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SymBio Pharmaceuticals Limited
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(Securities Code: 4582)

SymBio Pharmaceuticals Announces Publication of Research Showing Antiviral Drug Brincidofovir Inhibits Infectious Viral Production of Polyomavirus

TOKYO, Japan, July 12, 2024 – SymBio Pharmaceuticals Limited (Headquarters: Tokyo, "SymBio" or the "Company") today announced that Penn State College of Medicine (Pennsylvania, United States) has published the results of preclinical research showing the antiviral activity of brincidofovir ("BCV") against polyomavirus.

In November 2022, SymBio entered into Material Transfer Agreement (MTA)[1] with Penn State College of Medicine (Professor Aron Lukacher) to evaluate the potential usefulness of BCV in a mouse model infected with polyomavirus. SymBio is pleased to announce that new findings from the research have been published by Professor Lukacher in the journal *mBio®*.

Highlights of the published findings include:
Primary culture in vitro test using mouse kidney cells and brain cortical cells:

- BCV inhibited virus production after Murine Polyomavirus (MuPyV) infection
- Findings suggest that the suppression of infectious virus production involves a reduction of viral T antigen[2]

In vivo studies in mouse models:

- BCV suppresses infectious virus production in kidney and brain from relatively low doses
- Preventive and therapeutic effects on chronic infection in an immunodeficient mouse model

Statement from Professor Aron Lukacher: "I am very pleased that our study provides new insights into an antiviral agent that may be of great benefit to patients suffering from life-threatening diseases caused by polyomaviruses."

Statement from Fuminori Yoshida, President and CEO: "There are no drugs approved for severe polyomavirus infection, and effective agents are desperately needed. We will be working with Professor Lukacher on further studies to validate the anti-polyomavirus activity of BCV."

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1. Related news releases:

[24 November 2022: SymBio enters into Material Transfer Agreement with Penn State College of Medicine for a non-clinical study to evaluate the efficacy of brincidofovir in a polyomavirus model]

2. T antigen:

T antigen is a viral protein required for polyomavirus replication and virus production.

3. Mouse model of polyomavirus virus infection

Polyomavirus infections such as BK virus and JC viruses are asymptomatic in healthy individuals where they persist mainly in the urinary tract and lymphoid tissues. However, when the body's immune system is compromised, these viruses reactivate and can cause severe infections in the kidney, bladder, and brain. There are no antiviral drugs against polyomaviruses, and there are few preclinical models for these viruses that infect only humans. The model established in Prof. Lukacher's lab represents polyomavirus infection in mice using murine polyomavirus which has a genome structure and mode of infection similar to that of the human polyomaviruses. This mouse model allows us to examine the involvement of immune mechanisms as well as infection in the kidney and central nervous system.

Information of the Published Articles:

Butic AB, Katz ZE, Jin G, Fukushima K, Hazama M, Lukacher AE, Lauver MD. 2024. Brincidofovir inhibits polyomavirus infection *in vivo*. *mBio* e0104924.
https://doi.org/10.1128/mbio.01049-24

About the antiviral drug Brincidofovir

Brincidofovir (BCV) has a new mechanism of action as a lipid conjugate of cidofovir (CDV). CDV is an antiviral drug already approved and marketed in the United States, but unapproved in Japan. BCV is expected to be an effective treatment against a wide spectrum of dsDNA virus infections (cytomegalovirus, adenovirus, Epstein-Barr virus (EBV), herpes virus, BK virus, papillomavirus and smallpox virus including monkeypox, etc.), with superior features such as high activity antiviral effect in comparison with CDV and other antiviral drugs. Due to the breakthrough nature of the BCV molecule, in which a specific length of lipid chain is attached to the CDV, BCV is converted into a molecule that acts directly within the cell, thereby dramatically increasing the efficiency of cellular uptake and showing a high antiviral activity. In September 2019, SymBio entered into a license agreement with Chimerix for the exclusive worldwide rights to develop, market, and manufacture BCV for all diseases except orthopoxviruses (such as smallpox and monkeypox). The tablets and oral suspension (oral formulation) were approved on June 4, 2021 for the treatment of smallpox in adults and pediatric patients, including neonates. In addition to its high antiviral activity, BCV is also

expected to have anti-tumor effects. We are currently conducting collaborative studies with the National Cancer Centre Singapore, the University of California, San Francisco, and other institutions to confirm its anti-cancer activity and to identify synergistic effects when combined with its antiviral activity.

Clinical trials and important R&D collaborations with prominent research institutions include:

- Initiated a Phase 2a clinical trial in patients with adenovirus infection after hematopoietic stem cell transplantation (March 2021) and received Fast Track designation from the FDA (April 2021). Proof of Concept (POC) of antiviral efficacy established based on data up to cohort 3 (May 2023).
- Initiated a Phase 2a clinical trial in patients with CMV infection after Hematopoietic Stem Cell Transplantation in June 2024.
- Initiated a non-clinical trial at the University of California, San Francisco Neurosurgery Brain Tumor Center to evaluate the anti-tumor effect of BCV on refractory brain tumors (September 2021).
- A number of recent studies have demonstrated that EBV is a risk factor for MS. SymBio entered into CRADA with the NINDS at the NIH in March 2023 to establish a new antiviral treatment method for MS and has been conducting collaborative research to develop a clinical trial.
- CRADA with the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH to evaluate the efficacy of BCV for EB virus-associated lymphoproliferative diseases (April 2023).
- Research on the involvement of infection by reactivation of latent viruses in various neurological severity diseases of the brain, including Alzheimer's disease, has been ongoing for the past several years, and a simple three-dimensional mimicry of human neural stem cell cultures and brain tissue established by Tufts University in the United States, the A Sponsored Research Agreement was signed (December 2022) to examine the effect of BCV on HSV infection using a herpes simplex virus (HSV) infection/reactivation model established by Tufts University in the U.S., which uses human neural stem cells cultured to mimic brain tissue in three dimensions.

About SymBio Pharmaceuticals Limited

SymBio Pharmaceuticals Limited was established in March 2005 by Fuminori Yoshida who previously served concurrently as Corporate VP of Amgen Inc. and founding President of Amgen Japan. In May 2016, the Company incorporated its wholly-owned subsidiary in the U.S., SymBio Pharma USA, Inc. (Headquarters: Durham, North Carolina, Representative: John Houghton).

The Company's underlying corporate mission is to "deliver hope to patients in need" as it aspires to be a leading global specialty biopharmaceutical company dedicated to addressing underserved medical needs.