

March 23, 2018

Press Release

Nobelpharma Co., Ltd.

**SAKIGAKE Designation & Orphan Drug Designation**  
**RAPALIMUS GEL 0.2% (mTOR inhibitor), Treatment for Angiofibroma in Tuberous Sclerosis**  
**Marketing Approval Granted**

Nobelpharma Co., Ltd. (Head Office: Chuo-ku, Tokyo; President and CEO: Jin Shiomura) received marketing approval today for RAPALIMUS GEL 0.2% (general name: sirolimus), a drug for the treatment of angiofibroma in tuberous sclerosis complex.

Tuberous sclerosis is a rare genetic disease that can cause developmental disabilities, and tumor lesions over the entire body such as in the brain, on the skin, and kidneys. Among those, skin lesions such as angiofibroma occur frequently, and the symptoms become obvious during adolescence, causing anguish for patients, and degrading the quality of their lives. However, current treatments are invasive, such as surgery or laser treatment, which are difficult to administer to young children or patients with developmental disabilities, and we recognized that no treatment has been given until the condition became serious. That is why a safe, easy and effective treatment has been sought for many years.

Under these circumstances, the research group of Professor Mari Kaneda of the Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine of Osaka University, researched sirolimus, an mTOR inhibitor, as a topical treatment based on the pathology of tuberous sclerosis, and conducted investigator-led clinical trials (phases I and II) with the support of the Ministry of Health, Labour and Welfare Practical Research Project for Rare/Intractable Diseases, the Japan Agency for Medical Research and Development (AMED), the Department of Pharmacy, Osaka University Hospital, and the Department of Medical Innovation, Osaka University Hospital, on facial lesions of tuberous sclerosis patients. The trials showed that sirolimus gel is a safe and extremely effective treatment for the facial angiofibroma of this disease. These research results were described in the January 1, 2017 issue of JAMA Dermatology, Volume 153, Number 1 (the Journal of the American Medical Association).

Nobelpharma took the results of this research and conducted a phase III comparative trial and long-term dosage trial of Rapalimus Gel 0.2% to verify its effectiveness and safety, and in October 2017 became the first in the world to apply for marketing approval, and within the short period of less than 6 months obtained approval of the drug in March 2018.

Rapalimus Gel 0.2% was the first drug to receive the SAKIGAKE designation in October 2015, and then obtained orphan drug status in December 2015. In the initial developmental stages the national research and

development agency New Energy and Industrial Technology Development Organization (NEDO) provided support, and in later stages the national research and development agency National Institutes of Biomedical Innovation, Health and Nutrition provided support.

Rapalimus Gel 0.2% is the only drug with the possibility of local administration to provide treatment of facial angiofibroma from tuberous sclerosis, and it is expected to contribute to the improvement of the quality of life for patients.

The development of this drug was characterized by 1)the fruits of research by academia, 2)proof of safety and effectiveness in investigator-led clinical trials, 3)a private company following up on the investigator-led trials to conduct verification trials, 4)speedy marketing approval in less than 6 months based on the SAKIGAKE designation (particularly the concierge system) and orphan drug designation, 5)extremely good coordination between industry, government and academia, and 6)in accordance with the SAKIGAKE name, research has now begun overseas as well.

**【Contact】**

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