of IPA will result in better clinical outcome is valid, then every prasugrel regimen will be superior to clopidogrel, and there is no need to choose too aggressive prasugrel dosing risking higher bleeding rates. Conventional wisdom suggests that clopidogrel replaced ticlopidine not because of the superior efficacy, more potent IPA, or less ‘non-responder’ rates, but because of the better safety profile. Moreover, the incidence of bleeding in JUMBO, in contrast to the ‘similar rates’ stated in Introduction, was in fact 30% higher in the combined prasugrel arms (1.7%) when compared with the clopidogrel group (1.2%). Last but not least, it seems not appropriate to declare ‘no conflict of interest’ when most the authors are industry representatives, whose careers and stock option values are dependent heavily on the success of prasugrel.

References

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Prasugrel, clopidogrel, and combining Swedish apples with American oranges: reply

The authors appreciate the interest expressed by Dr Serebruany in our dose-ranging study of prasugrel, wherein the results reported are consistent with the previous reports demonstrating that prasugrel achieves faster onset, higher levels, and more consistent inhibition of ADP-induced platelet aggregation (IPA) than the approved doses of clopidogrel in subjects with coronary artery disease.1, 2 Given the interest, the authors would like to respond and clarify a number of issues.

As stated in the report, the primary purpose of this Phase 1b study was not to support dose selection for JUMBO-TIMI 26, but to generate comparative IPA data that could be used in conjunction with safety data (TIMI major and minor bleeding) and secondary efficacy data from JUMBO-TIMI 26 to make dose selection for TRITON-TIMI 38, the ongoing Phase 3 study comparing prasugrel with standard-dose clopidogrel in ACS subjects undergoing PCI. Indeed, together, these studies have demonstrated that the selected Phase 3 dosing regimen of prasugrel (60 mg loading and 10 mg maintenance dose) achieved faster, higher, and more consistent IPA than the approved clopidogrel dosing regimen, without a statistically significant increase in TIMI major plus minor bleeding after PCI.4

As to variation in IPA observed at the two study sites, a separate analysis of the data from each site confirmed the higher IPA responses achieved with prasugrel (Study Limitations). At both sites, compliance with study drug was closely monitored and aggregation was performed using similar methods in two experienced laboratories. The potential for non-compliance to explain the inter-site IPA variability is discounted by the results obtained at the two sites with loading doses (administered to subjects under direct supervision) and by the consistent dose-response pattern observed during maintenance dosing. Rather, the higher IPA levels at one site appear more likely related to different aggregometers and/or differing subject population responses. The lack of non-responders at the US site on day 28 is not surprising because only four subjects were randomized to clopidogrel at that site. Of these patients, one (23% IPA; Figure 3B) approached the non-responder criteria (<20% IPA to 20 μM ADP).

Further, the authors acknowledge that debate continues on how best to characterize clopidogrel response variability. However, clopidogrel resistance and its association with adverse clinical outcomes in PCI has been reported.3 The present study demonstrates for the first time in subjects with coronary artery disease that prasugrel has far fewer non-responders than clopidogrel, regardless of the criteria selected to define poor response.6

A statement regarding any conflict of interest was indeed submitted to the journal with the report, which unfortunately was not acknowledged in the published manuscript. However, information concerning institutional affiliations of the authors was clearly expressed in the manuscript itself.

We thank Dr Serebruany for highlighting that the current study provides new findings that clearly support the superior platelet inhibition achieved with prasugrel vs. clopidogrel. However, validation of the hypothesis that the improved antiplatelet profile of prasugrel will result in superior efficacy and acceptable safety in ACS subjects undergoing PCI must await the results of TRITON-TIMI 38.

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