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Chugai Files for Additional Indication of Evrysdi for Pre-Symptomatic Spinal Muscular Atrophy and Additional Dosage for Infants up to 2 Months of Age

- The application was based on an overseas phase II RAINBOWFISH study that demonstrated the efficacy and safety of Evrysdi in infants with pre-symptomatic spinal muscular atrophy (SMA)
- As the only approved oral drug for SMA, it is expected to contribute to early treatment before onset of SMA including infants up to 2 months of age

TOKYO, February 15, 2024 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) today announced that it filed regulatory application with the Ministry of Health, Labour and Welfare (MHLW) of "Evrysdi® Dry Syrup 60 mg " (Hereafter Evrysdi), a treatment for spinal muscular atrophy, for an additional indication of pre-symptomatic SMA, and an additional dosage for infants up to the 2 months of age. The drug received orphan drug designation from the MHLW in March 2019, for SMA, and the application for additional indication is also subject to priority review.

"There is great significance in filing for additional indication for pre-symptomatic SMA, as initiation of treatment before onset of symptoms may possibly maximize treatment benefit. In addition, availability of this drug in all ages including infants from birth may enable treatment to be started promptly after diagnosis. We remain committed towards obtaining additional indication approval of Evrysdi, to provide benefit as the only approved oral treatment for SMA" said Chugai's President and CEO, Dr. Osamu Okuda.

The application is based on results from the RAINBOWFISH study, an overseas Phase II study (does not include Japan) for pre-symptomatic SMA infants. The RAINBOWFISH study included babies with two or more copies of the SMN2 gene. Generally, the lower the number, the more severe the disease.[1]

The study met its primary endpoint with 80% of the primary efficacy population (n=5) sitting without support for at least five seconds after 1 year of Evrysdi treatment, assessed by Bayley Scales of Infant and Toddler Development, third edition (BSID-III). The primary efficacy population included babies with two SMN2 copies and a CMAP(compound muscle action potential) amplitude of ≥1.5 mV at baseline. CMAP amplitude measures the muscle response to a stimulus, and a low score correlates with symptom onset in SMA patients and worse functional outcomes. Patients in the primary efficacy population are expected to progress similarly to the natural history of SMA Type I without treatment, and in that case, children with Type 1 SMA would not be expected to sit.[2] Of the 26 babies in the study, 81% could sit independently for 30 seconds, including all patients with low CMAP amplitude at baseline (<1.5 mV) and the majority were standing and walking.

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Adverse events (AEs) were more reflective of the age of the babies than underlying SMA. The majority of AEs were not considered treatment-related, and there were no deaths or AEs leading to withdrawal or treatment discontinuation. The most common AEs were teething, COVID-19, pyrexia, gastroenteritis, eczema and constipation. The AEs observed in the RAINBOWFISH primary analysis are generally consistent with those AEs seen in other Evrysdi trials in SMA.

In SMA, the loss of motor neurons may begin before symptoms start[3,4] so initiating treatment early is critical for better outcomes, and newborn screening plays an important role for early diagnosis. Evrysdi is expected to offer high medical value by enabling immediate start of treatment after diagnosis.

[Reference Information]
Majority of newborn babies with spinal muscular atrophy (SMA) treated with Roche's Evrysdi able to sit independently after 1 year of treatment (Press release by Roche issued on October 4, 2023)
https://www.roche.com/media/releases/med-cor-2023-10-04

About the RAINBOWFISH study
The RAINBOWFISH study [NCT03779334] is an open-label, single-arm, multicentre study, investigating the efficacy, safety, pharmacokinetics, and pharmacodynamics of Evrysdi in babies (n=26), from birth to six weeks of age (at first dose) with genetically diagnosed SMA who are not yet presenting with symptoms. Proportion of infants in the primary efficacy population who are sitting without support for at least 5 seconds at month 12 assessed by the BSID-III (Bayley Scales of Infant and Toddler Development - Third Edition) gross motor scale. Japan is not included in this study.

About Evrysdi
Evrysdi is a survival motor neuron 2 (*SMN2*) splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Evrysdi is designed to treat SMA by increasing and sustaining the production of the survival motor neuron (SMN) protein. SMN protein is found throughout the body and is critical for maintaining healthy motor neurons and movement. Evrysdi was approved in the U.S. in August 2020, in Europe in March 2021, and in Japan in June 2021.

About spinal muscular atrophy (SMA)[5]
Spinal muscular atrophy (SMA) is a genetic neuromuscular disease that causes muscule atrophy and muscle weakness due to degeneration of the motor neuron.[6] The causative gene for SMA is the survival motor neuron (*SMN*) gene. The disease develops because of insufficient production of functional SMN protein from *SMN2* genes alone, in addition to the dysfunction of the *SMN1* gene.[7]

Source:
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3. Kolb SJ, et al. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol. 2017

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4. Govoni A, et al. Time Is Motor Neuron: Therapeutic Window and Its Correlation with Pathogenetic Mechanisms in Spinal Muscular Atrophy. Mol Neurobiol. 2018 Aug;55(8):6307-6318.
5. With your SMA. Walking with everyone involved in spinal muscular atrophy (SMA). Available from: https://with-your-sma.jp/. Accessed February 2024. (Japanese only)
6. Farrar MA and Kiernan MC. The genetics of spinal muscular atrophy: progress and challenges. Neurotherapeutics. 2015;12:290-302.
7. Kolb SJ and Kissel JT. Spinal muscular atrophy. Neurol Clin. 2015;33:831-46.

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