conclusion with prasugrel.

While I remain concerned about pooling these subgroups of ACS (very different from what was done in TRITON), treatment effects were similar in subjects for whom the planned treatment strategy was medical or invasive, and for those for whom the final diagnosis was STEMI or NSTEMI.

[17] *You should still consider the case for use of high-dose aspirin for a time after stents and in diabetics.*



I remain concerned that the study results pool whatever proportions there were for the various ACS presentations and treatment strategies, but that issue has been discussed internally and by the Advisory Committee.

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/s/

NORMAN L STOCKBRIDGE
07/08/2011