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SBI Holdings, Inc.

SBI Pharmaceuticals Co., Ltd.

**Research Paper on the Safety and Usefulness of 5-ALA in the Patients
with Type 2 Diabetes in Bahrain in the Food Intervention Test
Published in the “Journal of Diabetes Research”**

SBI Pharmaceuticals Co., Ltd., (Head office: Minato-ku, Tokyo; Representative Director & President: Yoshitaka Kitao; “SBI Pharmaceuticals”), a subsidiary of SBI Holdings, Inc., engaged in research and development of pharmaceuticals, health foods and cosmetics using 5-aminolevulinic acid (“5-ALA”)*¹, hereby announces that the research paper on the safety and usefulness of 5-ALA in the patients living in Bahrain with type 2 diabetes mellitus was published on September 23, 2016 in the “Journal of Diabetes Research”.

SBI Pharmaceuticals and Bahrain Defense Force Hospital/Royal Medical Services conducted a food intervention test using the nutritional supplement comprising 5-ALA and sodium ferrous citrate (SFC) *², which is already on market with the approval of Bahrain National Health Regulatory Authority (NHRA), at high doses of 5-ALA (up to 200mg per day) and SFC (up to 229.42mg per day) in the patients living in Bahrain with type 2 diabetes mellitus who are taking concomitant antidiabetic medications.

Fifty-three patients were enrolled as the subjects, with 35 patients receiving 5-ALA and SFC and 18 patients receiving placebo (without 5-ALA or SFC) as well as concomitant antidiabetic medications for 12 weeks. Blood glucose and HbA1c, together with the parameters of hepatic and renal functions and iron were measured.

No significant difference was found between the groups of 5-ALA and SFC and placebo in the adverse events reported during the study. Since no significant changes were observed in the measured values of the parameters on hepatic and renal functions and iron, the safety is confirmed to prescribe 5-ALA up to 200 mg per day in 2 divided doses for the patients with type 2 diabetes mellitus who are taking concomitant antidiabetic medications.

HbA1c, which is supposed to be closely related to diabetes, showed in the group of 5-ALA and SFC a steady gradual decline during the study and decreased by 0.8% at week 12; whereas in the group of placebo taking only existing medications for type 2 diabetes mellitus, HbA1c gradually decreased until week 6, but then turned to increase, causing the overall decrease by 0.5% at week 12. In the patients whose blood glucose does not decrease in spite of the

treatment with sulfonyl urea^{*3}, which should induce insulin secretion, the intake of 5-ALA and SFC was observed to lower the level of blood glucose by 0.95% at week 12 and indicated to overcome insulin resistance. The supplementary intake of 5-ALA and SFC is indicated to benefit the patients with type 2 diabetes taking concomitant antidiabetic medications.

【Journal】

Name of the Journal : Journal of Diabetes Research

Title of the Research Paper : The safety and tolerability of 5-aminolevulinic acid phosphate with sodium ferrous citrate in patients with type 2 diabetes mellitus in Bahrain

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

An amino acid created in mitochondria. It is an important substance that serves as a functional molecule related to energy production in the form of heme and cytochromes, and its productivity is known to decrease with age. 5-ALA is contained in food such as shochu lees, red wine and Asian ginseng. It is also known as a material forming chloroplasts in plants.

5-ALA has been approved as an intraoperative diagnostic agent for glioma by using its characteristics where 5-ALA is specifically metabolized to protoporphyrin IX only in cancer cells.

(*2): Sodium ferrous citrate (SFC)

SFC is a chemical compound effective for treating and preventing anemia and has been used widely in medical products and health foods for many years.

(*3): Sulfonyl urea

Sulfonyl urea is an oral anti-diabetic agent developed next to insulin. It stimulates the secretion of insulin and exerts hypoglycemic activity. A typical drug is Amaryl Tab. (generic name: glimepiride).

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