Lubiprostone Increases Spontaneous Bowel Movement Frequency and Quality of Life in Patients With Chronic Idiopathic Constipation

Q32 Shin Fukudo,* Michio Hongo,‡ Hiroshi Kaneko,§ Masahiro Takano,‖ and Ryuji Ueno¶

*Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; ‡Department of Medicine, Kurokawa Hospital, Miyagi, Japan; §Division of Psychosomatic Medicine, Hoshigaoka Maternal Hospital, Nagoya, Japan; ‖Department of Surgery, Takano Hospital, Kumamoto, Japan; ¶Sucampo AG, Zug, Switzerland

Q7 **BACKGROUND & AIMS:** **Lubiprostone is an activator of the type 2 chloride channel that facilitates spontaneous bowel movement (SBM). We performed phase 3 studies to determine whether lubiprostone increases the frequency of SBM in patients with chronic idiopathic constipation (CIC) in Japan, and whether long-term administration of lubiprostone increases the quality of life of patients with CIC.**

METHODS: **We performed a randomized, double-blind, placebo-controlled, phase 3 trial of lubiprostone. Patients with CIC (n = 124) were assigned randomly to groups given placebo (48 μg/d; n = 62) or lubiprostone (48 μg; n = 62) for 4 weeks. The primary efficacy end point was the change from baseline in the weekly average number of SBMs after 1 week of administration. In a long-term study of efficacy and safety, 209 patients with CIC were given lubiprostone (24 μg twice daily) for 48 weeks.**

RESULTS: **Daily administration of lubiprostone induced a significantly greater change, from baseline, in the weekly average number of SBMs at week 1 (increase of 3.7 ± 2.8), compared with placebo (increase of 1.3 ± 1.8; $P < .001$). The frequency of SBMs during each week of the study period was significantly higher after subjects began receiving lubiprostone than at baseline ($P < .0001$ at all weeks). Long-term administration of lubiprostone significantly increased scores from the Short-Form health survey and irritable bowel syndrome quality-of-life questionnaire, compared with baseline. We did not observe any severe adverse reactions to lubiprostone.**

CONCLUSIONS: **In phase 3 studies in Japan, lubiprostone increased the weekly average number of SBMs and increased the quality of life of patients with CIC. Clinical Trial Notification of the Japanese Regulatory Authorities: 20-3296 and 20-3300.**

Keywords: IBS; Rome III Criteria; Functional Disorder; QOL; Intestine; Small-Bowel Transit.

Q8 Q9 Q10 Chronic constipation is a very common condition in developed countries.[1] Constipation-related functional gastrointestinal disorders include functional constipation, irritable bowel syndrome with constipation (IBS-C),[2] and functional anorectal disorders.[3] Constipation impairs quality of life (QOL) and has an economic impact on patients and care providers.[2] An epidemiologic survey in Japan showed that the prevalence of constipation, defined as a frequency of less than a daily bowel movement, was high in both women (31.8%) and men (11.9%).[4] Furthermore, this survey highlighted an increased risk of colonic cancer from constipation or laxative use.[4] Therefore, the development of a novel effective and well-tolerated treatment for constipation represents an unmet medical need.

Q11 Lubiprostone is a novel type 2 chloride channel activator that promotes the secretion of a chloride-rich intestinal fluid without altering the serum concentration of electrolytes.[5,6] Lubiprostone has been shown to accelerate small-bowel and colonic transit.[7] Lubiprostone increased the percentage of patients who experienced spontaneous bowel movements (SBMs) within 24 hours of administration compared with placebo (56.7% vs 36.9% or 61.3% vs 31.4%) in phase III clinical Q12 trials for chronic idiopathic constipation (CIC) conducted

Abbreviations used in this paper: **CIC, chronic idiopathic constipation; FAS, full-analysis set; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; QOL, quality of life; SBM, spontaneous bowel movement; SES, safety-evaluable set; SF-36, Short-Form Health Survey Questionnaire.**

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in the United States.[8,9] The time to first SBM in patients taking lubiprostone was shorter than for those patients taking placebo.[8,9] Lubiprostone also improved gastrointestinal (GI) symptoms including abdominal bloating,[10] abdominal discomfort, stool consistency, and straining.[8,9] Lubiprostone therefore is considered a promising agent that alleviates pathophysiological features of CIC.

We previously reported the efficacy and safety of lubiprostone in patients with CIC in Japan.[11] In that study, a total of 170 patients with CIC randomly received a placebo or 16 μg, 32 μg, or 48 μg of lubiprostone a day for 2 weeks. There was a dose-dependent increase in the change from baseline in the weekly average number of SBMs at the first week.[11] No severe adverse drug reactions were produced by lubiprostone. The results from this phase II trial conducted in Japan were essentially similar to results from studies conducted in the United States.[12] However, treatment effectiveness and tolerability shown in the US population may differ from outcomes in Japan, thus warranting further study of the product in this population. For example, recent publications have supported the belief that microbiota plays a crucial role in functional bowel disorders,[13] and gut microbiota may differ substantially by ethnicity.[14] Ethnicity includes geography, genes, food habits, cultural traditions, and lifestyles. For this reason, it is scientifically important to confirm the safety and efficacy profile of lubiprostone in Japanese patients with CIC. We therefore tested the main hypothesis that oral administration of 48 μg of lubiprostone improves SBM frequency in Japanese CIC patients. We also tested the additional hypothesis that long-term treatment with lubiprostone improves QOL in patients with CIC.

Patients and Methods

Patient Population

The studies consisted of 2 parts. Study 1 was a phase III, double-blinded, randomized, placebo-controlled trial for the treatment of Japanese patients with CIC. Multiple centers (11 centers total) participated, with 11.3 ± 1.1 (means ± SE) patients per center. The treatment arms (means ± SE, 5.6 ± 0.6 patients) were well balanced between the centers. Study 2 was a phase III, nonblinded, long-term safety trial for the treatment of Japanese patients with CIC. Multiple centers (17 centers total) participated with 12.3 ± 1.4 (means ± SE) patients per center. All participants provided written informed consent. The protocol and all study procedures were approved by the Institutional Review Board and the studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice, and applicable Japanese governmental regulations (Clinical Trial Notification of the Japanese Regulatory Authorities: 20-3296 and 20-3300).

CIC in these studies was defined as a subpopulation of the Rome III–defined functional bowel disorders with constipation,[3] which is essentially the same definition used in a previous phase II study of lubiprostone in Japanese CIC patients[11] (see "Patient Population" in the Supplementary Methods section).

Study Protocol

Patients who met the eligibility criteria entered the 2-week baseline/screening period before their second visit. After screening, patients discontinued agents that affected GI function including laxatives and supplements. Patients completed a daily diary including the time and number of SBMs, the degree of incomplete evacuation (0, absent; 1, mild; 2, moderate; 3, severe; and 4, very severe), straining (0, absent; 1, mild; 2, moderate; 3, severe; and 4, very severe), the Bristol Stool Form Scale[2] (1, separate hard lumps; 2, sausage-shaped but lumpy; 3, like a sausage but with cracks; 4, like a sausage, smooth and soft; 5, soft blobs with clear cut edges; 6, a mushy stool; and 7, watery), abdominal bloating/discomfort (0, absent; 1, mild; 2, moderate; 3, severe; and 4, very severe), and use, if any, of rescue medication. The definition of SBM was the same as in earlier[8,9,15] and previous[11] reports.

At the second visit, the investigators registered the patients after reconfirmation of all eligibility criteria. The patients scored the Medical Outcome Study 36-item Short-Form Health Survey Questionnaire (SF-36),[16,17] the IBS-QOL,[15,18–20] and global assessments of constipation severity and treatment effectiveness at each evaluation point.

In study 1, the patients were assigned randomly to 1 of 2 treatment arms: placebo or lubiprostone 48 μg/d. Patients were instructed to take 1 capsule of double-blinded medication twice daily (after breakfast and dinner) for 28 days. One (visit 3), 2 (visit 4), 4 (visit 5), and 6 (visit 6) weeks after the start of the double-blind treatment, patients visited the clinic. Patients were asked to submit their diary and underwent a physical examination, global assessments of constipation severity, treatment efficacy, and degree of satisfaction with relief of bowel symptoms[21] (see "Study Protocol" in the Supplementary Methods section for more detail).

In study 2, after confirmation of patient eligibility, patients who were enrolled in the study were instructed to take 1 capsule of lubiprostone 24 μg twice daily (after breakfast and dinner) for up to 48 weeks (336 days, see "Study Protocol" in the Supplementary Methods section).

Efficacy and Safety End Points

In study 1, the primary efficacy end point was the change from baseline in the weekly average number of SBMs reported during the first week after treatment initiation. SBM frequency improvement from baseline was the primary marker of treatment response not only