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Symbio Pharmaceuticals Limited

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Representative Director

President and Chief Executive Officer

(Securities Code: 4582)

Confirmed Antitumor Effects of Brincidofovir in Peripheral T-Cell Lymphoma Suppression of the oncogenic MYC and Induction of Expression of Immunogenic Response Pathways

TOKYO, Japan, June 24, 2024 – Symbio Pharmaceuticals Limited (Headquarters: Tokyo, “Symbio” or the “Company”) is currently collaborating with the National Cancer Centre Singapore (“NCCS”) to evaluate its anti-tumor effects of brincidofovir (“BCV”). The result of the study was presented at the EHA2024 Hybrid Congress held in Madrid, Spain from June 13 to 16, 2024.

Results of our collaborative research with NCCS showing the anti-tumor effect of BCV on NK/T-cell lymphomas were reported at the 2022 American Society of Hematology meeting and the 2023 International Conference on Malignant Lymphoma. In this presentation, we report that BCV was evaluated using human T-cell lymphoma cell lines, including peripheral T-cell lymphoma (PTCL), and xenograft mouse models, and showed similar anti-tumor effects against these lymphomas as against NK/T-cell lymphomas.

Highlights of the research results presented include:

- 1) BCV showed high concentration-dependent cytotoxicity in all T-cell lymphoma cell lines examined.
- 2) In a xenograft mouse model, intraperitoneally administered BCV significantly and clearly inhibited tumor growth compared to the control group.
- 3) Similar changes were observed in BCV-treated PTCL cells in gene expression changes in the NK/T-cell lymphoma model, particularly in gene expression of immunomodulatory functions such as decreased MYC-related gene expression and increased IFN γ expression, which indicate anti-tumor effects.

Statement from Fuminori Yoshida, President and CEO: “As we promote the BCV business platform, the anti-tumor effect was confirmed in PTCL as well as NK/T-cell lymphoma, and we aim to start clinical trials for NK/T-cell lymphoma and PTCL, which are currently unmet therapeutic areas, as soon as possible. The anti-tumor effect is also expected to be contributed by suppression of Myc expression and induction of immune-related gene expression, suggesting anti-tumor effects not only

in hematological malignancies but also in solid tumors.”

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(Note)**Peripheral T-cell lymphoma (PTCL)**

PTCL is a general term for a variety of lymphoid tumors derived from T cells that have differentiated and matured in the thymus and migrated to peripheral tissues, and is a rare cancer classified as a rapidly progressing aggressive lymphoma. PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), ALK-positive anaplastic large cell lymphoma (ALCL), and ALK-negative ALCL are the major types. Primary treatment involves multidrug chemotherapy and radiation, but they are not always effective enough. Although various therapeutic agents have been clinically used for relapsed or refractory PTCL in recent years, no standard treatment has been established, and the development of new therapeutic agents is desired.

Mouse Xenograft Model

Xenograft models using highly immunocompromised mice have been used to transplant human cancer cell lines for the evaluation of anticancer drugs targeting cancer cells.

European Hematology Association

The European Hematology Association holds annual meetings attended by experts from around the world.

About the anti-viral 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 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), affiliated with the 3 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.