Press Release

VFMCRP and Cara Therapeutics announce European Medicines Agency has accepted to review the Marketing Authorization Application for difelikefalin

- **Companies have successfully submitted the EU regulatory application for marketing authorization for difelikefalin**
- **If approved, difelikefalin injection will be the first therapy available in Europe for treatment of pruritus associated with chronic kidney disease in hemodialysis patients**

St.Gallen, Switzerland, and Stamford, Conn., 30 March 2021 – Vifor Fresenius Medical Care Renal Pharma (VFMCRP) and Cara Therapeutics, Inc. (Nasdaq: CARA) today announced that the European Medicines Agency (EMA) accepted to review the Marketing Authorization Application (MAA) for difelikefalin injection for the treatment of pruritus associated with chronic kidney disease in hemodialysis patients. The EMA will review the application under the centralized marketing authorization procedure.

The EMA filing is supported by positive clinical data from the two pivotal phase-III trials KALM-1 and KALM-2, as well as supportive data from an additional 32 clinical studies. If approved, difelikefalin would receive marketing authorization in all member states of the European Union (EU), as well as in Iceland, Liechtenstein and Norway. EMA's decision on the EU MAA is expected Q2-2022.

"Following the US FDA's acceptance and priority review for the New Drug Application for difelikefalin at the beginning of March 2021, this is another major step forward on our mission to help kidney patients around the world lead better, healthier lives," commented Stefan Schulze, CEO of Vifor Pharma Group. "Together with our partner Cara Therapeutics, we remain focused on making this innovative therapy available in Europe, if approved, for patients with chronic kidney disease-associated pruritus, a condition that has been historically underdiagnosed and undertreated."

"The acceptance of the EU regulatory application for difelikefalin marks another major milestone towards our goal of bringing this first-in-class therapeutic to the significant number of hemodialysis patients worldwide with chronic intractable pruritus," said Derek Chalmers, Ph.D., D.Sc., President and Chief Executive Officer of Cara Therapeutics. "We look forward to working closely with our partner, Vifor Pharma, through the EMA review process and in preparation for commercial launch across European territories, if approved."

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About Vifor Pharma Group
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 a partner of choice for 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 and Vifor Fresenius Medical Care Renal Pharma (a joint company with Fresenius Medical Care). 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 viforpharma.com.

About Cara Therapeutics
Cara Therapeutics is a clinical-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pruritus by selectively targeting peripheral kappa opioid receptors, or KORs. Cara is developing a novel and proprietary class of product candidates, led by KORSUVA™ (CR845/difelikefalin), a first-in-class KOR agonist that targets the body's peripheral nervous system, as well as certain immune cells. In two Phase 3 trials, KORSUVA injection has demonstrated statistically significant reductions in itch intensity and concomitant improvement in quality of life measures in hemodialysis patients with moderate-to-severe chronic kidney disease-associated pruritus (CKD-aP). Oral KORSUVA™ has successfully completed a Phase 2 trial for the treatment of pruritus in patients with CKD and is currently in Phase 2 trials in atopic dermatitis, primary biliary cholangitis and notalgia paresthetica patients with moderate-to-severe pruritus.

About Chronic Kidney Disease-associated Pruritus (CKD-aP)
CKD-aP is an intractable systemic itch condition that occurs with high frequency and intensity in patients with chronic kidney disease undergoing dialysis. Pruritus has also been reported in patients with stage III-V CKD who are not on dialysis. The majority of dialysis patients (approximately 60 to 70%) report pruritus, with 30 to 40% reporting moderate or severe pruritus.[1,2,3] Recent data from the ITCH National Registry Study showed that among those with pruritus, approximately 59% experienced symptoms daily or nearly daily for more than a year. Given its association with CKD/ESRD, most afflicted patients will continue to have symptoms for months or years, with currently employed antipruritic treatments, such as antihistamines and corticosteroids, unable to provide consistent, adequate relief. Moderate-to-severe chronic pruritus has repeatedly been shown to directly decrease quality of life, contribute to symptoms that impair quality of life (such as poor sleep quality), and is associated with depression.[4] CKD-aP is also an independent predictor of mortality and the risk for hospitalization among hemodialysis patients.

Forward-looking Statements
Statements contained in this press release regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of these forward-looking statements include statements concerning the potential regulatory approval of difelikefalin solution for injection and the potential timeline for EMA review and approval of the MAA and the potential of difelikefalin solution for injection to be a therapeutic option for CKD-aP in dialysis dependent patients. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Risks are described more fully in Cara's filings with the Securities and Exchange Commission, including the "Risk Factors" section of Cara's Annual Report on Form 10-K for the year ended 31 December 2020 and its other documents subsequently filed with or furnished to the Securities and Exchange Commission. All forward-looking statements contained in this press release speak only as of the date on which they were made. Except to the extent required by law, Cara undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

References:

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[2] Ramakrishnan K, et al. Clinical characteristics and outcomes of end-stage renal disease patients with self-reported pruritus symptoms. International Journal of Nephrology and Renovascular Disease. 2014; 7: 1-12.
[3] Sukul et al. Self-reported Pruritus and Clinical, Dialysis-Related, and Patient-Reported Outcomes in Hemodialysis Patients. Kidney Med. 2020 Nov 21;3(1):42-53.
[4] Mathur VS, et al. A longitudinal study of Uremic Pruritus in hemodialysis patients. Clin J Am Soc Nephrol. 2010; 5(8):1410-1419.