Oral sGC Stimulator Vericiguat in Patients with Worsening Chronic Heart Failure and Reduced Ejection Fraction - The SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with REDUCED EF (SOCRATES-REDUCED) Study

Mihai Gheorghiade, Northwestern Univ, Chicago, IL; Aldo P Maggioni, ANMCO Res Ctr, Florence, Italy; Carolyn Lam, Natl Heart Ctr Singapore, Singapore, Singapore; Eliana Samano, Bayer S.A, Sao Paulo, Brazil; Elisabeth Kraigher-Krainer, Charité Univ Med Berlin, Berlin, Germany; Gerasimos Filippatos, Athens Univ Hosp, Athens, Greece; Javed Butler, Stony Brook Univ, Stony Brook, NY; Stephen J Greene, Duke Univ Medical Ctr, Durham, NC; Katharina Mueller, Lothar Roessig, Bayer Pharma AG, Wuppertal, Germany; Piotr Ponikowski, Medical Univ, Wroclaw, Poland; Sanjiv Shah, Northwestern Univ, Chicago, IL; Scott David Solomon, Brigham and Women's Hosp, Boston, MA; Burkert Pieske, Charité Univ Med Berlin, Berlin, Germany

Introduction: Worsening chronic heart failure (WCHF) is a major public health problem. The objective of this study was to determine the safety, efficacy, and optimal dose of vericiguat, a soluble guanylate cyclase stimulator, in patients with WCHF with reduced left ventricular ejection fraction (LVEF).

Methods: The SOCRATES-REDUCED trial was a phase II, dose-finding study of stable patients with LVEF<45% within 4 weeks of a WCHF event. Patients were randomized to placebo or 1 of 4 target doses of vericiguat (1.25 mg, 2.5 mg, 5 mg, 10 mg) for 12 weeks. The primary end point was the change from baseline to week 12 in log-transformed NT-proBNP level. Primary analysis specified pooled comparison of the 3 highest dose vericiguat arms with placebo. Pre-specified secondary analyses included effects of individual vericiguat dose arms and testing for a vericiguat dose-response relationship.

Results: Overall, 456 patients were randomized and 351 patients were eligible for primary end point analysis. In primary analysis, change in log-transformed NT-proBNP from baseline to week 12 was not significantly different between the pooled vericiguat group and placebo (ratio of geometric means 0.885, p=0.151). In secondary analysis, there was a dose-response relationship (p=0.017) and the 10 mg vericiguat arm showed greater reductions in log-transformed NT-proBNP than placebo at 12 weeks (ratio of geometric means 0.779, p=0.048). In the 10 mg vericiguat arm, LVEF increased at 12 weeks compared to placebo (+3.7% vs +1.5%, p=0.021). There were no significant differences in blood pressure and heart rate at 12 weeks between 10 mg vericiguat and placebo arms and adverse events were not increased. At 12 weeks, numerically fewer patients in the 5 mg (11 patients) and 10 mg vericiguat groups (10 patients) experienced cardiovascular death or HF hospitalization compared to placebo (18 patients).

Conclusions: Although the primary analysis of the primary end point was not achieved, compared to placebo, patients receiving vericiguat 10mg daily experienced a greater reduction in NT-proBNP, greater improvement in LVEF, and fewer clinical events. As titrated in this study, vericiguat doses up to 10 mg daily were safe and did not meaningfully influence blood pressure and heart rate at 12 weeks.

Disclosure:
M. Gheorghiade: Consultant/Advisory Board; Modest; Abbott Laboratories, Astellas, AstraZeneca, Bayer Healthcare AG, CorThera, Cytokinetica, DebioPharm SA, Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Takeda, Trevena Therapeutics. A.P. Maggioni: Research Grant; Modest; Cardiorentis, Bayer, Novartis, Servier. C. Lam: Research Grant; Modest; Medtronic, Vifor Pharma. Research Grant; Significant; Boston Scientific. Consultant/Advisory Board; Modest; Bayer, Novartis, Takeda, Merck, Astra
Zeneca, Janssen Research&Development, LL. **E. Samano:** Employment; Modest; Bayer SA. **E. Kraigher-Krainer:** Consultant/Advisory Board; Modest; Bayer Healthcare. **G. Filippatos:** Research Grant; Modest; European Union. Consultant/Advisory Board; Modest; Bayer, Novartis, Cardiorentis. **J. Butler:** Research Grant; Modest; National Institutes of Health, European Union. Consultant/Advisory Board; Modest; Amgen, Bayer, Cardiocell, Novartis, Boehringer-Ingelheim, Trevena, Relypsa, Z Pharma, Pharmain, Zensun. **S.J. Greene:** None. **K. Mueller:** Employment; Modest; Bayer Pharma AG. **L. Roessig:** Employment; Significant; Bayer Pharma AG. **P. Ponikowski:** Consultant/Advisory Board; Modest; Bayer Pharma AG. **S. Shah:** Research Grant; Significant; NIH, Actelion. Consultant/Advisory Board; Modest; AstraZeneca, Bayer, Alnylam. Consultant/Advisory Board; Significant; Novartis. **S.D. Solomon:** Consultant/Advisory Board; Modest; Bayer. **B. Pieske:** Speakers Bureau; Modest; Bayer Healthcare, Novartis, Stealth Peptides, AstraZeneca. Consultant/Advisory Board; Modest; Stealth Peptides, Daiichi Sankyo, BMS. Consultant/Advisory Board; Significant; Bayer Healthcare, Novartis.