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SBI Holdings, Inc.

SBI ALA promo Co., Ltd.

Nobelpharma Co., Ltd.

Announcement of initiation of Phase III clinical study of orally active *in vivo* diagnostic agent  
for malignant glioma

SBI ALA promo Co., Ltd. (head office: Minato-ku, Tokyo; Representative Director and CEO: Yoshitaka Kitao; “SBI ALA promo”), a subsidiary of SBI Holdings, Inc., that conducts the research and development of cosmetics, health foods and medicines containing 5-aminolevulinic acid (ALA)<sup>\*1</sup>, has reached agreement in principle with Nobelpharma Co., Ltd. (head office: Tokyo; President: Jin Shiomura; “Nobelpharma”)<sup>\*2</sup> on collaborative commercialization of an *in vivo* diagnostic agent of the surgical resection of malignant glioma<sup>\*3</sup>, a type of brain tumor (active pharmaceutical ingredient: 5-aminolevulinic acid hydrochloride; “the ALA diagnostic agent”) and will initiate a Phase III clinical study with Nobelpharma.

The ALA diagnostic agent is an orally active product that is indicated for use in the photodynamic diagnosis (PDD) for visualization of tumor tissues during the surgical resection of malignant glioma. With approval from the European Medicines Evaluation Agency (EMA), it has already been marketed in ten European countries, including Germany and U.K., by Medac GmbH, a business partner of SBI ALA promo. Under an agreement between SBI ALA promo and Medac GmbH, SBI ALA promo and Nobelpharma are now going to initiate a clinical study of the ALA diagnostic agent as part of their collaboration. This ALA diagnostic agent is the first diagnostic agent in Japan that is indicated for oral use in the surgical resection of tumors.

Malignant glioma is one of the most aggressive types of brain tumor, for which the standard of care is the surgical resection of tumors under microscopy. However, as malignant glioma is characterized by invasion and cell proliferation in normal brain, leading to poor demarcation between malignant glioma tissues and normal tissues, it is difficult to remove tumors completely. This clinical study is designed to verify the efficacy and safety of the diagnostic agent orally administered several hours before the surgical resection of tumors to allow for complete discrimination from normal tissues by making tumor tissues glow red applying a special light to the affected area during operation.

If this clinical study confirms the efficacy and safety of the ALA diagnostic agent for malignant

glioma, it can be expected to contribute toward improving tumor resection rates and outcomes in Japan as well as reducing patients' physical burden intra- and post-operatively.

SBI ALA promo and Nobelpharma will continue with further efforts to provide clinical practice as early as possible with access to the ALA diagnostic agent as a novel treatment option for individuals suffering from malignant glioma.

**\*1: ALA (5-aminolevulinic acid)**

"ALA" is a type of natural amino acid that has survived the last 3,600 million years and is contained even in food products such as red wine and radish sprouts. It is known to get involved in production of chlorophyll, which is essential for photosynthesis in plants, and in production of vitamin B12, blood constituents and intracellular energy in animals. "ALA" is well known as an extremely important and essential ingredient for any species. It is used in a wide range of applications from intraoperative diagnosis of brain tumors and cancer screening in the medical field, anemia prophylaxis in the health foods field, to care for pimples and rough skin in the cosmetics field.

**\*2: Nobelpharma Co., Ltd.**

Nobelpharma Co., Ltd. was founded in 2003 with the mission to develop pharmaceutical products for important unmet needs and deliver them to patients in need of them.

The company is contributing to medical care by devoting itself to research and development of pharmaceuticals for critical unmet needs, such as orphan drugs, drugs for off-label use, and drugs for children, and supplying them where they are needed. For more information about Nobelpharma Co., Ltd., please go to the company's website: <http://www.nobelpharma.co.jp>

**\*3: Glioma**

Glioma is a tumor that arises from the glial cells of the brain, many of them malignant tumors with poor prognosis. Gliomas account for about 30% of all primary brain tumors, classified into several types according to the form of cells composing tumors. Astrocytomas, the most common gliomas, are broadly grouped by malignancy into four grades (Grade I-IV). In particular, Grade IV, called glioblastoma, represents the most malignant tumors with extremely poor prognosis. The treatment for gliomas is typically done by surgical operations (craniotomies), but complete tumor removal is so difficult that postoperative radiotherapy and chemotherapy are applied in many cases.

