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VOYAGER PAD Trial - Landmark Trial Demonstrates the Efficacy and Safety of Novel Therapy in Patients with Peripheral Artery Disease (PAD) after Lower-Extremity Revascularization

The VOYAGER PAD study demonstrated that low dose rivaroxaban (2.5 mg twice daily) plus aspirin significantly reduces the risk of major adverse limb and cardiovascular (CV) events in PAD patients undergoing intervention.

Overall ~6 times more ischemic events (MACE & MALE) were prevented versus TIMI major bleeding events caused, demonstrating a net benefit for this strategy

Aurora, CO, March 28, 2020 –CPC Clinical Research, an academic research organization affiliated with the University of Colorado Anschutz Medical Campus, announced today that the VOYAGER PAD study met its primary efficacy endpoint. The study tested a strategy of rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily against aspirin alone in treating patients with symptomatic peripheral artery disease (PAD) after lower-extremity revascularization. The VOYAGER PAD study investigated outcomes in a high-risk patient population by enrolling patients with symptomatic PAD requiring limb revascularization. Patients were enrolled after intervention, a setting in which there is a particularly high risk for limb events and bleeding. VOYAGER PAD is the first randomized placebo-controlled trial to demonstrate a benefit for an antithrombotic strategy in reducing risk in PAD patients after revascularization. The results of this global, multi-site, randomized, Phase 3 trial were presented as a Late-Breaker held during the American College of Cardiology's Annual Scientific Session Together with World Congress of Cardiology

(ACC.20/WCC) and simultaneously published in *The New England Journal of Medicine.*

PAD affects an estimated 8 million people in the U.S. and over 200 million people worldwide. PAD is caused when there is limited blood flow to the limbs because of accumulation of plaque in the arteries. This limited blood flow condition causes health and lifestyle difficulties ranging from limb pain and trouble walking, to acute limb ischemia, limb amputation, heart attack, ischemic stroke and/or cardiovascular death. As symptoms become increasingly severe for patients with PAD, the common treatment involves revascularization. The current guidelines recommend that patients take an antiplatelet therapy, such as aspirin or clopidogrel, to prevent cardiovascular events. There are currently no class I recommendations for more intensive antithrombotic strategies to reduce the risk of limb and cardiovascular outcomes after intervention. The absence of studies demonstrating efficacy for these outcomes, and in this setting, leaves an important treatment gap in clinical practice.

"Adding low-dose rivaroxaban (2.5 mg twice daily) to aspirin after peripheral artery intervention significantly reduced the spectrum of complications that we fear most in PAD, which is acute limb ischemia, major vascular amputation, heart attack, and stroke. This benefit was apparent early on and was maintained over time," said Marc P. Bonaca, MD, associate professor and director of vascular research at the University of Colorado School of Medicine, CPC's Executive Director, and the study's lead author. "These data provide evidence of an antithrombotic regimen that effectively reduces risk, and although bleeding rates were higher, the overall risk-benefit remains quite favorable. There are few studies in this population and in this setting to inform practice. These results complement those of the COMPASS trial and demonstrate efficacy for low dose rivaroxaban (2.5 mg twice daily) plus aspirin initiated after intervention and maintained through long-term secondary prevention."

For the primary efficacy endpoint, rivaroxaban along with aspirin, reduced the risk of major adverse limb and CV events by 15% (17.3% with rivaroxaban versus 19.9% with placebo, HR 0.85, 95% CI 0.76 – 0.96, p=0.0085) compared to aspirin alone. This benefit was apparent within the first three months of treatment and stayed consistent for the duration of the treatment. Due to the high baseline risk, with approximately 1 in 5 having a first event over three years, this translated into an absolute risk reduction of 2.0% at year 1 and 2.6% overall and a number needed to treat at 1 year of 50 and at 3 years of 39.

Rates of TIMI major bleeding, the principal safety outcome, were higher with rivaroxaban plus aspirin than with aspirin alone (2.7% with rivaroxaban versus 1.9% with placebo, HR 1.43, 95% CI 0.97 – 2.10, p=0.0695); translating into an absolute risk increase of 0.8% at 3 years (0.27% per year) or a number needed to harm of 125. Importantly there was no excess in irreversible harm events such as intracranial hemorrhage (13 with rivaroxaban versus 17 with placebo) or fatal bleeding (6 with rivaroxaban versus 6 with placebo).

Putting efficacy and safety together, treating 10,000 patients for 1 year with a strategy of rivaroxaban 2.5 mg twice daily plus aspirin compared to aspirin alone would prevent 181 first primary endpoint events at a cost of 29 TIMI major bleeds but with no excess in intracranial hemorrhage or fatal bleeding.

About VOYAGER PAD

The Phase 3 VOYAGER PAD study included 6,564 patients from 534 sites across 34 countries worldwide. Patients were selected on the basis of symptomatic lower extremity PAD requiring revascularization without further enrichment for cardiovascular or limb risk. Patients were randomized at a 1:1 ratio to receive either rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily (n=3,286) or aspirin 100 mg once daily alone (n=3,278). Patients were included regardless of the mode of revascularization (surgical or endovascular) and use of concomitant clopidogrel was allowed for up to 6 months. Patients were followed for a median of 28 months. The primary efficacy endpoint was a composite of acute limb ischemia

and major amputation of a vascular etiology, heart attack (myocardial infarction, MI), ischemic stroke or cardiovascular death. The primary safety outcome was major bleeding according to the TIMI classification. The study was funded by Bayer AG and Janssen Research and Development.

ABOUT CPC

CPC Clinical Research, an academic research organization and affiliate of the University of Colorado Anschutz Medical Campus, has led innovative research in cardiovascular disease and particularly peripheral artery disease and cardiometabolic disease for more than 30 years. Founded in 1989 to lead the Appropriate Blood Pressure Control in Diabetes (ABCD) trial (www.ncbi.nlm.nih.gov/pubmed/8960857), CPC is recognized for its expertise in comprehensive clinical trial management for both national and international clinical research. Over the past three decades, the organization's services have evolved to stay at the forefront of the everchanging landscape of clinical research.

CPC also leads innovative programs to help vulnerable populations across Colorado to achieve health without disparities. As a result of these efforts, CPC Community Health has provided health education and/or coaching to over 82,000 individuals and made significant improvements in the lives of those at risk for cardiovascular disease. The results of these Community Health programs, focused on rural and Latino populations, have been recognized by the CDC.

CPC offers full-service clinical trial design, oversight, and management with rapid access to Key Opinion Leaders in a variety of therapeutic areas. These individuals are on the cutting edge of scientific, clinical and regulatory developments. Many of CPC's leadership team have chaired and/or served on FDA advisory committees including the Cardiovascular and Renal, Endocrine and Metabolism, and Reproductive Health committees. For more information, go to www.cpcclinicalresearch.org/news-and-presentations/ and www.cpccommunityhealth.org

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