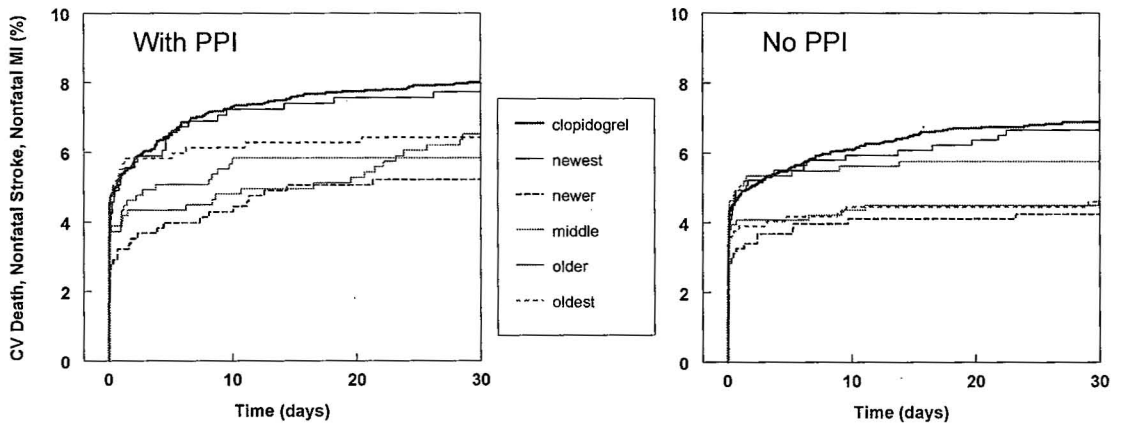
Figure 6: 1° Efficacy Endpoint by Age of Prasugrel Lot Administered Through Day 30



Because the sponsor asserts that there was at least some conversion of salt to base during storage, the review team also assessed efficacy as a function of the age of the prasugrel lot used to supply each subject with their initial 30 day supply, in the presence and absence of PPI use (age = date administered minus date of manufacture). Of note, use of PPIs was transient or intermittent in some subjects; subjects with recorded PPI use at any time were considered PPI users for the purpose of this analysis. In both the presence and absence of PPIs, there was no relation between age of lot administered during the initial 30 days and efficacy (Figure 6, from secondary review).

These analyses suggest that prasugrel's efficacy was at least similar to clopidogrel for the vast majority of lots, and efficacy was not importantly affected by pill age. (The lot with the highest event rate included only 36 subjects.)

Association between Use of Proton Pump Inhibitors and Efficacy

If PPI had importantly diminished prasugrel's pharmacodynamic effects in the setting of salt-to-base conversion, one would expect diminished efficacy in subjects who were receiving PPI. Approximately 40% of the subjects in each treatment group reported use of PPI as a concomitant medication. The Cox proportional hazard ratio favored prasugrel over clopidogrel in subsets of subjects who received and did not receive PPI, and was virtually the same in both subsets. Hazard ratios were 0.82 and 0.80 in subjects who reported and did not report use of PPI, respectively.

Impact of Salt-to-Base Conversion on Safety

The principal risk of prasugrel is bleeding. In essence, salt-to-base conversion has the potential to lead to lower bioavailability in the presence of PPI or H2 antagonists, which would tend to cause less bleeding. Thus, potentially lower bioavailability does not pose a safety risk, per se.

Table 4: Non-CABG-Related TIMI Major or Minor Bleeding Events Through 3 Days by PPI Medication Use and H2 Receptor Blocker Use

Study Population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)
	N	n	%	N	n	%	
Overall	6741	138	4.5	6716	113	3.4	
PPI Yes	2760	70	2.5	2719	62	2.3	1.11 (0.79, 1.56)
PPI No	3981	68	1.7	3997	51	1.3	1.35 (0.94, 1.94)
H2 Antagonist Yes	1027	30	2.9	1017	25	2.5	1.19 (0.70, 2.02)
H2 Antagonist No	5714	108	1.9	5699	88	1.5	1.23 (0.93, 1.63)

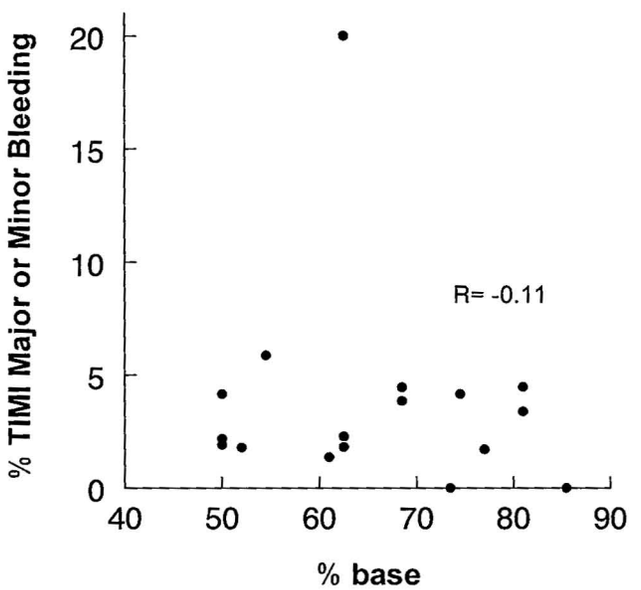
Table 4 shows the incidence of TIMI Major and Minor bleeding events through 3 days, dichotomized by PPI use or non-use (top) or H2 receptor antagonists use or non-use (bottom) through 3 days. If higher gastric pH decreased the bioavailability of prasugrel, one would expect to observe fewer bleeding events in patients who received PPI or H2 antagonists in the prasugrel group, relative to the clopidogrel group.

For both treatment groups, the incidence of bleeding was higher in subjects who received gastric pH-raising drugs than in those who did not. This may be related, in part, to the fact that PPI and H2 antagonists were discretionary, and physicians may have been more willing to prescribe them for patients perceived to be at higher risk of bleeding events.

Given to the limited numbers of bleeding events, due in part to considering events through only Day 3, the analysis is not robust. Whereas the data do not suggest a bioavailability issue, neither do they provide much reassurance to refute one. They do suggest that prasugrel's bleeding risk, with or without PPIs or H2 receptor antagonists, is consistent with the study as a whole.

When the review team analyzed TIMI Major or Minor bleeding rates by lot administered during the first 30 days, there was no relation between salt-to-base conversion and bleeding (Figure 7).

Figure 7: TIMI Major or Minor Bleeding Versus Base Content of Lot Administered Through Day 30



Importance of Dose to Safety and Efficacy:

Finally, when considering the potential influence of salt-to-base conversion on safety and efficacy, it is useful to place the potential differences in bioavailability into perspective. If we assume a worst-case scenario, that is, that salt-to-base conversion cannot be controlled, that this phenomenon results in a 38% difference in C_{max} between the low- and high-conversion lots at the 30 minute time point, and that the impact on platelet aggregation, although transient, is important, it should be recognized that the variability is only moderate when compared to the variability in weight-adjusted dose between patients of higher and lower weight (all patients receive the same dose of prasugrel). Of course the critical issue is whether higher weight patients taking gastric pH raising medications could receive lots with higher salt-to-base conversion and experience reduced efficacy. Fortunately, the clinical data provide a fair measure of reassurance in this regard.

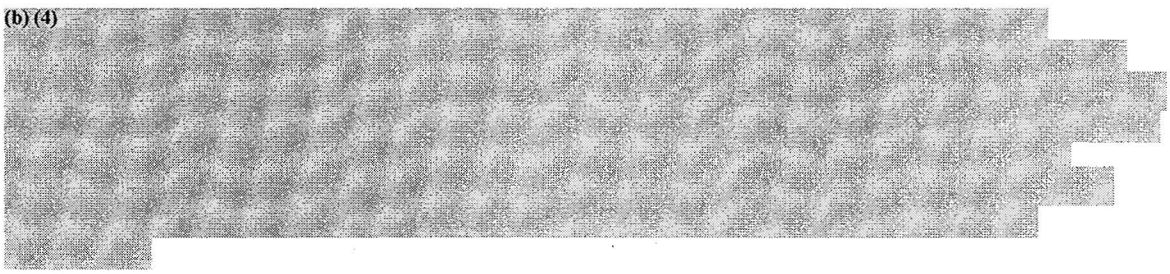
Conclusions:

The conversion of the drug product from salt to base is a heretofore-unknown phenomenon that could have been discovered as a result of following the Quality by Design paradigm of drug development. Conversion affects the pharmacokinetics of the product when it is co-administered with a PPI or H2 receptor antagonist; the high-conversion drug substance is technically bio-inequivalent to the low- and medium-conversion lots. The difference in bioavailability is evident in C_{max}, but not AUC, and translates into less biological activity than the low- and medium-conversion products at the 0.5- and 1-hour time points. However, at 2 hours and beyond, the difference disappears. This can be conceptualized as a delay of approximately 20 minutes in achieving maximal inhibition of platelet aggregation. On the other hand, inhibition

of platelet aggregation resulting from prasugrel greatly exceeds that of clopidogrel at all time points. Thus, even when conditions are most unfavorable for prasugrel (high salt-to-base conversion with high gastric pH), its pharmacodynamic effect is greater than that of clopidogrel.

The clinical data are also reassuring with regard to salt-to-base conversion. In terms of efficacy, the results for essentially all prasugrel lots administered during the first 30 days trended favorably relative to clopidogrel (Figure 5). Moreover, the use of PPI had no discernable effect on the efficacy of prasugrel in relation to clopidogrel. From the standpoint of safety, the importance of salt-to-base conversion is more difficult to assess, because the analyses are based on bleeding events, which were relatively uncommon. In any case, a product with high salt-to-base conversion administered in the presence of a PPI or H2 receptor antagonist has reduced bioavailability, which would lead to *less* bleeding. In actual use, the relation between PPI use and bleeding for subjects who received prasugrel was similar to that of clopidogrel, and there was no apparent relation between the salt/base content of the lots used during the first 30 days and bleeding events.

(b) (4)



In conclusion, although the conversion of the product from the salt to base form is counter to product purity, it could have been detected as a result of the QbD initiative. Such conversion may be an issue for marketed products, although this is purely conjecture. More importantly, approval of a product with significant conversion sets a poor precedent. On the other hand, the biological activity of prasugrel on inhibition of platelet aggregation exceeds clopidogrel at all time points, and the clinical data argue strongly that the salt-to-base conversion has no clinically important effect on the performance of prasugrel. Its performance exceeds that of clopidogrel, and therefore salt-to-base conversion should not be a reason to deny approval of this NDA.