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BMS-986231, a novel HNO donor as a potential therapy for acute heart failure patients

Background/Introduction: Acute heart failure continues to be a dominant cause of morbidity and mortality worldwide and hospitalization for acute decompensated heart failure are a growing global problem. Nitroxyl (HNO) donor is a modulator of the cardiovascular system, with effects including vasodilation, increased inotropy and enhanced lusitropy in preclinical models. BMS-986231 is a second-generation intravenous HNO donor that may provide these beneficial effects in acute heart failure patients.

Purpose: This study was designed to evaluate the safety, tolerability and haemodynamic effects of BMS-986231 effects in hospitalized heart failure patients with decompensated heart failure and reduced ejection fraction (HFrEF).

Methods & Findings: This study is a double-blind, randomized, placebo-controlled Phase 2a trial. Forty-six patients with advanced HFrEF, were enrolled into 4 sequential dose-escalation cohorts. Patients received a 6-hour continuous infusion of BMS-986231 (at doses of 3, 5, 7 and 12 µg/kg/min) *vs*. placebo. Doses of BMS-986231 ≥5 µg/kg/min resulted in significant ~5 mmHg reductions in time-averaged PCWP. Maximum reductions in PCWP ranged from 4.8 to 6.9 mmHg compared with 2.0 mmHg in the placebo group. Pulmonary artery and right atrial pressures were consistently reduced in BMS-986231 groups. Cardiac index, as measured by a non-invasive whole-body bioimpedance device, was increased in all BMS-986231 groups by 18 to 62%, compared with 2% for placebo. Stroke volume index was also increased from baseline of ~ 28 mL/m2 in all BMS-986231 groups. Transient, sporadic and asymptomatic reductions in systolic blood pressure of ≥ 20 mmHg during CXL-1427 infusion were noted in 21% of patients versus 17% in the placebo group and resolved without intervention during the remainder of infusion. Heart rates were not increased on BMS-986231 versus placebo and no arrhythmias were noted during infusion in patients on active study drug. Analyses of adverse events throughout the 30 day follow-up period did not identify BMS-986231-specific toxicities, with the potential exception of infrequent headaches during infusion of study drug. There were no treatment-related serious adverse events.

Conclusions: BMS-986231 was safe and well-tolerated in a group of patients with advanced heart failure. Pharmacodynamic effects observed were reductions in right and left ventricular filling pressures and increase in cardiac index, without an increase in heart rate, supporting the beneficial effects of BMS-986231. Based on these findings, BMS-986231 is currently evaluated in patients with heart failure (HF) and reduced systolic function admitted to the hospital with signs and symptoms of ADHF in an ongoing Phase 2b trial (STAND-UP AHF, NCT03016325).

Biography

Borentain M is a graduate from the University of Paris Medical School. She was trained in Cardiology with subsequent sub-specialization in Echocardiography and Sports Medicine, and holds a Master's in Cardiovascular Pharmacology and Biostatistics. She is currently a Medical Director in Global Development Cardiovascular at Bristol-Myers Squibb. After several years in clinical practice, she joined Bristol-Myers Squibb 13 years ago and held various positions in Medical Affairs, Field Medical Management and Global Clinical Development. She is involved in early and clinical development of several assets in Heart Failure. Her interests also include Innovative Clinical Trial Designs and Patient Engagement.

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