

Pharming reports positive data from first investigator-initiated study of rhC1-Inhibitor (RUCONEST®) in Contrast-induced Nephropathy

Primary Endpoint was met, with rhC1INH treatment reducing neutrophil gelatinase-associated lipocalin (NGAL), a widely recognized marker of acute renal damage

Leiden, The Netherlands, 17 October 2018: Pharming Group N.V. (“Pharming” or “the Company”) (Euronext Amsterdam: PHARM) today announced positive results from a Phase II investigator-initiated study of RUCONEST® (recombinant human C1 esterase inhibitor, or “rhC1INH”) in a double-blind, placebo-controlled clinical trial in patients at risk of nephropathy resulting from contrast-enhanced examinations.

The study was led by Dr. Michael Osthoff at the University Hospital Basel, Basel, Switzerland. 75 eligible patients with known moderate to severe renal function impairment were given either 50 units per kg (up to 4200 units) of RUCONEST® (n=37) or placebo (n=38) immediately prior to treatment with standard-of care contrast medium as part of an elective coronary angiography with or without a percutaneous coronary intervention (“PCI”), and then a second identical treatment four hours after the intervention .

In the overall study, RUCONEST® showed a statistically-significant effect ($p=0.038$) in reducing the rise in urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL), the primary endpoint for the study and a generally recognized early marker of acute renal injury, in patients with diagnosed renal function impairment undergoing interventions enhanced with standard contrast media such as PCIs.

The results were especially clear in the sub-group of patients (n=30) undergoing PCI. The intent-to-treat analysis in this group showed that patients on RUCONEST® had a median increase in peak urinary NGAL concentration within 48 hours of 1.8 ng/ml compared with an increase of 26.2 ng/ml in the placebo arm ($p=0.04$). This corresponds to a clear difference in the median percentage change in the peak urinary NGAL level within 48 hours of 11.3% in the RUCONEST® arm and 205.2% in the placebo arm ($p=0.001$).

The overall assessment of the study also showed trends that patients undergoing more invasive interventions and procedures requiring higher volumes of contrast medium experienced a stronger benefit from the RUCONEST® treatment.

The treatment also showed an excellent safety profile comparable to the placebo group – a particularly significant observation considering the high-risk patient group included in the study (average age approximately 77 years, with multiple comorbidities and impaired kidney function)

This data therefore supports additional clinical investigations for the use of rhC1INH in a new indication where there is significant unmet medical need.

A secondary endpoint measured was Troponin T, a marker of cardiovascular damage caused by the examination or intervention itself, but this did not show a meaningful difference in the overall study population: the power of the study and the variety of interventions applied were not suitable to perform an appropriate evaluation.

Following these positive results, Pharming will continue discussions with Dr. Osthoff and other experts in this area with the aim to perform further clinical development to establish the efficacy and efficiency

of RUCONEST® treatment in the patient group likely to experience the greatest benefit. Dr. Osthoff will be publishing the full results of his study in due course.

Dr Michael Osthoff, Basel University Hospital Basel, Basel, Switzerland and Primary Investigator, said:

“We are very pleased that we were able to provide an early proof-of-concept that dosing RUCONEST® ahead and following contrast enhanced investigations and interventions, particularly in those patients that have to undergo PCI, may limit subsequent damage to these patients’ kidneys. We believe that these positive results merit further clinical investigations and confirmation in a larger trial, and we are very keen to continue the collaboration with Pharming.”

Dr Bruno Giannetti, Chief Operations Officer of Pharming, said:

“Reaching a significant difference already in a small number of patients in this well-run exploratory trial gives a surprisingly clear positive signal in what could become a large new indication for RUCONEST®.

Furthermore, invasive interventions requiring contrast medium applications, like PCI, are known to cause damage to organs like the kidney and the brain through small thromboembolic events triggering complement cascade activation. RUCONEST® is a recombinant form of the most important element of the body’s own complement activation braking system. NGAL is a sensitive indicator to detect and assess this combined damage in this particular situation. These results therefore also provide important predictive information on the potential protective effects of RUCONEST® in a number of other indications like pre-eclampsia or reperfusion injuries, in which complement activation is thought to play an important role.”

As planned, Pharming has filed for regulatory approval in the Netherlands and shortly also in Australia to begin the first clinical study of RUCONEST® in pre-eclampsia.

About Contrast-induced Acute Kidney Injury (“CI-AKI”)

Acute kidney injury (AKI) affects 13-18% of all patients admitted to hospital in developed countries. The estimated general incidence of CI-AKI is approximately 7%. Its incidence may increase to >50% in the presence of risk factors such as chronic kidney disease, diabetes mellitus and nephrotoxic drugs¹. These estimates apply to over 38 million contrast-enhanced investigations in the USA alone, and around the same number in the rest of the world. In practice, the vast majority of the patients affected are those with existing kidney impairment, which is estimated variously at between 13%-21% of the total. This implies a potential maximum addressable market size of several million patients in each of those main markets.

About Contrast-induced Nephropathy

Contrast-induced nephropathy (CIN) is a very serious form of AKI, a complication of angiographic procedures resulting from the administration of contrast media. It is the third most common cause of hospital-acquired acute renal injury and represents about 12% of the cases. CIN is defined as an elevation of serum creatinine of at least 25% or ≥ 0.5 mg/dl (44 μ mol/l) from baseline within 48 h. The

¹ Source: [Contrast Medium-Induced Acute Kidney Injury](#): Umar Sadat, Ammara Usman, Jonathan R. Boyle, Paul D. Hayes, Richard J. Solomon *Cardiorenal Med.* 2015 Jun; 5(3): 219–228.

incidence of CIN varies between 0 and 24% depending on a patient's risk factors. It is generally a transient and reversible form of acute renal failure. However, the development of CIN is associated with longer hospital stays and an increased morbidity and mortality, in addition to a higher financial cost. A meta-analysis that included 40 studies found a 6% incidence of CIN after contrast-enhanced computed tomography (CT) scans, 9% after peripheral angiography and 4% after intravenous pyelography. The incidence of CIN is low in patients with normal renal function (0-5%). However, several prospective controlled trials reported an incidence of 12-27% in patients with pre-existing renal impairment. Furthermore, in one study, an incidence as high as 50% was reported in patients with diabetic nephropathy undergoing coronary angiography in spite of the use of low-osmolar contrast media and adequate hydration. Notably, up to 15% of those patients required dialysis.²

The best care available today still results in very serious consequences for some patients (with 6%-11% proceeding to dialysis or worse outcomes depending on the medium used and their level of renal performance prior to the scan, according to various studies), although this is improving slowly as new less-damaging contrast media are introduced.

About NGAL

NGAL (neutrophil gelatinase-associated lipocalin, also known as lipocalin-2 and as siderocalin) is a protein involved in innate immunity responses. It is expressed in neutrophils and in low levels in the kidney, prostate, and epithelia of the respiratory and alimentary tracts, including the renal tubules. Renal expression of NGAL is dramatically increased in kidney injury from a variety of causes, and NGAL is released primarily into both urine but also plasma. NGAL levels rise very quickly after the event triggering kidney difficulty, making NGAL an early and sensitive biomarker of kidney injury. Both plasma and urine NGAL concentrations correlated highly with serum creatinine concentrations. Kidney biopsies in these patients showed intense accumulation of immuno-reactive NGAL in 50 % of the cortical tubules. These results identified NGAL as a widespread and sensitive response to established AKI in humans³. Specifically, the predictive utility of NGAL for AKI in CIN has been confirmed in a recent meta-analysis⁴.

About Pharming Group N.V.

Pharming is a specialty pharmaceutical company developing innovative products for the safe, effective treatment of rare diseases and unmet medical needs. Pharming's lead product, RUCONEST® (conestat alfa) is a recombinant human C1 esterase inhibitor approved for the treatment of acute Hereditary Angioedema ("HAE") attacks in patients in Europe, the US, Israel and South Korea. The product is available on a named-patient basis in other territories where it has not yet obtained marketing authorization.

RUCONEST® is distributed by Pharming in Austria, France, Germany, Luxembourg, the Netherlands, the United Kingdom and the United States of America. Pharming holds commercialisation rights in Algeria, Andorra, Bahrain, Belgium, Ireland, Jordan, Kuwait, Lebanon, Morocco, Oman, Portugal, Qatar, Syria,

² Source: Contrast-induced Nephropathy: Nazar M. A. Mohammed, Ahmed Mahfouz, Katafan Achkar, Ihsan M. Rafie, Rachel Hajar. Heart Views. 2013 Jul-Sep; 14(3): 106–116.

³ Neutrophil gelatinase-associated lipocalin (NGAL): A new marker of kidney disease: Prasad Devarajan, Scand J Clin Lab Invest Suppl. 2008; 241: 89–94.

⁴ Neutrophil Gelatinase-Associated Lipocalin in the prediction of Contrast-Induced Nephropathy, a systemic review and meta-analysis: Tong j, Li H, Zhang H et al, J Cardiovasc Pharmacol 2015; 66: 239-45.

Spain, Switzerland, Tunisia, United Arab Emirates and Yemen. In some of these countries distribution is made in association with the HAEi Global Access Program (GAP).

RUCONEST® is distributed by Swedish Orphan Biovitrum AB (publ) (SS: SOBI) in the other EU countries, and in Azerbaijan, Belarus, Georgia, Iceland, Kazakhstan, Liechtenstein, Norway, Russia, Serbia and Ukraine.

RUCONEST® is distributed in Argentina, Colombia, Costa Rica, the Dominican Republic, Panama, and Venezuela by Cytobiotech, in South Korea by HyupJin Corporation and in Israel by Kamada.

RUCONEST® is also being examined for approval for the treatment of HAE in young children (2-13 years of age) and evaluated for various additional follow-on indications.

Pharming's technology platform includes a unique, GMP-compliant, validated process for the production of pure recombinant human proteins that has proven capable of producing industrial quantities of high quality recombinant human proteins in a more economical and less immunogenetic way compared with current cell-line based methods. Leads for enzyme replacement therapy ("ERT") for Pompe and Fabry's diseases are being optimized at present, with additional programs not involving ERT also being explored at an early stage at present.

Pharming has a long-term partnership with the China State Institute of Pharmaceutical Industry ("CSIPI"), a Sinopharm company, for joint global development of new products, starting with recombinant human Factor VIII for the treatment of Haemophilia A. Pre-clinical development and manufacturing will take place to global standards at CSIPI and are funded by CSIPI. Clinical development will be shared between the partners with each partner taking the costs for their territories under the partnership.

Additional information is available on the Pharming website: www.pharming.com

Forward-looking Statements

This press release of Pharming Group N.V. and its subsidiaries ("Pharming", the "Company" or the "Group") may contain forward-looking statements including without limitation those regarding Pharming's financial projections, market expectations, developments, partnerships, plans, strategies and capital expenditures.

The Company cautions that such forward-looking statements may involve certain risks and uncertainties, and actual results may differ. Risks and uncertainties include without limitation the effect of competitive, political and economic factors, legal claims, the Company's ability to protect intellectual property, fluctuations in exchange and interest rates, changes in taxation laws or rates, changes in legislation or accountancy practices and the Company's ability to identify, develop and successfully commercialise new products, markets or technologies.

As a result, the Company's actual performance, position and financial results and statements may differ materially from the plans, goals and expectations set forth in such forward-looking statements. The Company assumes no obligation to update any forward-looking statements or information, which should be taken as of their respective dates of issue, unless required by laws or regulations.

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