

Shionogi announces positive results from a Phase IIa study of S-2367, a novel neuropeptide Y5 receptor antagonist for the treatment of Obesity

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Shionogi & Co, Ltd. today announced positive top-line efficacy results from a Phase IIa proof-of-concept trial with S-2367, an internally discovered drug candidate for obesity and related conditions. The unique mechanism of action of S-2367 involves blocking receptor binding of neuropeptide Y (NPY), a neurotransmitter 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. S-2367 was designed to counteract elevated NPY levels, thereby promoting weight loss and continued weight loss maintenance. Shionogi assessed the safety and efficacy of S-2367 once-daily treatment on a population of 342 obese subjects across 20 sites in the United States. In summary, the study met its primary endpoint and demonstrated a statistically significant effect in maintaining and continuing weight loss in these obese subjects, validating the concept and utility of S-2367. A full analysis of the current study data, including secondary efficacy and metabolic parameters is underway.

Study Design

A unique study design was used to examine the safety and effectiveness of S-2367 treatment in the Phase IIa proof-of-concept study. In the principal arm of the study, obese subjects (BMI between 30 and 40) were first assigned to a 4-week fixed 900-950 kcal/day low-calorie diet (LCD) intended to produce an initial weight loss. Following completion of the LCD period, subjects were randomized in a 1:1:1 allocation to placebo, 400 or 1600 mg/day of S-2367 once-daily and began a 12-week double blind treatment period with dietary counseling on a reduced calorie diet (RCD). The RCD consisted of a 500 kcal/day reduction in daily caloric intake relative to the subject's resting metabolic rate. This innovative study design allowed for the clinical assessment of the S-2367 concept and its utility as a weight-loss maintenance and continuation treatment. In a second arm of the Phase IIa study, subjects did not undergo an initial LCD period, but were directly randomized in a 1:1:1 allocation to placebo, 400 or 1600 mg/day of S-2367 once-daily for a 12-week double blind treatment period with a reduced calorie diet (RCD). The two arms in the Phase IIa study are referred to as the DWR (delayed weight reduction) arm, which included the initial 4-week LCD period, and the IWR (immediate weight reduction) arm, which did not include the initial LCD period. Study subjects were randomized into the DWR and IWR arms in a 2:1 allocation.

Study Results

The top-line results from the DWR arm showed that S-2367 produced a clear and significant continuation of weight-loss following the LCD period, resulting in a statistically significant decrease in body weight versus placebo for both dose groups. In addition, there was a clear dose response between the 400mg/day and 1600mg/day dosing groups. Over the 12-week treatment period following LCD, subjects on the high dose of

S-2367 lost on average an additional 2.2 kg or 2.5% of baseline weight, versus no weight change for those on placebo ($p < 0.0001$). Including the weight-loss observed in the LCD period, subjects in the high dose group of S-2367 lost an average of 5.3 kg over 16 weeks, or 5.6% of baseline weight, versus 2.5 kg or 2.7% of baseline weight for placebo. All analyses were conducted using Last Observation Carried Forward (LOCF) on the intent-to-treat (ITT) population.

Results for the IWR treatment arm showed a positive directional trend of enhanced weight loss versus placebo, though not statistically significant at the end of the 12-week treatment period. In this arm, subjects in the high dose group lost an average of 3.6 kg over 12 weeks, or 3.7% of baseline weight, versus a loss of 2.4 kg or 2.4% of baseline weight for placebo ($p=0.0638$). It is worth noting that a Repeated-Measures (RM) analysis of the IWR arm showed a statistically significant difference at the high dose ($p = 0.0479$). In addition, there was also a clear dose response between the 400mg/day and 1600mg/day dosing groups in the IWR arm. Given these positive trends, as well as the strong results from the DWR arm, we believe longer duration studies will also demonstrate the clear benefit of S-2367 in this setting.

In the Phase IIa study, S-2367 was extremely well tolerated at all doses with no significant or serious safety issues, a finding consistent with subject experience in previous clinical studies. The overall percentage of subjects who initiated and completed treatment in the present Phase IIa study was 84%. Additional study results, including detailed safety data and secondary efficacy parameters, will be released once a full analysis of the study database is complete.

In commenting on the results, Dr. Isao Teshirogi, Director of the Board and Senior Executive Officer responsible for Research and Development in Shionogi & Co., Ltd., said, “We are very encouraged by these promising top-line results, as well as those from previous Phase I studies, which demonstrate that S-2367 has an attractive efficacy and outstanding safety profile for the treatment of obesity. The novel approach and rapid development from candidate selection to clinical proof-of-concept highlight the strengths of Shionogi’s Research and Development organization.”

Dr. Sapan Shah, President & CEO of Shionogi USA, Inc., remarked “The current Phase IIa results with S-2367 are very exciting and represent a significant milestone for Shionogi as we seek to further establish our global presence. We look forward to working closely with obesity experts and regulatory authorities to design and execute longer-term clinical studies which we hope will confirm the unique profile, safety and benefit of S-2367 treatment for patients.”

Commented Dr. Stan Heshka, an obesity expert at the Obesity Research Center, St. Luke’s-Roosevelt Hospital and Columbia University who played a major role in conceiving the unique study design, “With these study results, S-2367 has demonstrated its potential to help obese individuals maintain and increase their achieved weight loss. These results are particularly encouraging since weight regain is one of the major problems with current obesity treatments.”

About S-2367

S-2367 is a small molecule, oral, once-daily neuropeptide Y5 receptor antagonist discovered by Shionogi Research Laboratories. Neuropeptide Y is an orexigenic signaling molecule that plays a role in meal initiation and regulation of energy balance, and is believed to be especially potent 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 reduced body weight. In addition, an NPY antagonist could be particularly effective for weight-loss maintenance or continuation in 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. Shionogi USA, Inc.'s current development activities take place independently or in partnership with other pharmaceutical companies.

For Further Information Contact:

Shionogi & Co., Ltd.
1-8, Doshomachi 3-chome
Chuo-ku, Osaka 541-0045, Japan
Tel: 81-6-6202-2161
www.shionogi.co.jp

Shionogi USA, Inc.
100 Campus Drive, Suite 105
Florham Park, New Jersey 07932
Tel: 973-966-6900
www.shionogiusa.com