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Notice Regarding Publication of Research Paper on Phase II Clinical Trial Results of HGF Gene Therapy Product in the United States

A Phase II clinical trial of an HGF gene therapy product was conducted in the United States from 2020 to 2023, targeting patients with comprehensive advanced chronic limb-threatening ischemia (CLTI) who had mild to moderate lower limb ulcers. Anges is pleased to announce that a research paper detailing the results of this clinical trial has now been published.

Since February 2020, our HGF gene therapy product has been undergoing a Phase II clinical trial in the United States, targeting patients with CLTI who have mild to moderate lower limb ulcers. In June 2024, preliminary results demonstrated favorable outcomes. Subsequently, in September 2024, the product was designated as a Breakthrough Therapy by the U.S. Food and Drug Administration (FDA).

In patients with CLTI, the target disease for the HGF gene therapy product, progression to severe stages requiring major lower limb amputation (proximal to the ankle) is associated with a five-year mortality rate of 57%, second only to lung cancer at 80%, according to a report by Professor David Armstrong and colleagues at the Keck School of Medicine, University of Southern California. Similar to cancer treatment concepts, early intervention is critical. For CLTI, initiating treatment with the HGF gene therapy product at a relatively early stage—before surgical revascularization becomes necessary—offers the potential to heal ulcers, extend the time before amputation, and ultimately improve patients' future quality of life (QOL).

The research paper detailing the results of this clinical trial has been published in *Circulation: Cardiovascular Interventions*, a journal issued by the American Heart Association (AHA). We are pleased to share the details of the clinical trial results as follows.

Overview of Phase II Clinical Trial of HGF Gene Therapy Product (AMG0001)

- Multicenter, randomized, double-blind, placebo-controlled comparative study
- Total enrollment: 75 patients
- Patients with neuro-ischemic ulcers (TP/$TcPO_2$: 30–59 mmHg)
- Four injections of either AMG0001 (4 mg or 8 mg) or placebo at one-month intervals
- Observation period: 12 months following the start of administration

Results of Phase II Clinical Trial of HGF Gene Therapy Product (AMG0001)

- Median time to healing was 84 days in the AMG0001 treatment group, compared to 280 days in the placebo group ($p = 0.007$).

- The proportion of ulcers healed within 12 months was 77.6% in the AMG0001 treatment group, compared to 46.2% in the placebo group (p = 0.010).
- The proportion of complete healing within 6 months was 63.3% in the AMG0001 treatment group, compared to 38.5% in the placebo group (p = 0.053).

Based on these results, AMG0001, the HGF gene therapy product, significantly shortened the time to complete ulcer healing in patients with moderate CLTI and demonstrated a favorable safety profile. These findings suggest that HGF gene therapy may offer a promising treatment option for patients with CLTI.

For more details on the published paper, please visit:

Circulation: Cardiovascular Interventions

https://www.ahajournals.org/doi/abs/10.1161/CIRCINTERVENTIONS.125.015648

This publication does not entail any changes to our consolidated earnings forecast for the fiscal year ending December 2025; however, we believe it will contribute to enhancing our medium-term corporate value.

About the HGF Gene Therapy Product

The HGF gene therapy product is a plasmid DNA that expresses hepatocyte growth factor (HGF), a factor originally discovered in the liver—the organ with the highest regenerative capacity. When administered to ischemic tissue, it produces and secretes HGF, which promotes collateral vessel formation, increases local blood flow, and improves ischemic conditions. HGF plays a key role not only in the liver but also in the formation and regeneration of various organs and tissues, including blood vessels, lymphatic vessels, and nerves. Focusing on HGF's ability to induce angiogenesis, our company has developed this product as a novel therapeutic agent for ischemic diseases caused by vascular occlusion and impaired blood flow—offering a mechanism of action that creates new blood vessels, which has led to its commercialization.

About *Circulation: Cardiovascular Interventions*

Circulation: Cardiovascular Interventions is a peer-reviewed academic journal published by the American Heart Association (AHA), specializing in the field of cardiovascular interventions—minimally invasive treatments for heart and vascular diseases using techniques such as catheter-based procedures. The journal focuses on interventional techniques for coronary artery disease, structural heart disease, and vascular disorders, emphasizing original research, randomized trials, and large-scale registry studies.