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UPDATED ANALYSIS OF PIVOTAL STUDY REVEALS: PROACTIVE, HIGH DOSAGE OF VENOFER® SIGNIFICANTLY REDUCES RISK OF DEATH OR MAJOR CARDIOVASCULAR EVENTS IN HAEMODIALYSIS PATIENTS

Re-analysis of the PIVOTAL data by the investigators has revealed that proactive, high-dose Venofer® compared to reactive, low-dose Venofer® resulted in:

- **Superiority and statistically significant reduction in the risk of death or major cardiovascular events (P=0.04)**
- **Fewer myocardial infarctions or fewer hospitalisations for heart failure**
- **Reduction in recurrent cardiovascular events**
- **Lower need/use of erythropoiesis-stimulating agents and a lower incidence of blood transfusion**
- **No difference in the infection rate**

Further to the announcement on 29 October 2018, Vifor Pharma provides an update to the results of the **P**roactive **IV** ir**O**n **T**herapy in haemodi**AL**ysis patients (PIVOTAL) trial. This update was necessitated by identification of a programming error in the original analysis by the investigators. The re-analysis of the data revealed a statistically significant improvement in the treatment effects of a higher dose of Venofer® (i.v. iron sucrose) compared with a lower dose. These results supersede those presented at the High-Impact Clinical Trial session at ASN Kidney Week 2018 and published on *The New England Journal of Medicine* website, NEJM.org, on 26 October 2018. The updated results can be viewed on: www.NEJM.org (DOI: 10.1056/NEJMoa1810742).

In the updated results, the primary endpoint – which was the composite of nonfatal myocardial infarction, nonfatal stroke, hospitalisation for heart failure, or death – reached statistically significant superiority (P=0.04) for the proactive, high-dose Venofer® regimen compared with the low-dose Venofer® group. Similarly, the rates of the individual components of fatal or non-fatal myocardial infarction and hospitalisation for heart failure were lower among patients receiving high-dose i.v. iron. Results on deaths, as well as all safety endpoints (vascular access thrombosis, hospitalisation for any cause and for infection), reduction in ESA dose requirements and number of blood transfusions did not differ between the two treatment arms.

“The PIVOTAL trial was the first trial to assess optimal dosing strategy of intravenous iron in patients undergoing haemodialysis and demonstrated that exposing those patients to higher doses of iron over time significantly reduced the risk of mortality or major nonfatal cardiovascular events.” said Stefan Schulze, President of the Executive Committee and COO of Vifor Pharma Group.

Francesco Locatelli, Professor of Nephrology, Hospital Alessandro Manzoni, Lecco, Italy said, “PIVOTAL was a long-awaited landmark study in nephrology and the results mark a significant milestone in the treatment of

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haemodialysis patients. It is expected that the results from this study will impact guidelines and clinical practice for the benefit of these patients."

Javed Butler, Professor of Cardiology, University of Mississippi, Jackson, MS, USA added that "the effect of iron levels on cardiovascular events in haemodialysis patients has previously been given little recognition. The PIVOTAL trial has demonstrated the significant benefits of effective treatment with intravenous iron by improving major cardiovascular outcome parameters in this high risk population."

FURTHER INFORMATION

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About the trial
The **P**roactive **IV** ir**O**n **T**herapy in haemodi**AL**ysis patients (PIVOTAL) trial was a randomised controlled study designed to investigate the effects of two i.v. iron dosing strategies among patients on maintenance haemodialysis.[1] The PIVOTAL trial assessed the efficacy and safety of a proactive, high dose i.v. iron sucrose (Venofer®) regimen (permitting ferritin up to 700 µg/L and TSAT up to 40%) vs. a reactive low dose i.v. iron sucrose (Venofer®) regimen (keeping patients near a serum ferritin of 200 µg/L and TSAT of 20%). The primary endpoint was the composite of nonfatal myocardial infarction, nonfatal stroke, hospitalisation for heart failure, or death. Other secondary endpoints included death, infection rate, and dose of an erythropoiesis-stimulating agent.[1] After non-inferiority of the primary endpoint was established (P>0.001), superiority for the pro-active high dose i.v. iron sucrose (Venofer®) treatment strategy was demonstrated for the primary endpoint as well (P=0.04). The PIVOTAL trial followed 2,141 patients from 50 sites in the United Kingdom for up to 4.5 years.[2]

The PIVOTAL trial was funded by Kidney Research UK and was supported by an unrestricted grant from Vifor Fresenius Medical Care Renal Pharma Ltd. (VFMCRP). However, the company had no input into the study design or delivery of the trial. VFMCRP also provided Venofer® (iron sucrose) for the trial, free of charge.

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, and ISIN: CH0364749348). For more information, please visit www.viforpharma.com.

Vifor Fresenius Medical Care Renal Pharma Ltd., 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.vfmcrp.com, www.viforpharma.com and www.freseniusmedicalcare.com.

Venofer®, the originator iron sucrose, is an intravenous iron therapy developed by Vifor Pharma. Venofer® is authorised 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 Organisation (WHO) it is estimated that about 700 million people have iron deficiency anaemia (IDA)[3].

References

1. Macdougall IC, White C, Anker SD, et al. Randomized trial comparing proactive, high-dose versus reactive, low-dose intravenous iron supplementation in hemodialysis (PIVOTAL): study design and baseline data. Am J Nephrol 2018;48:260-268.
2. Macdougall IC, White C, Anker, SD, et al. Intravenous Iron in Patients Undergoing Maintenance Hemodialysis. N Engl J Med 10.1056/NEJMoa1810742.
3. World Health Organization. Preventing and controlling iron deficiency anaemia through primary health care. 1989; http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/ida_preventng_control_primary_healthcare.pdf Accessed October 17, 2018.