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**Start of an Investigator-Initiated Clinical Trial for
Treatment-Resistant Breast Cancer Patients with Novel siRNA Nucleic Acid
Formulation “TDM-812” at the National Cancer Center**

The company hereby announces that an investigator-initiated clinical trial (first-in-human, Phase I study) for a novel siRNA nucleic acid formulation, “TDM-812” (RPN2siRNA/A6K complex), has been started at the National Cancer Center Hospital (Director: Yasuaki Arai). TDM-812 was developed by a collaboration research with the National Cancer Center (President: Tomomitsu Hotta, Tokyo, Japan) and the National Cancer Center Research Institute (Director: Hitoshi Nakagama). TDM-812 was successfully administered to the first subject at the National Cancer Center Hospital.

Intended for patients suffering from treatment-resistant breast cancer with local mass and conducted at the Department of Breast and Medical Oncology of the National Cancer Center Hospital (Department Chief: Kenji Tamura), this investigator-initiated clinical trial is the first first-in-human Phase I study in Japan. Safety and tolerability of intratumorally administered TDM-812 will be evaluated, and the recommended dose of intratumoral administration is aimed to be determined. This is the first time in Japan where discovery of a particular gene led to formulation of a breast cancer treatment nucleic acid drug for clinical trial. On June 30th 2015, a patient with triple-negative breast cancer with subcutaneous metastasis has been treated with TDM-812 as the first subject of this investigator-initiated clinical trial.

In treatment-resistant locally advanced or recurrent breast cancer, large mass or skin ulcers (with partial loss of skin) commonly form when lesions progress to the skin around the primary tumor or surrounding lymph nodes. Local pain, bleeding, malodor, and exudate are also often experienced, which affects the patient’s Quality of Life (QOL). It is hard to control local lesions with existing therapies, hence development of a new treatment is sort after to improve patient’s QOL.

The researchers at National Cancer Center Research Institute’s Division of Molecular and Cellular Medicine (Chief: Takahiro Ochiya) have discovered that RPN2 gene regulates the drug resistance involved in treatment-resistant breast cancer, and have published their findings on Nature Medicine in 2008. They

have also found that RPN2 gene controls “cancer stem cells”, which produce new cancer cells, and also regulate the treatment-resistibility. Furthermore, it has been proven that the knockdown of expression of RPN2 by introducing siRNA nucleic acid suppresses the nature and the proliferation of drug-resistant breast cancer cells.

However being easily degradable in vivo, siRNA and other nucleic acid drugs in naked form is hard to be delivered into cells, resulting in little efficacy. To efficiently deliver siRNA into cancer cells while avoiding degradation, it is necessary to develop a suitable drug formulation. The company has been selected for the Ministry of Health, Labour and Welfare Grant-in-Aid for Scientific Research, "National Cancer Center Phase I Center Early Development Research" from 2011 with respect to the formulation of siRNA of RPN2 gene (RPN2siRNA) in collaboration with the National Cancer Center.

TDM-812 is a complex drug consisting of RPN2siRNA and surfactant-like peptide A6K, which is one of the company’s fundamental technologies with hopes of possibly solving problems of drug delivery into cells. Efficacy of TDM-812 has already been proven by treatment of breast cancer in large animal models in collaboration with Tokyo University of Agriculture and Technology Animal Medical Center (Professor: Hiroshi Ito). The treatment with TDM-812 is expected to be a highly specific therapy for cancer cells because RPN2 is localized in cancer stem cells and almost no expression of RPN2 is seen in normal tissues. As nucleic acid drug acts to suppress abnormal genes, it has fewer side effects and it can be expected to treat the root cause of the disease. Starting with this investigator-initiated clinical trial, we will work towards the first nucleic acid drug for treatment of breast cancer in the world.

The company will continue to promote the research and development of TDM-812 in relation to this investigator-initiated clinical trial. New applications using peptides and commercialization will also be explored.

This announcement does not influence the earning forecast of the company at this moment.