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Press Release

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NEW MEDICATION CLASS MAY SAFELY AND EFFECTIVELY TREAT ANEMIA

Highlights

- Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) create a low-oxygen state to stimulate the body to make more red blood cells.
- The drugs generated promising results in several phase 2 clinical trials in kidney disease patients with anemia.

Anemia commonly arises in patients with chronic kidney disease or kidney failure.

Washington, DC (October 22, 2015) — Investigational drugs that produce effects in the body similar to what occurs at high altitudes may offer a new way to stimulate red blood cell production and treat patients with anemia, according to studies appearing in an upcoming issue of the *Journal of the American Society of Nephrology* (JASN). The findings may lead to safer alternatives than currently used anemia medications.

Patients with chronic kidney disease or kidney failure often experience severe degrees of anemia, or low levels of red blood cells, which limits oxygen delivery to tissues. Anemia commonly arises in patients with kidney dysfunction because the kidneys secrete most of the hormone erythropoietin, which stimulates red blood cell production. Anemia is assessed by a patient's level of hemoglobin, the component of red blood cells that transports oxygen throughout the body.

Current therapies for anemia include recombinant human erythropoietins, erythropoiesis-stimulating agents (ESAs), and intravenous iron, all of which carry considerable safety concerns. Investigators now report promising results of a new class of oral medications, called hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), to treat anemia in patients with kidney disease. These drugs produce effects in the body similar to what occurs at high altitude, essentially causing the body to make more red blood cells that carry oxygen to where it is needed.

In a phase 2 randomized clinical trial, Anatole Besarab, MD (FibroGen, Inc.) and his colleagues enrolled 60 dialysis patients who received no iron, oral iron, or intravenous iron while treated with a HIF-PHI called roxadustat (also known as FG-4592) for 12 weeks. Roxadustat increased erythropoietin and concomitantly improved several processes that increased the availability of iron for incorporation into hemoglobin in red

blood cells. Roxadustat with only moderate oral iron supplementation corrected anemia (as assessed by patients' hemoglobin levels) as well as roxadustat with intravenous iron. Average hemoglobin increases of ≥2 g/dl were achieved within 7 weeks in study participants.

"As anemia is associated with an increased risk of cardiac events and death as well as decreased quality of life, the availability of such an oral therapy could change the landscape of treatment of anemia in kidney failure patients," said Dr. Besarab.

In 2 other phase 2 clinical trials, a team led by Louis Holdstock, PhD and Alexander Cobitz, MD, PhD (GlaxoSmithKline) enrolled 73 nondialysis patients with chronic kidney disease and 83 hemodialysis patients to test the effects of a HIF-PHI called GSK1278863 (0.5mg, 2mg, or 5 mg) compared with control (placebo for the nondialysis study; continuing on recombinant human erythropoietin for the hemodialysis study). In the nondialysis study, GSK1278863 produced dose-dependent effects on hemoglobin, with the highest dose resulting in an average increase of 1 g/dl at week 4. In the hemodialysis study, treatment with GSK1278863 in the 5-mg arm maintained average hemoglobin concentrations after the switch from recombinant human erythropoietin, whereas average hemoglobin decreased in the lower-dose arms.

"This research lays the foundation for future longer-term trials that will examine whether GSK1278863 can manage anemia in patients with CKD with a reduced incidence of cardiovascular events and death," said Dr. Holdstock.

In an accompanying editorial, Colin Lenihan, MD (Stanford University School of Medicine) and Wolfgang Winkelmayer, MD, MPH, ScD (Baylor College of Medicine) noted that the kidney community has been put on high alert by various safety issues with other anemia treatments in the past decade and a half. While they believe that phase 3 clinical trials of HIF-PHIs will help address some of these concerns, the safety of these medications with regard to rare events will require careful postmarketing surveillance after the drugs are approved.

Dr. Besarb's study co-authors include Elena Chernyavskaya, MD, Igor Motylev, MD, Evgeny Shutov, MD, Lalathaksha Kumbar, MD, Konstantin Gurevich, MD, Daniel Tak Mao Chan, MD, Robert Leong, MD, Lona Poole, MD, Ming Zhong, PhD, Khalil Saikali, PhD, Marietta Franco, MS, Stefan Hemmerich, PhD, RAC, Kin-Hung Peony Yu, MD, and Thomas Neff, MDhc. Disclosures: Dr. Besarab reports grants from FibroGen, Inc., grants and personal fees from Great Lakes Pharma, grants and personal fees from Rockwell Int., personal fees from • Vasc-Alert, grants and personal fees from • Akebia, grants and personal fees from • Affymax, personal fees from • Amgen , personal fees from • Bayer, personal fees from • Bioconnect, grants and personal fees from • Fibrogen , personal fees from • Hospira, other from • IMS Health, personal fees from • Medgenics, personal fees from • Pharmacos, personal fees and other from • Hoffman La Roche, grants from Vasc-Connect, outside the submitted work; and Reviewer for UpToDate on a variety of

subjects related to dialysis, anemia, iron metabolism. Dr. Motylev reports personal fees received from FibroGen, Inc., during the conduct of the study. Dr. Shutov reports personal fees received from FibroGen, Inc., during the conduct of the study. Dr. Kumbar reports personal fees received from FibroGen, Inc., during the conduct of the study. Dr. Gurevich reports personal fees received from Fresenius Medical Care, Amgen, and Roche. Dr. Leong reports being an employee of FibroGen, Inc., during the conduct of the study and receiving personal fees from FibroGen, Inc., outside the submitted work. During the 36 months prior to publication, he received consulting fees from FibroGen. Dr. Poole reports receiving salary and stock options from FibroGen, Inc. Dr. Zhong reports receiving salary and stock options from FibroGen, Inc. Dr. Saikali reports receiving salary, stock options and personal fees from FibroGen, Inc. Ms. Franco reports being an employee of FibroGen, Inc. during the conduct of the study and receiving personal, consulting, and other fees outside the submitted work. Dr. Hemmerich reports receiving salary and stock options from FibroGen, Inc. during the conduct of the study and outside the submitted work. Dr. Yu reports being a shareholder and an employee of FibroGen, Inc. during the conduct of the study and outside the submitted work. Dr. Neff reports being a shareholder and an employee of FibroGen, Inc. during the conduct of the study and outside the submitted work.

The article, entitled “Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients,” will appear online at http://jasn.asnjournals.org/ on October 22, 2015.

Dr. Holdstock and Dr. Cobitz’s study co-authors include Amy Meadowcroft, PharmD, Rayma Maier, MSc, Brendan Johnson, PhD, Delyth Jones MSc, Anjay Rastogi, MD, Steven Zeig, MD, John Lepore, MD. Disclosures: Louis Holdstock: Employee of, and owns stock in, GlaxoSmithKline; Amy Meadowcroft: Employee of, and owns stock in, GlaxoSmithKline; Rayma Maier: Employee of, and owns stock in, GlaxoSmithKline; Brendan Johnson: Former employee of GlaxoSmithKline; owns stock and stock options in GlaxoSmithKline; Delyth Jones: Employee of, and owns stock and stock options in, GlaxoSmithKline; Anjay Rastogi: Received research grants from GlaxoSmithKline; John Lepore: Employee of, and owns stock and stock options in, GlaxoSmithKline; Alexander Cobitz: Employee of, and owns stock and stock options in, GlaxoSmithKline.

The article, entitled “Four-Week Studies of Oral Hypoxia-Inducible Factor–Prolyl Hydroxylase Inhibitor GSK1278863 for Treatment of Anemia,” will appear online at http://jasn.asnjournals.org/ on October 22, 2015.

The editorial, entitled “The Dawning of a New Day in CKD Anemia Care?” will appear online at http://jasn.asnjournals.org/ on October 22, 2015.

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Founded in 1966, and with nearly 16,000 members, the American Society of Nephrology (ASN) leads the fight against kidney disease by educating health professionals, sharing new knowledge, advancing research, and advocating the highest quality care for patients.

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