Shionogi announces positive top-line efficacy results from year-long studies of velneperit, a novel NPY Y5 receptor antagonist being investigated for the treatment of obesity

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Shionogi & Co, Ltd. today announced that two distinct year-long studies of velneperit, a novel neuropeptide Y (NPY) Y5 receptor antagonist also known as S-2367, each met their primary endpoint of demonstrating a statistically significant reduction in body weight. These clinical studies further demonstrate the potential for the NPY Y5 receptor as a target for obesity treatment.

Shionogi assessed the long term efficacy and safety of velneperit over the course of one year in two distinct studies, comprising a total randomized population of 1,566 obese subjects across 80 centers in the United States. Each respective study assessed the efficacy and safety of velneperit under different reduced calorie diet and low calorie diet conditions. In the strongest performing group relative to placebo across the two studies, subjects undergoing velneperit treatment of 800mg once-daily in combination with a reduced calorie diet responded with 5% or greater weight loss at a percentage nearly three times higher than those on placebo (35% vs. 12%). In addition, velneperit treatment resulted in statistically significant differences with respect to secondary parameters such as decreased waist circumference and improved serum lipid profile. In terms of safety, velneperit was well tolerated in all groups over the course of one year treatment, a finding consistent with subject experience in previous clinical studies. A full analysis of the current study data, including secondary efficacy endpoints as well as safety and laboratory parameters is currently underway.

Study Design and Results

Two distinct double-blind, placebo controlled trials were employed to examine the safety and effectiveness of long-term velneperit treatment under different diet conditions. The unique mechanism of action of velneperit involves blocking the Y5 binding receptor for neuropeptide Y (NPY), a centrally acting signaling molecule thought to be involved in regulation of energy balance and food consumption. NPY levels are particularly elevated in reduced weight or food deprived subjects, resulting in stimulation of food intake. Velneperit was designed to counteract elevated NPY levels, thereby promoting weight loss and continued weight loss maintenance. In order to assess the long-term effectiveness of velneperit in weight loss and weight loss maintenance settings, two different studies were initiated under distinct diet conditions, denoted as the Reduced Calorie Diet (RCD) and Low Calorie Diet (LCD) studies.

In the RCD study, obese subjects (BMI between 30 and 45) were first assigned to a 6-week reduced calorie diet consisting of an 800 kcal/day reduction in the amount of food required to maintain the subject's starting body weight. Following completion of the 6-week run-in diet period, subjects were randomized to receive placebo (0mg), 800mg or

1600mg of velneperit once daily in conjunction with the same 800 kcal/day reduction in daily food intake for an additional 54 weeks.

In the LCD study, study subjects were immediately randomized to one of three treatment groups for a period of 60 weeks. The first group received placebo treatment in conjunction with a fixed low calorie diet of 950 kcal/day for 6 weeks, followed by placebo treatment with a reduced calorie diet identical to that of the RCD study for 54 weeks (treatment group denoted as placebo/placebo). Subjects in the second group of the LCD study received placebo treatment in conjunction with a fixed low calorie diet of 950 kcal/day for 6 weeks, followed by 54 weeks of 1600mg velneperit once-daily treatment with the same reduced calorie diet as that of the RCD study (treatment group denoted as placebo/velneperit). Finally, subjects in the third group of the LCD study received 1600mg velneperit once-daily in combination with a fixed low calorie diet of 950 kcal/day for 6 weeks, followed by 54 weeks of 1600mg velneperit once-daily treatment combined with the same reduced calorie diet as that of the RCD study (treatment group denoted as velneperit/velneperit).

Efficacy calculations for both the RCD and LCD studies are based on subjects who received at least one dose of randomized study drug and had at least one scheduled body weight measurement collected after receiving drug. Subjects in this group are identified as the modified intention-to-treat (MITT) population. The statistical analyses use the last regularly scheduled body weight measurement projected forward for missing data, also referred to as last observation carried forward (LOCF).

The MITT population for the RCD study consisted of 656 total subjects. Both velneperit treatment groups demonstrated a statistically significant reduction in body weight as compared to placebo. The strongest performing treatment group relative to placebo was the 800mg velneperit treatment group, in which subjects lost 3.8 kg of their baseline body weight taken after the 6-week reduced calorie diet run-in period, versus 0.8 kg for the placebo group (p-value <0.0001). The percentage of weight lost during this 54-week period was 3.9% for the 800mg velneperit treatment group versus 0.9% for the placebo group (p-value <0.0001). Individual subjects who lost greater than or equal to 5% of their baseline weight were identified as treatment “responders”. The percentages of responders in the 800mg velneperit treatment group was 35%, versus 12% in the placebo group (p-value <0.0001).

The MITT population for the LCD study consisted of 771 subjects. Again, both velneperit treatment groups demonstrated a statistically significant reduction in body weight compared to placebo. The strongest performing treatment group relative to placebo was the placebo/velneperit treatment group, in which subjects lost 7.1 kg of their baseline body weight taken at the initiation of the fixed low calorie diet, versus 4.3 kg for the placebo/placebo group (p-value <0.0001). The percentage of weight lost during this 60-week period was 6.9% for the placebo/velneperit treatment group versus 4.4% for the placebo/placebo group (p-value <0.0002). The percentages of responders in the placebo/velneperit treatment group was 52%, versus 35% for the placebo/placebo group (p-value <0.0001).

Analysis of secondary efficacy parameters for both the RCD and LCD studies is currently ongoing. Preliminary findings indicate velneperit treatment resulted in statistically significant differences with respect to secondary endpoints such as decreased waist circumference and improved serum lipid profile.

In terms of the safety findings, velneperit was well tolerated in all treatment groups, a finding consistent with subject experience in previous clinical studies. The overall withdrawal rate due to treatment emergent adverse events in the RCD study was 7% in the placebo group, 7% in the 800mg group and 7% in the 1600mg group. For the LCD study, the withdrawal rate due to treatment emergent adverse events was 5% in the placebo/placebo group, 7% in the placebo/velneperit group and 10% in the velneperit/velneperit group. The most frequently observed adverse events across the two studies were nasopharyngitis, upper respiratory infection, sinusitis, and headache, all of which showed no significant differences in incidence versus placebo. Review of adverse event and psychological assessment data did not indicate any psychiatric side effects related to the use of velneperit.

Preliminary laboratory findings across the RCD and LCD studies included a mild decrease in hematocrit, hemoglobin and red blood cell count, along with a corresponding mild increase in reticulocytes across all active treatment groups. However, the magnitudes of the observed hematological changes were minor in nature, with the individual values remaining within the "normal" reference range. A full analysis of the current study data, including secondary efficacy endpoints as well as safety, laboratory and metabolic parameters, is currently underway.

In commenting on the results, Dr. Isao Teshirogi, President and Representative Director of Shionogi & Co., Ltd., said, "The results from the RCD and LCD studies further confirm the attractive potential of velneperit, along with the NPY Y5 receptor antagonist class, for the treatment of obesity and related metabolic disorders. Based on these results, we will continue to further investigate the potential of velneperit in our ongoing clinical program, including exploring other settings or regimens where velneperit treatment can demonstrate maximal benefit. In addition, we will accelerate pursuit of additional NPY Y5 receptor antagonist candidates."

Dr. Sapan Shah, President & CEO of Shionogi USA, Inc., remarked, "The completion of these two long-term studies of velneperit is a significant milestone for Shionogi as we seek to build a global clinical development platform to progress novel, internally discovered drug candidates. We look forward to working with our scientific experts and the appropriate regulatory agencies to determine the path forward for velneperit and our broader NPY Y5 receptor antagonist program."

About velneperit

Velneperit, also known as S-2367, is a once-daily, oral, centrally acting, small molecule neuropeptide Y (NPY) Y5 receptor antagonist that was discovered by Shionogi Research Laboratories. NPY is an orexigenic signaling molecule that plays a role in meal initiation

and regulation of energy balance, and is believed to be especially important under conditions of food deprivation or reduced weight. An NPY antagonist has the potential to be effective in inducing a negative energy balance and therefore reducing body weight. In addition, an NPY antagonist could be particularly effective for weight-loss maintenance or stabilizing individuals below their usual weight by inhibiting NPY signaling.

About Shionogi

Shionogi & Co., Ltd. is one of Japan's largest research-based pharmaceutical companies. It develops, manufactures, distributes, imports, and exports pharmaceuticals and diagnostics. Shionogi aims to provide innovative medicines that make a positive contribution to health worldwide.

Shionogi USA, Inc. serves as a primary vehicle for Shionogi & Co., Ltd.'s overseas development, bringing innovative compounds originated in Shionogi Research Laboratories to the US and Europe for clinical development and regulatory approval. Shionogi USA, Inc.'s current development activities take place independently or in partnership with other pharmaceutical companies.

Forward-Looking Statements

This announcement contains forward-looking statements. These statements are based on expectations in light of the information currently available, assumptions that are subject to risks and uncertainties which could cause actual results to differ materially from these statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise. This announcement contains information on pharmaceuticals (including compounds under development), but this information is not intended to make any representations or advertisements regarding the efficacy or effectiveness of these preparations nor provide medical advice of any kinds.

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