Press release
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Topline Data from Phase 3 Study of KP-100IT in Acute Spinal Cord Injury

Kringle Pharma, Inc. (Head office located in Ibaraki, Osaka; President & CEO, Kiichi Adachi; "KRINGLE"), a late clinical-stage biopharmaceutical company, today announces topline data from a nonrandomized, multicenter, confirmatory Phase 3 study investigating KP-100IT, the intrathecal formulation of recombinant human HGF, in subjects with acute spinal cord injury. This Phase 3 study was conducted in Japan from July 2020 to December 2023. Based on the results of this study and the previous Phase 1/2 study, KRINGLE will continue discussions with the Japanese regulatory agency and prepare to submit an application for manufacturing and marketing approval in Japan.

In Phase 3 study, KP-100IT was administered intrathecally once weekly for 5 doses starting 72 hours after injury and followed for 6 months in AIS grade A subjects with complete cervical spinal cord injury. A total of 26 subjects were enrolled, 25 of whom were evaluable for efficacy. The primary endpoint of the study was the percentage of subjects with an improvement of at least two AIS grades, A to C or better, at 6 months after treatment with KP-100IT as compared to the patient database ("Database") maintained by the Spinal Injuries Center in Japan.

Key results from the topline data are summarized below:

- The percentage of improvement to AIS C or better at 6 months after treatment with KP-100IT was 12.0%, considerably higher than the 8.6% improvement rate to AIS C or better in the Database. The difference, however, was not statistically significant.
- The percentage of improvement to AIS B or better at 6 months after treatment with KP-100IT was 56.0%, while the improvement in the Database to AIS B or better was only 19.8%. This large difference was statistically significant and is considered highly encouraging.
- The total ASIA motor score showed an average improvement of 7.1±5.7 points at 6 months after treatment with KP-100IT when compared to the baseline.
- Regarding safety, no serious adverse events or deaths due to KP-100IT administration were observed. Importantly, no anti-HGF antibodies were generated.

Interesting and perhaps relevant differences in the precipitating cause of the acute spinal cord injury were noted between this study and the previous Phase 1/2 study. Based on statistical analysis, the Phase 3 study did not meet its primary endpoint. However, a comparison of the subject's cause of injury in the Phase 3 study with that in the Phase 1/2 study showed that while there were fewer cases of falls as the precipitating cause of injury, there were more cases of traffic or other accidents generating more severe injuries. One reason for this difference may be that subjects were enrolled under behavioral restrictions associated with the COVID-19 pandemic. In addition, the Phase 3 study included a large number of subjects with high blood C-reactive protein (CRP) levels at 72 hours post-injury. This protein is found in blood plasma and its circulating concentrations rise in response to inflammation. It has been reported to be a significant independent prognostic factor in the progression of secondary spinal cord injury (Ozaki et al. *Spinal cord* 2021 Nov;59(11):1155-1161.). These findings suggest that the subjects' cause of injury in this study may be different from that in the Phase 1/2 study.

Overall, KRINGLE is confident that the safety profile and efficacy signals of KP-100IT in the acute phase of spinal cord injury have been demonstrated in both the Phase 1/2 and Phase 3 studies. Given the importance of developing an effective treatment for acute spinal cord injury, for which there is currently no effective treatment, KRINGLE will continue to conduct a detailed analysis of the study data, including further stratified analysis in consideration of the significant differences in subjects' background and casue of injury, and prepare to file a manufacturing and marketing authorization application for KP-100IT by the end of 2024.

Professor Masaya Nakamura, M.D., Ph.D., of the Department of Orthopaedic Surgery at Keio University School of Medicine stated as a coordinating investigator of the Phase 3 study, "During the study period, the incidence of spinal cord injury decreased due to the influence of activity restrictions under the COVID-19 pandemic. As a result, more extremely severe subjects' injury caused by high-energy trauma were enrolled than expected, which may have resulted in a lack of statistical significance in the primary endpoint. On the other hand, more than half of the AIS A subjects enrolled in this study improved to AIS B/C, while most AIS A subjects remained completely paralyzed in the real world, indicating that treatment with KP-100IT in the acute phase suppressed secondary damage and protected spinal nerves. It is expected that KP-100IT treatment in the acute phase will enhance the effectiveness of rehabilitation and cell transplantation therapies currently under development."

"We are proud to announce the completion of the Phase 3 study, although it took longer than initially expected to enroll subjects under the COVID-19 pandemic. We would like to express our gratitude to all those involved in the study." said Kiichi Adachi, Ph.D., President and CEO of KRINGLE. "This study demonstrated the safety of HGF administration in subjects with acute cervical spinal cord injury. The study also showed favorable results in terms of therapeutic efficacies. In the acute treatment of spinal cord injury, the most important issue is how to reduce spinal nerve cell death due to secondary damage. We believe that this study verified that KP-100IT can be used as a novel therapeutic drug for the treatment of acute spinal cord injury. We will make concerted efforts to apply for manufacturing and marketing approval in Japan, so that we can deliver the therapeutic drug to spinal cord injury subjects as soon as possible. We will also continue our ongoing preparations for clinical development in the United States."

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. HGF exerts neurotrophic effects and enhances neurite outgrowth, and the therapeutic effect of HGF on spinal cord injury has been demonstrated in animal models by Professors Hideyuki Okano and Masaya Nakamura at Keio University School of Medicine. Expectations for HGF as a novel therapeutic agent are increasing for spinal cord injury.

A group led by Professor Shigeru Hirano of the Department of Otolaryngology and Head and Neck Surgery, Kyoto Prefectural University of Medicine, focused on the anti-fibrotic effects of HGF and demonstrated its pharmacological effects on vocal cord scar. HGF is also expected to have the potential to be an effective therapeutic agent for various fibrotic diseases including vocal fold scar.

About Spinal Cord Injury

Spinal cord injury is caused by trauma, leading to a variety of paralytic or painful symptoms. In descending order of incidence, the main causes of spinal damage: tripping over, traffic accidents and falls from height. Recently, due to the rise in the elderly population, tripping over is becoming an increasingly common cause. In Japan, there are approximately 100,000 to 200,000*[1] chronic spinal cord injury patients with an incidence of about 6,000 new cases per year*[1]. Worldwide*[2], approximately 60,000 people*[3] are injured annually, and the number of patients, including those in the chronic phase, is estimated to be approximately 1.1 million*[3]. By appropriate early treatment after the injury and specialized rehabilitation, some degree of functional recovery can be expected, but complex severe symptoms, including motor paralysis, muscular spasticity, sensory paralysis, dysfunction of internal organs (rectal and bladder disorder, thermoregulatory dysfunction, decreased visceral function, decreased respiratory function) may often remain. For these reasons, therefore, there is a strong need for the development of a novel drug for the treatment of acute spinal cord injury.

Source:

*[1] Miyakoshi et al. *Spinal Cord* 2021 Jun;59(6):626-634., Sakai H et al. *J Spine Res.* 2010 1(1):41-51.

*[2] Developed countries where advanced treatment is available

*[3] Internal estimates based Spinal Cord Injury Facts and Figures at a Glance (2021), The International Spinal Cord Injury Society web site, World Population Trends by Statistics Bureau, Ministry of Internal Affairs and Communications, etc.

About ASIA impairment scale (AIS) Grade

The American Spinal Injury Association Impairment Scale (AIS) is widely used to classify the severity of injury in spinal cord injury individuals, with complete (AIS grade A), sensory incomplete (AIS grade B), motor incomplete (AIS grade C and grade D), or normal (AIS grade E). Please see the following URL for more details:
https://asia-spinalinjury.org/wp-content/uploads/2019/10/ASIA-ISCOS-Worksheet_10.2019_PRINT-Page-1-2.pdf

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 conducts two Phase 3 clinical studies, which is the final stage of the drug development, in spinal cord injury and vocal fold scar among other target indications. 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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