

PRESS RELEASE

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PIVOTAL TRIAL CONFIRMS LONG-TERM SAFETY AND EFFICACY OF INTRAVENOUS IRON DOSING STRATEGY ALLOWING HIGHER FERRITIN CONCENTRATION AND TRANSFERRIN SATURATION IN PATIENTS UNDERGOING HAEMODIALYSIS

- Results from the PIVOTAL trial were presented during the High-Impact Clinical Trials session at American Society of Nephrology (ASN) Kidney Week 2018
- The trial met its primary endpoint of noninferiority as assessed by a composite of death and cardiovascular events, demonstrating that a liberal, proactive intravenous (IV) iron dosing regimen did not expose patients to an increased level of harm
- Treatment with greater doses of iron, allowing for higher ferritin and transferrin saturation (TSAT) levels, was associated with significantly reduced rates of the primary outcome when the components were analysed as recurrent events and was less likely to result in hospitalisation for heart failure
- Among patients on maintenance haemodialysis, a proactive, high-dose regimen of IV iron significantly reduced dose requirements for erythropoiesis-stimulating agents (ESAs) and the need for blood transfusions, without adversely impacting mortality or safety endpoints such as hospitalisation or infection
- Across Europe and the United States, more than 70% of patients on maintenance haemodialysis receive IV iron¹⁻⁴

Detailed results from the Proactive IV iron Therapy in haemodialysis patients (PIVOTAL) trial were announced today as a late-breaking oral presentation at ASN Kidney Week 2018 in San Diego, California, US. PIVOTAL is a randomised controlled trial designed to investigate the effects of two IV iron dosing strategies among patients on maintenance haemodialysis.⁵ The reactive, low-dose IV iron arm was intended to maintain patients near the lowest acceptable iron limits (serum ferritin of 200 µg/L and TSAT of 20%). In contrast, the proactive, high-dose IV iron regimen encouraged more liberal iron dosing and permitted higher ferritin and TSAT levels (up to 700 µg/L and 40%, respectively), as has been observed in the US.^{6,7} Although liberal IV iron dosing is known to improve ESA response and to allow for reduced ESA doses, the effect of this strategy on other objective outcomes was previously unclear.⁸

The PIVOTAL trial followed 2,141 patients from 50 sites in the United Kingdom for up to 4.4 years (median follow-up after 2.1 years). The trial met its primary endpoint by demonstrating noninferiority of the proactive dosing regimen as assessed by the risk of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for heart failure (HR=0.88, 95% CI: 0.76–1.03, $P<0.001$). Additionally, the proactive iron dosing regimen was associated with a significant 22% reduced risk of death or cardiovascular events when analysed as recurrent events. As suggested by prior data, higher doses of iron allowed for a significant, nearly 20% reduction in monthly median ESA dose. Notably, the proactive dosing strategy, and

attendant increases in serum ferritin concentrations and TSAT, was not associated with any increase in the risk of hospitalisation, infection, or vascular access thrombosis. The results of the PIVOTAL trial were simultaneously published online in *The New England Journal of Medicine* (available online at NEJM.org).

“These robust data add a wealth of information to the evidence base supporting an optimal IV iron dose for the management of anaemia in this patient population. As the market leader for IV iron, we are committed to ensuring safe therapy for patients. With this study, a knowledge gap in the anaemia treatment of HD patients can be closed.” said Stefan Schulze, President of the Executive Committee and COO of Vifor Pharma Group.

The trial was supported by an unrestricted research grant from Vifor Fresenius Medical Care Renal Pharma Ltd. (VFMCRP) to Kidney Research UK. In addition to financial support, VFMCRP also provided Venofer[®] (iron sucrose) free of charge for the duration of the trial.

David C. Wheeler, Professor of Kidney Medicine at University College London, UK, is a member of the PIVOTAL study steering committee. He said “PIVOTAL represents the first rigorously designed scientific study to prospectively examine the impact of IV iron dosing regimens on hard clinical outcomes among patients undergoing haemodialysis.” He also commented that the results “support the safety of a proactive approach to IV iron dosing that results in higher serum ferritin as well as TSAT levels and allows for reduced reliance on ESAs.”

Initiated in 2013, PIVOTAL represents the largest prospective, controlled clinical trial of IV iron in patients with CKD. It also stands as the largest nephrology clinical trial ever conducted exclusively in the UK. “This is the first trial of its kind and size to have taken place in the UK and we are immensely proud of everyone who took part. There was a gap in the understanding of intravenous iron therapy which needed to be addressed and we now believe the results will lead to improved treatments and better outcomes for patients.” said Sandra Currie, Chief Executive of Kidney Research UK.

FURTHER INFORMATION

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Vifor Pharma Group is a global pharmaceuticals company. It aims to become the global leader in iron deficiency, nephrology and cardio-renal therapies. The company is the partner of choice for specialty pharmaceuticals and innovative patient-focused solutions. Vifor Pharma Group strives to help patients around the world with severe and chronic diseases lead better, healthier lives. The company develops, manufactures and markets pharmaceutical products for precision patient care. Vifor Pharma Group holds a leading position in all its core business activities and consists of the following companies: Vifor Pharma; Vifor Fresenius Medical Care Renal Pharma, a joint company with Fresenius Medical Care; Relypsa; and OM Pharma. Vifor Pharma Group is headquartered in Switzerland, and listed on the Swiss Stock Exchange (SIX Swiss Exchange, VIFN, ISIN: CH0364749348). For more information, please visit www.viforpharma.com.

Vifor Fresenius Medical Care Renal Pharma Ltd., is a joint company of Vifor Pharma Group and Fresenius Medical Care, develops and commercialises innovative and high quality therapies to improve the life of patients suffering from chronic kidney disease (CKD) worldwide. The company was founded at the end of 2010 and is owned 55% by Vifor Pharma Group and 45% by Fresenius Medical Care. For more information about Vifor Fresenius Medical Care Renal Pharma and its parent companies, please visit www.vfmcpr.com, www.viforpharma.com and www.freseniusmedicalcare.com.

Venofer[®], the originator iron sucrose, is an intravenous iron therapy developed by Vifor Pharma. Venofer[®] is authorized worldwide in more than 80 countries for the treatment of iron deficiency and iron deficiency anaemia where there is a clinical need for a rapid iron supply or when oral iron is ineffective, not tolerated or patient non-compliance is an issue. Venofer[®] is the leading intravenous iron brand in terms of volume usage worldwide and is the trusted gold standard in iron therapy for dialysis patients. Overall monitored usage of Venofer[®] now correlates to over 23 million patient-years of clinical experience.

Iron deficiency (ID) is defined as a state in which iron stores are inadequate for normal blood formation, as the iron requirements exceed the supply. Iron deficiency anaemia results from low or depleted stores of iron. In severe cases red cells in a patient with IDA are both microcytic (small) and hypochromic (pale), and values for mean corpuscular volume (MCV) and mean corpuscular Hb concentration (MCHC) are characteristically changed. According to the World Health Organization (WHO) it is estimated that about 700 million people have iron deficiency anaemia (IDA).⁹

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