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Bentricimab Immediately and Significantly Reverses the Antiplatelet Effects of Ticagrelor in Older People

Dr. Bhatt:

Hello, my name is Dr. Deepak Bhatt from Brigham and Women's Hospital at Harvard Medical School. It is my pleasure to be able to present to you a recap of a Phase 2B study of bentricimab that I presented as a late breaking clinical trial at the American College of Cardiology in 2022. My disclosures include research funding from PhaseBio and AstraZeneca. And this presentation includes off-label and investigational uses of drugs.

Ticagrelor is a reversible oral antiplatelet agent, meaning that it binds reversibly to the P2Y12 receptor on the platelet. That characteristic has allowed the development of bentricimab, a recombinant human IgG1 monoclonal antibody fragment that binds to free ticagrelor with high affinity and specificity.

What I presented at ACC was the Phase 2B trial of bentricimab versus placebo. This was a trial of 50- to 80-year-old volunteers pretreated with ticagrelor for 48 hours in addition to aspirin. They were then randomized in a three to one ratio to bentricimab or placebo. The primary endpoint was inhibition of PRU, an assay of platelet reactivity. And what we found by the VerifyNow PRU analysis and also the VASP PRI analysis, was an immediate and sustained reversal of ticagrelor with bentricimab. And these effects were highly, statistically significant across the various time points that we examined.

The primary endpoint specifically, was minimum percentage in inhibition of PRU within four hours. And this as well, was significantly, favorably influenced by bentricimab. This effect on reversing ticagrelors antiplatelet activity by bentricimab was consistent across multiple subgroups including men and women, white and black patients and a variety of other demographic descriptors. In fact, not only were the benefits consistent, but these effects on platelet inhibition were highly, statistically significant in these various subgroups.

We also examined markers of platelet activation to make sure there was no rebound platelet hyper-reactivity due to either the infusion or cessation of the infusion. And we found no evidence of platelet activation as assessed by P-Selectin or Mean Platelet Volume with bentricimab.

We also examined the safety profile of bentricimab and compared with placebo, there was no significant difference for any treatment emergent adverse events. And there were no drug-related serious adverse events, and no thrombotic events. So overall the drug seemed to be quite safe in this population.

So in conclusion, compared with placebo, bentricimab significantly restored platelet function as measured by multiple assays, by binding and eliminating free ticagrelor and also ticagrelor active metabolite. No thrombotic events, and no serious adverse events were reported in volunteers randomized in bentricimab, confirming the safety profile. Based on these data, bentricimab appears to be a very promising option for ticagrelor reversal. Assessment of bentricimabs clinical effect on patients with bleeding, awaits completion of the ongoing REVERSE-IT study, which is a Phase 3 trial that is designed hopefully for approval of this compound. We'll have to see what the results of that trial are. I've already presented some interim data that were pre-specified data at the American Heart Association in 2021 as a late breaker. And in the largely surgical patients on ticagrelor that were enrolled in that study, there seemed to be, as assessed by independent adjudicators, excellent rates of hemostasis. The part of the trial that's ongoing now, is an assessment of

patients with bleeding who've received ticagrelor, so hopefully within the next year or so we'll finish up the study, and if approved by the FDA, this could be a new option to reverse ticagrelors effect when emergency surgery or bleeding occurs. Thank you very much for your attention.