



Press release  
24 November, 2022

### **Initiation of Phase III Study of HGF in Vocal Fold Scar**

Kringle Pharma, Inc. (Head office located in Osaka, Japan; President & CEO, Kiichi Adachi; “KRINGLE”), a late clinical-stage biopharmaceutical company, today announced the start of Phase III, a placebo-controlled, double-blind clinical study, to confirm the efficacy and safety of recombinant human HGF (KP-100LI) administered in patients with vocal fold scar.

KRINGLE aims to develop and commercialize HGF as an innovative therapeutic agent for various fibrotic diseases, focusing on vocal fold scar as the initial target indication. KRINGLE already submitted a Phase III clinical trial application to the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, as announced by the KRINGLE news release dated October 24, 2022. Since then, the review process by PMDA was completed and the regulatory clearance was obtained to initiate the Phase III study. KRINGLE and Kyoto Prefectural Public University Corporation (Chairman: Akihiro Kinda) have signed a clinical trial agreement for the Phase III study, and University Hospital, Kyoto Prefectural University of Medicine, is ready to enroll patients in this study. The Phase III study will be conducted at five clinical sites in Japan including University Hospital, Kyoto Prefectural University of Medicine. Each clinical site will begin screening patients subsequently once contracts and other preparations are all set.

#### [Phase III Study Outline]

Condition	Vocal fold scar or sulcus vocalis
Study design	Multicenter randomized trial -Double-blind period: Weekly intracordal administration of KP-100LI or placebo for four times, followed by the 24-week observation. -Open-label extension period: Weekly intracordal administration of KP-100LI for four times to subjects who wish to continue the KP-100LI treatment, followed by the 24-week observation.
Age	18 to 75 years
Estimated enrollment	62 subjects (31 subjects for each arm)
Primary outcome measures	Improvement rate in Voice Handicap Index-10 (VHI-10) score at week 24 of the double-blind observation period
Clinical sites	University Hospital, Kyoto Prefectural University of Medicine, and other four clinical sites in Japan

The Phase III study has been supported by the Japan Agency for Medical Research and Development (AMED) as its CiCLE program (Project title: Clinical development of recombinant HGF protein for the treatment of refractory fibrosis).



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***About Hepatocyte Growth Factor (HGF)***

HGF was originally discovered as an endogenous mitogen for mature hepatocytes. Subsequent studies demonstrated that HGF exerts multiple biological functions based on its mitogenic, motogenic, anti-apoptotic, morphogenic, anti-fibrotic and angiogenic activities, and facilitates regeneration and protection of a wide variety of organs including not only liver, but also kidneys, heart, lungs, nerve tissues and skin.

***About Vocal Fold Scar***

Vocal fold scar is a fibrotic disease which causes severe dysphonia. In patients with vocal fold scar, fibrosis is formed in the vocal fold mucosa due to inflammation or injury, hardening the mucosa and impairing the function of the vocal cords. Dysphonia makes daily communication difficult, leading to a significant deterioration in QOL (Quality of Life). No effective treatment has been established and there are huge unmet medical needs for the patients who suffer greatly. It is estimated that there are approximately 10,000 patients with vocal fold scar in Japan<sup>1</sup>.

1) Koichi Tsunoda, “Research to formulate guidelines for establishment and standardization of diagnosis and treatment of vocal fold abnormalities” Research paper on epidemiology of intractable diseases, the Ministry of Health, Labour and Welfare of Japan. 2009.

***About VHI-10***

Voice Handicap Index (VHI) consists of a self-administered questionnaire that quantifies the quality of life of patients with voice disorders. In using the VHI-30, patients are asked to answer 30 questions related to their physical, functional, or emotional conditions, rating from 0 (no impairment) to 4 (maximum impairment). VHI-10 is later developed as a shortened version of VHI-30 to ask 10 questions. A Japanese translated form of VHI is available by The Japan Society of Logopedics and Phoniatics<sup>2</sup>.

2) Clinical practice guidelines for the diagnosis and management of voice disorders 2018, The Japan Society of Logopedics and Phoniatics, The Japan Laryngological Association.

***About Kringle Pharma, Inc.*** <https://www.kringle-pharma.com/en/>

Kringle Pharma is a late clinical-stage biopharmaceutical company established in December 2001 to develop novel biologics based on HGF. Currently, Kringle promotes clinical development for acute spinal cord injury, ALS and vocal fold scar. Kringle’s mission is to contribute to societal and global healthcare through the continued research, development, and commercialization of HGF drug for patients suffering from incurable diseases.

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