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## **VM202, a DNA-based Potential Disease-Modifying Treatment for Painful Diabetic Neuropathy and Foot Ulcer**

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VM202 is a DNA-based medicine designed to simultaneously express two isoforms of a protein called hepatocyte growth factor (HGF). Currently, VM202 is being tested for 4 major cardiovascular or neurological diseases, including Diabetic Peripheral Neuropathy (DPN), Chronic Non-healing Diabetic Foot Ulcer (NHU), Ischemic Heart Disease (IHD) and Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig's disease). VM202 is in a Phase 3 trial and was granted Regenerative Medicine Advanced Therapy (RMAT) designation for painful DPN on May 21, 2018.

DPN is a serious complication of diabetes mellitus, with painful DPN being a frequent manifestation of neuropathy. Tight glycemic control and treatment of other cardiovascular risk factors are effective preventive measures, but DPN remains the most common complication of DM, affecting 60-70% of diabetics. Progressive DPN may result in loss of function in affected extremities, infection, and amputation. Current treatments provide only symptomatic relief of the pain associated with DPN. There is a clear unmet medical need for treatments that address the underlying pathology of DPN and prevent the progressive destruction and loss of function associated with this disease.

VM202 has demonstrated its capabilities of inducing angiogenesis increasing blood flow, producing significant analgesic effects, regenerating damaged nerves, indeed, significant reductions of various pathologies had been observed in several animal models. The development of new blood vessels in patients with DPN may replace damaged capillary beds – including the neural microvasculature - and improve peripheral blood flow. In addition, the local, transient expression of hHGF produced from VM202 has been shown to downregulate the expression level of pain related factors such as  $\alpha 2\delta 1$ , 5HTT, CSF-1, and IL-6 among others. HGF expressed from VM202 may also have a direct effect on neural tissues by repairing damaged nerves through the promotion of axon outgrowth by directly interacting with Schwann cells and/or sensory neurons. The combination of improved vascularity and direct effects on neurons is expected to durably decrease neuropathic pain, improve quality of life and exercise capacity, and potentially prevent further progression of DPN.

Data from the completed Phase 2 trial show sustained pain relief lasting more than three months after a single treatment course. The first of two independent phase III trials of VM202-DPN is going smoothly in the US. As of March 22, 2019, all the intended total of 493 patients have been randomized and completed the treatment. This is the world's first phase III clinical trial of a DNA-based medicine for diabetic neuropathy, and the results are supposed to be released between Sep. and Nov. this year.

VM202-PAD, targeting chronic non-healing diabetic foot ulcer (NHU), began patient enrollment in the US in August 2017. As of March 22, 2019, among the 300 intended, 44 have been randomized. Another important development regarding VM202-PAD is a new study on intermittent claudication (IC), launched with the support of the US NIH (National Institute of Health). Called Hi-PAD, the trial is investigating the effect of VM202 on mobility and calf perfusion in older adults with peripheral artery disease (PAD).

VM202 studies for other cardiovascular and neurological indications are also moving forward as planned. Phase II for coronary artery disease (VM202-CAD) is under preparation in Korea and is recruiting patient subjects. VM202-ALS, which obtained *Orphan Drug* and *Fast Track* designation from the US FDA, is also in preparation to initiate the phase II trial. In this presentation, major pre-clinical and clinical development results of VM202 will be shared.