Safety and efficacy of the sodium-glucose cotransporter 1 inhibitor mizagliflozin for functional constipation: a randomised, placebo-controlled, double-blind phase 2 trial

Shin Fukudo, Yuka Endo, Michio Hongo, Atsushi Nakajima, Tatsuya Abe, Hiroyuki Kobayashi, Tomohiro Nakata, Toshio Nakajima, Kanako Sameshima, Kohei Kaku, and the Mizagliflozin Study Group

Summary

Background Mizagliflozin is a novel oral sodium-glucose cotransporter 1 (SGLT1) inhibitor that increases luminal glucose and water. This study assessed the efficacy and safety of mizagliflozin in patients with functional constipation.

Methods In this multicentre, randomised, double-blind phase 2 trial at 32 hospitals and community outpatient clinics in Japan, we enrolled patients with functional constipation or constipation-predominant irritable bowel syndrome, aged 20 years or older. Patients were randomly assigned (1:1:1), by use of an independent centralised registration system and dynamic allocation method, to receive mizagliflozin 5 mg, mizagliflozin 10 mg, or placebo, orally once daily for 4 weeks. Patients, investigators, staff, and the sponsor were blinded to the group assignments. The primary outcome was the change from baseline in the number of spontaneous bowel movements per week after 1 week. Efficacy analysis was done in all patients except those who deviated from good clinical practice, did not receive at least one dose of the study drug, withdrew before starting treatment, were ineligible, or for whom the primary outcome could not be assessed, and safety was assessed in all patients except those who deviated from good clinical practice, who did not receive the study drug, or who withdrew before receiving treatment. This trial is registered with ClinicalTrials.gov, number NCT02281630, and is completed.

Findings Between Oct 15, 2014, and March 7, 2015, 258 patients with functional constipation were randomly assigned: 86 patients per group. Two patients from the placebo group and three from the 10 mg mizagliflozin group were excluded because the primary outcome could not be assessed, and one patient from the 5 mg mizagliflozin group was excluded for not receiving the study drug; therefore 84 patients in the placebo group, 85 in the 5 mg mizagliflozin group, and 83 in the 10 mg mizagliflozin group were included in the full analysis population. Mean change from baseline in the number of spontaneous bowel movements per week after 1 week with mizagliflozin 5 mg (3·85 [SD 3·96]) and mizagliflozin 10 mg (5·85 [6·01]) was significantly greater than those in the placebo group (1·80 [1·80]; p<0·0001 for both comparisons). The most common adverse events were nasopharyngitis (one [1%] of 86 patients in the placebo group, seven [8%] of 85 on mizagliflozin 5 mg, and five [6%] of 86 on mizagliflozin 10 mg), diarrhoea (none on placebo, four [5%] patients on mizagliflozin 5 mg, and eight [9%] on mizagliflozin 10 mg), and abdominal distention (three [3%] on placebo, four [5%] on mizagliflozin 5 mg, and seven [8%] on mizagliflozin 10 mg). Only diarrhoea and abdominal distention were deemed to be related to mizagliflozin treatment, whereas nasophanyngitis might not be related to mizagliflozin treatment, on the basis of clinical evaluation.

Interpretation The SGLT1 inhibitor mizagliflozin showed favourable efficacy and tolerability at 5 mg and 10 mg doses in patients with functional constipation, providing a potential alternative therapy to available drugs.

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Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan (Prof S Fukudo MD); **Department of Psychosomatic Medicine, Tohoku University Hospital, Sendai, Japan** (Prof S Fukudo, Y Endo MD); **Kurokawa Hospital, Miyagi, Japan** (M Hongo MD); **Department of Gastroenterology and Hepatology, Yokohama City University School of Medicine, Yokohama, Japan** (Prof A Nakajima MD); **Kunimoto Hospital, Asahikawa, Japan** (T Abe MD); **Kobayashi Medical Clinic Tokyo, Tokyo, Japan** (H Kobayashi MD); **Nakata Clinic, Yokohama, Japan** (T Nakata MD); **Nakajima Clinic, Nishinomiya, Japan** (T Nakajima MD); **Sameshima Hospital, Kagoshima, Japan** (K Sameshima MD); **and Department of Internal Medicine, Kawasaki Medical School, Kurashiki, Japan** (Prof K Kaku MD)

Correspondence to:
Prof Shin Fukudo, Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai 980–8575, Japan
sfukudo@med.tohoku.ac.jp

Introduction

Constipation is a common disorder, affecting about 15% of the population in France, Germany, Italy, UK, South Korea, Brazil, and USA,[1] with prevalence estimates from North America ranging from 2% to 27%.[2] Constipation is more frequent in women and elderly people.[2,3] The symptoms of functional constipation include decreased bowel movements, hard stools, straining during defecation, sense of incomplete evacuation, anorectal obstruction, and manual manoeuvres to facilitate defecation.[4] Constipation is associated with decreased quality of life and loss of productivity due to emotional distress.[1,5]

Traditionally, osmotic laxatives, bulking agents, and stimulant laxatives have been used to treat constipation,[3,4] but there are few long-term clinical studies on their effects. Anthraquinone derivatives, as representative stimulant laxatives, are potentially associated with laxative abuse and pseudomelanosis coli. Several new drugs are available worldwide, such as the chloride channel activator lubiprostone, which has a distinct clinical mechanism,[6] and the guanylate

Research in context

Evidence before this study

Traditional laxatives and several new drugs are available for the treatment of constipation. However, many patients still have adverse events and are non-responsive to some of these drugs. Therefore, novel pharmacological compounds are required. Mizagliflozin is an oral sodium-glucose cotransporter 1 (SGLT1) inhibitor that increases luminal glucose and water and is therefore expected to soften stools and improve constipation. Before this study, three exploratory phase 2 studies were done (NCT01600001, NCT01937663, and NCT01938196). In these studies, doses of mizagliflozin—ranging from 2·5 mg once per day to 20 mg three times per day—showed dose-dependent efficacy and good tolerability in patients with functional constipation. Because excessive frequency of defecation was observed in some patients treated with 20 mg per day, the optimal dose was expected to be lower than this amount. A clinical pharmacology study showed that the effect of postprandial administration of mizagliflozin on plasma glucose concentrations was negligible, and glucagon-like peptide-1 (GLP-1) secretion was enhanced by mizagliflozin. We searched PubMed for articles published up to Jan 25, 2018, using the terms "sglt1" and "constipation", and restricted the search to include only clinical trials; however, we found no studies investigating the effect of SGLT1 inhibitors on constipation.

Added value of this study

This randomised, placebo-controlled, double-blind phase 2 trial was done to assess the efficacy and safety of 5 mg and 10 mg doses of mizagliflozin in patients with functional constipation. Overall, stool frequency and consistency were significantly improved at both mizagliflozin doses over a period of 4 weeks. The most common adverse events related to mizagliflozin treatment were diarrhoea and abdominal distension. No specific adverse events related to the mechanism of action of mizagliflozin, such as hypoglycaemia-like symptoms, were observed. According to Rome III and IV criteria, patients with functional constipation and patients with constipation-predominant irritable bowel syndrome (IBS-C) are independent categories. However, functional bowel disorders are a spectrum of pathophysiological disorders that frequently overlap and are characterised by patient-specific differences in the quantity, intensity, and severity of symptom expression. Therefore, in this study, patients with IBS-C were allowed to participate. A subgroup analysis showed that spontaneous bowel movements and complete spontaneous bowel movements increased in patients with IBS-C, similar to the effect seen in all patients with functional constipation.

Implications of all the available evidence

The SGLT1 inhibitor mizagliflozin showed a favourable efficacy and safety profile at 5 mg and 10 mg doses in patients with functional constipation. Therefore, the SGLT1-inhibiting action of mizagliflozin might offer a novel alternative treatment option to available medicines. Regarding IBS-C, the US Food and Drug Administration guidance allows responder rates for stool frequency to be a primary endpoint for studies, depending on the pharmacological mechanism of drugs. In this study, mizagliflozin increased stool frequency in patients with IBS-C. Furthermore, in a previous study, elevated concentrations of GLP-1, which ameliorates abdominal pain, were recorded after the administration of mizagliflozin. Because mizagliflozin is considered a potential treatment option for IBS-C, further studies of IBS-C and mizagliflozin with the above endpoints are warranted.

cyclase-C agonist linaclotide, which has been shown to be clinically useful.[7] However, despite the development of new drugs to treat constipation, the number of patients who do not respond to treatment or who have adverse events[8] and inadequate relief of abdominal pain—the most bothersome symptom in constipation-predominant irritable bowel syndrome (IBS-C)[9]—suggests that further drugs with novel pharmacological actions are required.

Mizagliflozin (Kissei Pharmaceutical; Matsumoto, Japan; appendix) is a potent and highly selective inhibitor of the sodium-glucose cotransporter (SGLT) 1.[10–12] SGLT1 is expressed in the small intestine, trachea, kidney, heart, and colon.[13] In the small intestine, SGLT1 is localised in the apical membrane of the epithelial cells involved in glucose uptake by sodium gradient.[13] SGLT1 cotransports glucose and water.[14] Mizagliflozin has low absorption and its pharmacological activity occurs mostly in the small intestine.[15] By inhibiting glucose transport through SGLT1 in the small intestine, mizagliflozin suppresses water absorption and is thereby expected to soften stools and improve constipation.

The actions of SGLT1 contrast with the well known pharmacology of SGLT2 inhibitors for type 2 diabetes.[16] SGLT2 is responsible for reabsorption of most of the glucose filtered by the kidney.[13,16] Unlike SGLT2 inhibitors, mizagliflozin has the potential to maintain fasting plasma glucose, suppress post-prandial hyperglycaemia, and improve constipation. Before this study, three exploratory phase 2 studies were done (NCT0160001, NCT01937663, and NCT01938196). In these, mizagliflozin doses of 2·5 mg once per day to 20 mg three times per day showed dose-dependent efficacy and good tolerability in patients with functional constipation. Because excessive frequency of defecation was observed in some patients treated with 20 mg per day, the optimal dose was expected to be lower. The aim of this study was to test the hypothesis that mizagliflozin doses of 5 mg or 10 mg once daily are effective and safe for patients with functional constipation.

See Online for appendix

Methods

Study design and participants

In this multicentre, randomised, placebo-controlled, double-blind phase 2 trial, we recruited patients with Rome III[17] functional constipation from 32 hospitals and community outpatient clinics in Japan. The study population included male and female Japanese patients aged 20 years or older. Functional constipation was defined as fewer than three spontaneous bowel movements per week for at least 6 months before the start of the study, fewer than three spontaneous bowel movements per week during the baseline period, and at least one of the following bowel-movement-related symptoms for at least 6 months before start of the study: straining during at least 25% of defecations, lumpy or hard stools in at least 25% of defecations, and sensation of incomplete evacuation for at least 25% of defecations. According to Rome III or IV criteria, functional constipation and IBS-C are independent categories.[17,18] However, functional bowel disorders are a spectrum of pathophysiological disorders that frequently overlap and are characterised by patient-specific differences in the quantity, intensity, and severity of symptom expression.[18] Therefore, in this study, patients with IBS-C, diagnosed per Rome III criteria, were allowed to participate. The main exclusion criteria were constipation associated with systemic diseases, organic diseases confirmed by colonoscopy or barium enema within 3 years before enrolment in the study, and drug-induced constipation, including that induced by opioids. We excluded patients taking antidiabetic drugs if they were prone to repeated development of asymptomatic or symptomatic hypoglycaemia. Patients with rectal prolapse or pelvic floor dysfunction and patients with hepatic, renal, or cardiovascular disorders were also excluded. Full inclusion and exclusion criteria are available in the trial protocol, which is available online. This study was approved by the institutional review board and ethics committee of the participating centres, on the basis of the Declaration of Helsinki. All patients provided written informed consent before the study-specified tests were done.

Randomisation and masking

Patients were randomly assigned (1:1:1; block size of 6) into three groups (mizagliflozin 5 mg, mizagliflozin 10 mg, and placebo) by an independent centralised registration system, using a dynamic allocation method stratified by functional constipation with or without IBS-C for randomisation. Patients, investigators, site staff, and the sponsor, including internal statisticians, were blinded to the study group assignments. The treatments used for this study were indistinguishable from each other. The study was unblinded to everyone after the database lock.

Procedures

The baseline assessments and treatment periods were based on the recommendations by the Rome III design of treatment trials committee.[19] Patients who were receiving treatment for constipation needed to stop these treatments at the start of a 2 week baseline period. After the baseline period, patients received 5 mg or 10 mg of mizagliflozin or placebo, once daily orally after breakfast for 4 weeks. Dose changes were not permitted during the study. Mizagliflozin was used in sebacate form (ratio of mizagliflozin to sebacic acid of 2:1). All study drugs were supplied by Kissei Pharmaceutical (Matsumoto, Japan).

As rescue medication, bisacodyl 10 mg suppository or, if necessary, 120 mL glycerine enema were permitted in patients who had not had a bowel movement for at least 72 consecutive hours. However, rescue medication was prohibited for at least 48 h before and after the start of the treatment period. The following concomitant medications were prohibited: other laxatives besides rescue medication, lubiprostone, herbal medicines or supplements for constipation, drugs that improve gastrointestinal function or inhibit intestinal motility, drugs for treating irritable bowel syndrome, macrolides, and any investigational product other than mizagliflozin. Linaclotide was not available in Japan during the study treatment period. Patients who met the following discontinuation criteria were withdrawn from the study: the onset of any adverse event or aggravation of constipation symptoms that would make study continuation difficult; patient request to discontinue; the detection of substantial protocol deviation; or any other reason that the investigators deemed warranted withdrawal from the study. The number of spontaneous bowel movements per week was calculated every 168 h, starting from the first dose of the study drug. Specifically, the number of spontaneous bowel movements recorded every 168 h was divided by the recording duration (h) and multiplied by 168. If spontaneous bowel movements were recorded for less than 96 h, these data were handled as missing data. Additionally, if rescue medication was used, bowel movements within 24 h after the use of rescue medication were subtracted from the number of spontaneous bowel movements, and 24 h were subtracted from the recording duration.

For the **protocol** see http://www.hosp.tohoku.ac.jp/sinryou/s08_sinryou.html

Patients recorded the following items in an electronic diary every day during the study period: time the drug was taken, timing of bowel movements, occurrence of straining during a bowel movement, feeling of incomplete evacuation, manual evacuation, stool form, occurrence of abdominal bloating and discomfort, and use of rescue medication. At the scheduled study visits (weeks 1, 2, and 4), other efficacy outcomes were assessed with a validated outcomes questionnaire, and safety endpoints were also evaluated. There were no changes to the study protocol or endpoints after enrolment started.

Outcomes

The primary endpoint was the change from baseline in the number of spontaneous bowel movements per

week at week 1, as previously used in other studies of drug development for chronic constipation.[20,21] A spontaneous bowel movement was defined as any bowel movements not occurring in the 24 h after the use of rescue medication or manual evacuation. The primary endpoint was set 1 week after treatment began because early effects of treatment were considered particularly important for patients with constipation.

The secondary endpoints were the frequency of complete spontaneous bowel movements with the feeling of complete evacuation; the responder rates for spontaneous bowel movements and complete spontaneous bowel movements (proportion of patients with three or more spontaneous bowel movements—complete or not—per week, with improvement of one or more times from the baseline); the percentage of patients who had spontaneous bowel movements within 24 h and 48 h after the initial dose of treatment; the time to first spontaneous bowel movement after the initial dose; stool consistency, according to the seven-point Bristol stool form scale (BSFS);[4,17] degree of straining, abdominal bloating, and discomfort; the use of rescue medications; global assessment of constipation severity; irritable bowel syndrome quality of life measure, Japanese version;[22,23] global assessment of treatment effectiveness; and the satisfaction rating for the condition of bowel movements. Full definitions of the efficacy endpoints are provided in the appendix.

The safety outcomes were adverse events (according to the Medical Dictionary for Regulatory Activities) graded as mild, moderate, or severe and assessed for association with the study drugs. Other safety outcomes were laboratory tests, including for alanine aminotransferase, γ-glutamyl transferase, and glycoalbumin, vital signs, bodyweight, and 12-lead electrocardiogram. Blood glucose concentrations were measured in patients taking antidiabetic drugs.

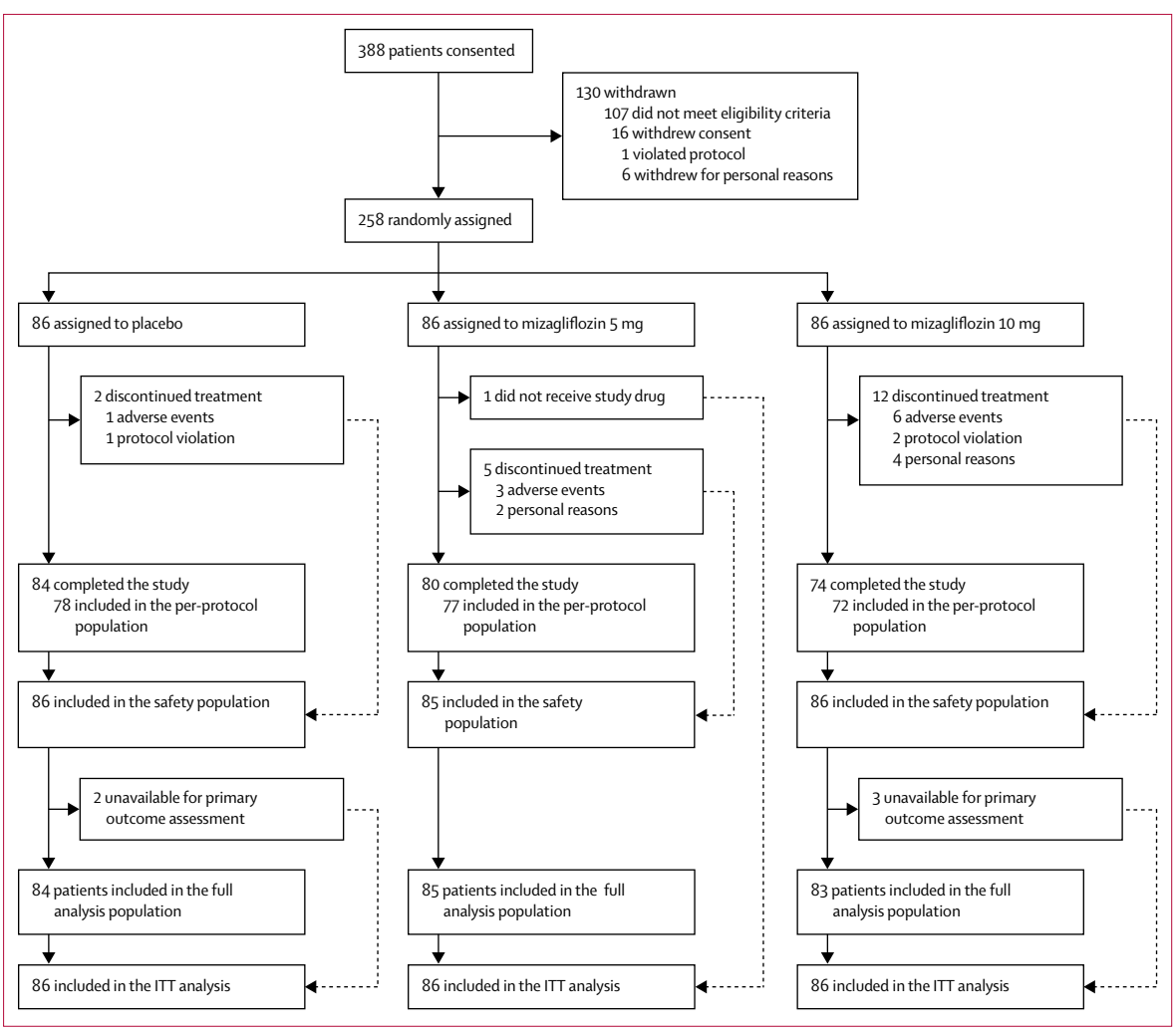

Figure 1: **Trial profile**
The number of patients that were discontinued and excluded from the full analysis population was listed by main reason. ITT=intention-to-treat.

Statistical analysis

To assess the change from baseline in the number of spontaneous bowel movements per week at week 1 by two-sample Student's *t* test, the necessary number of patients was determined to be 66 patients per group, with a difference in spontaneous bowel movements from placebo of 4·0, a common SD of 7·0, a significance level of 5% (two-sided), and a power of 90%. The difference in spontaneous bowel movements between mizagliflozin and placebo and the common SD were estimated on the basis of previous trials with mizagliflozin. The target number of patients was set at 70 patients per group to allow for some exclusions from the full analysis population. This full analysis population included all patients except those who deviated from good clinical practice (defined by the E6 guidance of the International Council for Harmonisation), who did not receive at least one dose of the study drug, who were withdrawn before starting the treatment period, who were ineligible, or for whom the primary endpoint data was not available. The full analysis population was in keeping with the guidelines of the International Council for Harmonisation of technical requirements for pharmaceuticals for human use.[24] The safety analysis was based on the safety population, which excluded patients who deviated from good clinical practice, who did not receive the study drug, or who withdrew before the treatment period.

Data were reported as the mean and SD for continuous variables and as the number and percentage for categorical variables. The superiority of mizagliflozin 5 mg and 10 mg groups compared with the placebo group was assessed with a two-sample Student's *t* test, and a two-sided 95% CI for the difference in change between the placebo and mizagliflozin groups. We adjusted for multiplicity with a closed testing procedure.[25] In a closed testing procedure for the primary endpoint, mizagliflozin 5 mg and placebo were only compared when mizagliflozin 10 mg compared with placebo had p values lower than 0·05. For the secondary endpoints, comparisons between mizagliflozin 5 mg or 10 mg and placebo were done with Fisher's exact test for categorical variables, Wilcoxon rank sum test for time to first spontaneous bowel movement, and two-sample Student's *t* test for other continuous variables. Missing values in the analysis from the full analysis population were not imputed. Sensitivity analysis was done for the per-protocol population. Analysis of covariance was used to adjust for imbalances in baseline characteristics between the groups. The primary outcome measure was also assessed with use of the stratified factor, functional constipation with or without IBS-C. For adverse events, the number of patients with events and the incidence were calculated. Relative risk and number needed to treat for responder rates of spontaneous bowel movements, and relative risk and number needed to harm for incidence of adverse events were calculated as post-hoc analyses.[26] We did ANCOVA with baseline spontaneous bowel movement, complete spontaneous bowel movement, and BSFS score as covariates—which were imbalanced among the three groups. We also analysed spontaneous bowel movement and complete spontaneous bowel movement responder rates for the intention-to-treat population as post-hoc analyses. Patients whose spontaneous bowel movements (complete or not) per week could not be calculated were treated as non-responders in the intention-to-treat analyses. No data monitoring committee oversaw the study. We used SAS version 9.4 (SAS Institute, Cary, NC, USA) for statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT02281630, and is completed.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors provided final approval to submit.

Results

Patients were enrolled between Oct 15, 2014, and March 7, 2015. Of the 388 patients who were assessed for inclusion and provided informed consent, 258 were randomly assigned to the three groups (86 patients per group; figure 1). 130 patients were withdrawn before randomisation, mostly for not meeting eligibility criteria. 84 patients in the placebo group, 85 in the mizagliflozin 5 mg group, and 83 in the mizagliflozin 10 mg group were included in the full analysis population. Two (2%) of 86 patients in the placebo group and three (3%) of 86 in the 10 mg mizagliflozin group were excluded from the full analysis population because it was not possible to calculate the number of spontaneous bowel movements per week at week 1 for the primary endpoint analysis. One (1%) of 86 patients in the mizagliflozin 5 mg group was excluded from the

	Placebo (n=84)	Mizagliflozin 5 mg (n=85)	Mizagliflozin 10 mg (n=83)
Age, years	43·4 (14·8)	44·0 (14·5)	45·0 (14·0)
Sex, women	69 (82%)	76 (89%)	71 (86%)
Disease duration, years	17·8 (12·4)	21·1 (13·4)	19·4 (14·3)
SBMs, number per week	1·52 (0·77)	1·74 (0·74)	1·69 (0·75)
CSBMs, number per week	0·34 (0·54)	0·51 (0·65)	0·52 (0·70)
BSFS, scale 1–7	2·35 (0·87)*	2·61 (1·10)†	2·33 (0·97)‡
Premedication for constipation	42 (50%)	48 (56%)	43 (52%)
Pharmacotherapy for diabetes	0	3 (4%)	2 (2%)
IBS-C	13 (15%)	13 (15%)	13 (16%)

Data are mean (SD) or n (%). SBMs=spontaneous bowel movements. CSBMs=complete spontaneous bowel movements. BSFS=Bristol Stool Form Scale. IBS-C=constipation-predominant irritable bowel syndrome. *Nine, †four, and ‡five patients could not be included for calculation because of use of rescue medication.

Table 1: **Baseline characteristics of the full analysis population**

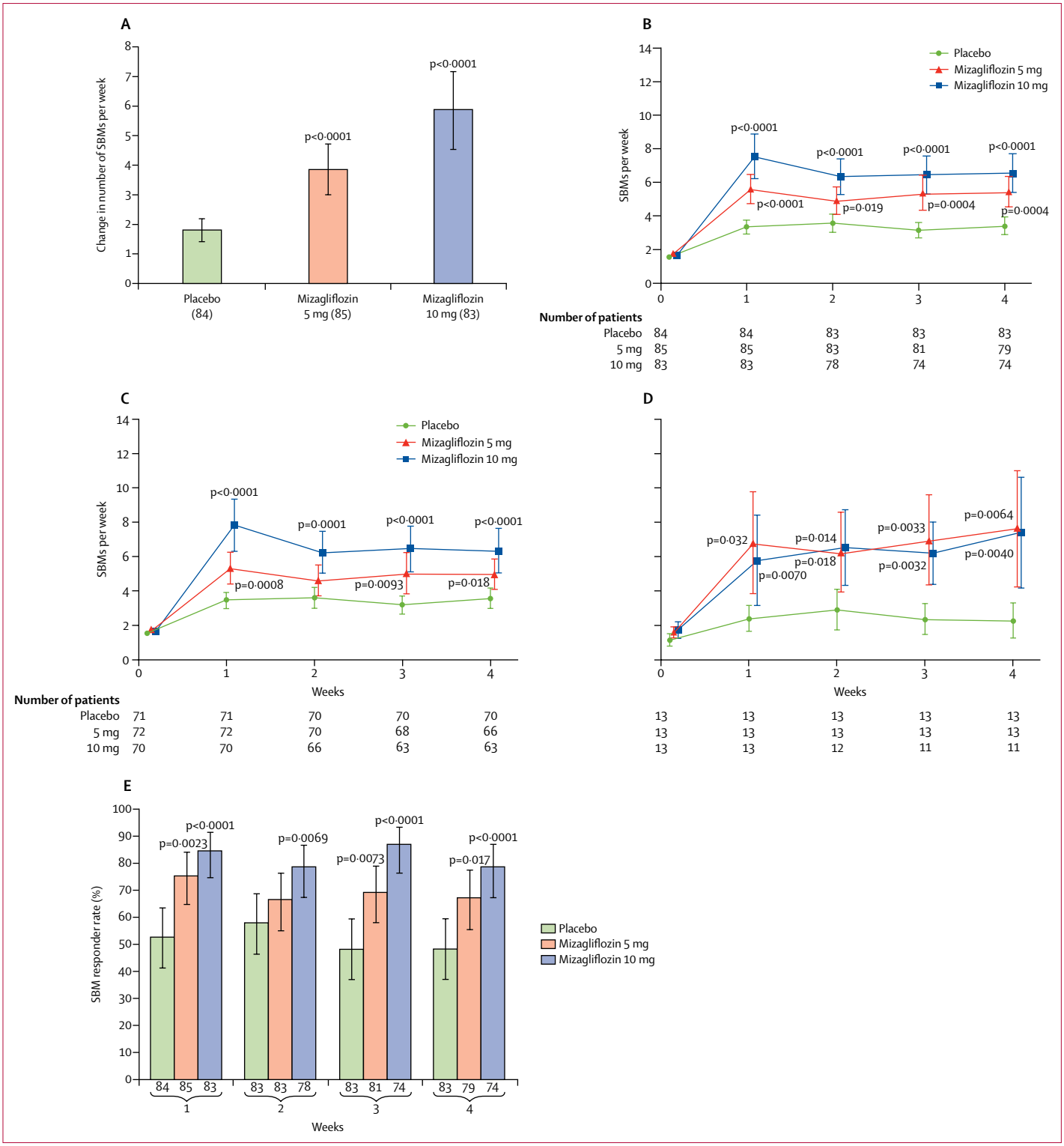

Figure 2: **Spontaneous bowel movements**
(A) Change from baseline in the number of spontaneous bowel movements (SBMs) per week at week 1 in the full analysis population (n values below bars); data presented as mean and error bars are 95% CI. (B) Number of SBMs per week for 4 weeks in the full analysis population with available data; data presented as mean and error bars are 95% CI. Number of SBMs per week for 4 weeks in the population subgroups of functional constipation (C) and irritable bowel syndrome with constipation (D); data presented as mean and error bars are 95% CI. (E) Responder rates for changes in the number of SBMs per week for 4 weeks in the full analysis population (n values below bars); data presented as percentage of patients and error bars are 95% CI. Two sample Student's *t* test was used in (A), (B), (C), and (D); Fisher's exact test was used in (E). All p values are versus placebo.

	Placebo	Mizagliflozin 5 mg	p value (5 mg *vs* placebo)	Mizagliflozin 10 mg	p value (10 mg *vs* placebo)
SBMs					
Time to first SBM, h	39·94 (35·63), n=81	33·16 (56·21), n=84	0·0010*	19·29 (27·97), n=82	<0·0001*
Had first SBM within 24 h of initial administration	29/84 (35%)	51/85 (60%)	0·0011†	54/83 (65%)	<0·0001†
Had first SBM within 48 h of initial administration	54/84 (64%)	66/85 (78%)	0·063†	74/83 (89%)	<0·0001†
CSBMs					
Number per week of CSBMs at week 1	1·16 (1·68), n=84	2·30 (3·51), n=85	..	3·76 (4·63), n=83	..
Change from baseline at week 1	0·82 (1·51), n=84	1·79 (3·35), n=85	..	3·24 (4·58), n=83	..
Difference *vs* placebo (95% CI)	..	0·97 (0·17 to 1·76)	0·017‡	2·42 (1·38 to 3·46)	<0·0001‡
Number per week of CSBMs at week 4	1·66 (2·07), n=83	2·04 (3·11), n=79	..	3·28 (4·27), n=74	..
Change from baseline at week 4	1·34 (1·87), n=83	1·56 (3·08), n=79	..	2·74 (4·13), n=74	..
Difference *vs* placebo (95% CI)	..	0·21 (−0·57 to 1·00)	0·59‡	1·40 (0·41 to 2·39)	0·0059‡
Responder rate of CSBMs at week 1	15/84 (18%)	28/85 (33%)	0·033†	39/83 (47%)	<0·0001†
Responder rate of CSBMs at week 4	15/83 (18%)	18/79 (23%)	0·55†	28/74 (38%)	0·0070†
Use of rescue medications					
Baseline	19/84 (23%)	29/85 (34%)	0·12†	21/83 (25%)	0·71†
Week 4	12/83 (14%)	4/80 (5%)	0·063†	3/74 (4%)	0·031†
Satisfaction rating for the condition of bowel movements					
Baseline	4/82 (5%)	9/82 (11%)	0·24†	4/79 (5%)	1·000†
Week 4	30/81 (37%)	36/78 (46%)	0·26†	33/73 (45%)	0·32†
Straining in SBM					
Change from baseline at week 4	−0·62 (0·83), n=72	−0·76 (0·97), n=73	..	−0·86 (0·91), n=71	..
Difference *vs* placebo (95% CI)	..	−0·13 (−0·43 to 0·16)	0·36‡	−0·24 (−0·53 to 0·05)	0·10‡
Degree of abdominal discomfort					
Change from baseline at week 4	−0·07 (0·65), n=83	−0·13 (0·86), n=79	..	−0·11 (0·58), n=74	..
Difference *vs* placebo (95% CI)	..	−0·06 (−0·29 to 0·18)	0·63‡	−0·04 (−0·24 to 0·16)	0·68‡
Degree of abdominal bloating					
Change from baseline at week 4	−0·06 (0·62), n=83	−0·12 (0·83), n=79	..	−0·09 (0·61), n=74	..
Difference *vs* placebo (95% CI)	..	−0·06 (−0·29 to 0·17)	0·60‡	−0·03 (−0·22 to 0·17)	0·78‡
Global assessment of constipation severity					
Change from baseline at week 4	−0·73 (1·14), n=81	−1·00 (1·25), n=79	..	−1·19 (1·00), n=73	..
Difference *vs* placebo (95% CI)	..	−0·27 (−0·65 to 0·10)	0·15‡	−0·46 (−0·81 to −0·12)	0·0083‡
IBS-QOL-J total score					
Change from baseline at week 4	8·01 (12·18), n=81	7·58 (14·14), n=79	..	6·30 (13·11), n=73	..
Difference *vs* placebo (95% CI)	..	−0·43 (−4·55 to 3·69)	0·83‡	−1·71 (−5·74 to 2·32)	0·40‡
Global assessment of treatment effectiveness					
Change from baseline at week 4	1·33 (1·29), n=81	1·77 (1·23), n=79	..	1·95 (1·19), n=73	..
Difference *vs* placebo (95% CI)	..	0·44 (0·04 to 0·83)	0·029‡	0·61 (0·21 to 1·01)	0·0027‡
SBM responder difference *vs* placebo at week 1 (95% CI)	..	22·9 (8·8 to 37·0)	0·0023‡	32·0 (18·7 to 45·2)	<0·0001‡
Relative risk for SBM responder at week 1 (95% CI)	..	1·44 (1·13 to 1·82)	..	1·61 (1·29 to 2·01)	..
NNT for SBM responder at week 1 (95% CI)	..	4 (3 to 11)	..	3 (2 to 5)	..

Data are mean (SD) or n (%), unless specified. SBMs=spontaneous bowel movements. CSBMs=complete spontaneous bowel movements. IBS-QOL-J=irritable bowel syndrome quality-of-life questionnaire, Japanese version. NNT=number needed to treat. *Wilcoxon rank sum test. †Fisher's exact test. ‡Two-sample Student's *t* test.

Table 2: **Secondary endpoints**

full analysis population for not receiving the study drug. Baseline characteristics of patients were similar in the three groups, except for spontaneous bowel movement and complete spontaneous bowel movement frequencies and BSFS score (table 1). Patients with IBS-C were equally distributed in each of the groups. 216 (86%) patients were women. The mean age was 44·1 years (SD 14·4) and the mean duration of constipation was 19·5 years (SD 13·4). 39 (16%) patients met the Rome III criteria for IBS-C. Five (2%) patients used antidiabetic drugs. The medication compliance rate was 98% in the 5 mg group, 97% in the 10 mg group, and 99% in the placebo group.

The mean change from baseline in the number of spontaneous bowel movements per week at week 1 was significantly greater in the mizagliflozin 5 mg (3·85 [SD 3·96], p<0·0001) and mizagliflozin 10 mg group (5·85 [6·01], p<0·0001) than in the placebo

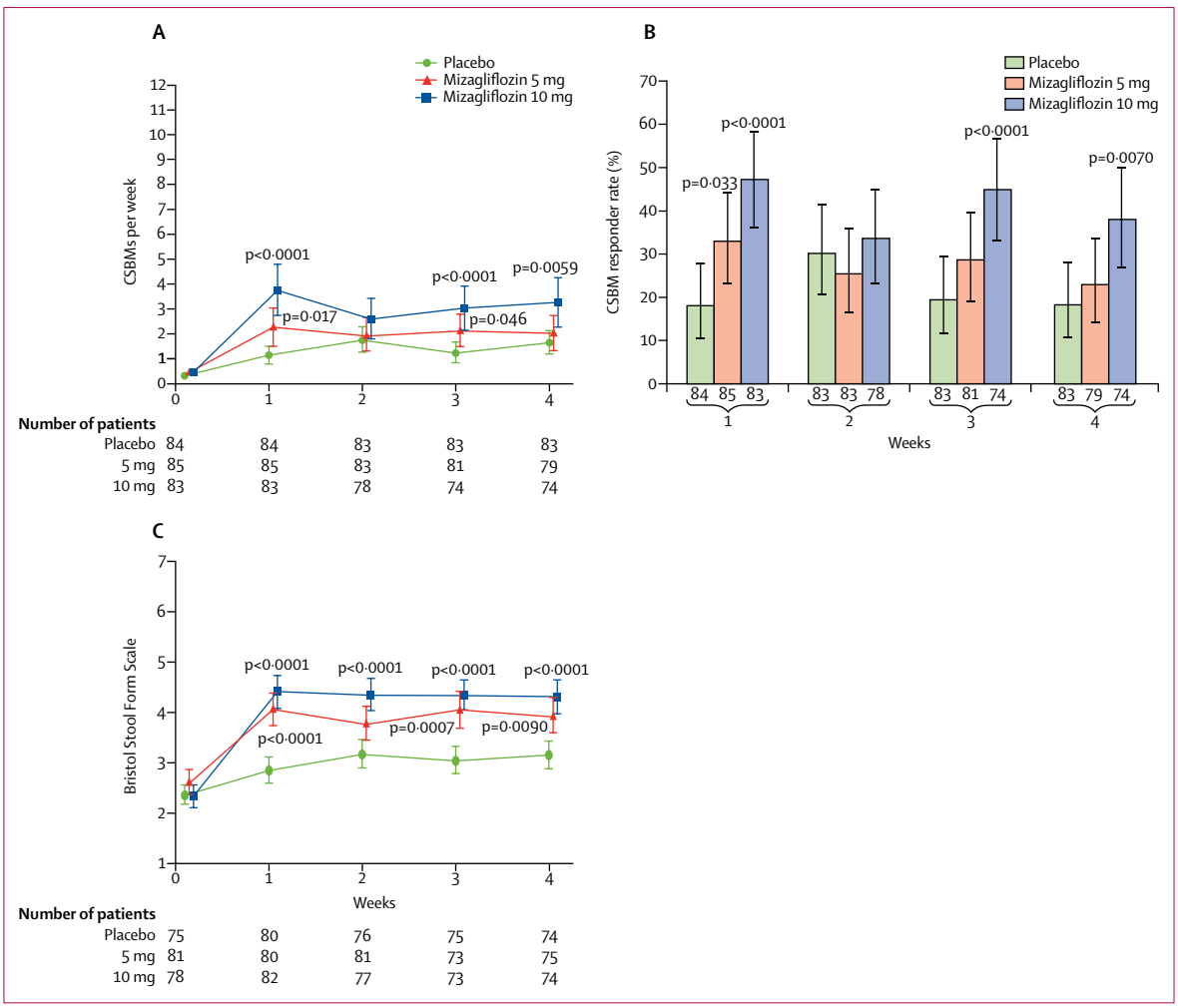

Figure 3: **Secondary endpoints**
(A) Number of complete spontaneous bowel movements (CSBMs) per week for 4 weeks in the full analysis population with available data; data presented as mean and error bars are 95% CI. (B) Responder rates for changes in the number of CSBMs per week for 4 weeks in the full analysis population (n values below bars); data presented as percentage of patients and error bars are 95% CI. (C) Weekly mean stool form for 4 weeks as measured by the Bristol Stool Form Scale (BSFS); data presented as mean and error bars are 95% CI. Two sample Student's *t* test was used in (A) and (C); Fisher's exact test was used in (B). All p values are versus placebo.

group (1·80 [1·80]; figure 2). The difference in mean number of spontaneous bowel movements per week at week 1 from placebo was 2·05 (95% CI 1·12–2·99) in the mizagliflozin 5 mg group and 4·05 (2·70–5·41) in the mizagliflozin 10 mg group.

The secondary endpoints supported the efficacy of mizagliflozin. The number of spontaneous bowel movements increased significantly over 4 weeks in both mizagliflozin groups (figure 2) compared with the placebo group. The responder rate for spontaneous bowel movements at week 1 was 64 (75%) of 85 patients with mizagliflozin 5 mg, 70 (84%) of 83 with mizagliflozin 10 mg, and 44 (52%) of 84 with placebo, with a significantly higher responder rate in both mizagliflozin groups (p=0·0023 with mizagliflozin 5 mg; p<0·0001 with mizagliflozin 10 mg; figure 2) than in the placebo group. The proportion of patients who had spontaneous bowel movements within 24 h of the initial dose was significantly higher in both mizagliflozin groups than in the placebo group, and the time to first spontaneous bowel movement after the initial dose was significantly shortened in the mizagliflozin groups (table 2). The change from baseline in the number of complete spontaneous bowel movements per week at week 1 showed significantly higher values in both mizagliflozin groups than in the placebo group, as did the responder rate for the number of complete spontaneous bowel movements at week 1, with the effect persisting at weeks 3 and 4 for the mizagliflozin 10 mg group (table 2, figure 3). The weekly mean BSFS score showed that mizagliflozin treatment softened stools in a dose-dependent manner from weeks 1 to 4 (figure 3). No significant differences were reported between the mizagliflozin groups and the placebo group

for straining during spontaneous bowel movements, abdominal discomfort and bloating, bowel movement satisfaction rating, or total scores from the irritable bowel syndrome quality-of-life measure questionnaire (Japanese version; table 2).

Subgroup analyses for the functional constipation and IBS-C populations showed significant increases from baseline in the number of spontaneous bowel movements per week at week 1 in both mizagliflozin groups (figure 2). In patients with functional constipation, the difference in mean spontaneous bowel movements between mizagliflozin treatment and placebo at week 1 was 1·71 (95% CI 0·71–2·70, p<0·0001) in the 5 mg group and 4·28 (2·75–5·81, p<0·0001) in the 10 mg group. In patients with IBS-C, the difference between mizagliflozin treatment and placebo in mean spontaneous bowel movements at week 1 was 3·96 (1·19–6·73, p=0·0070) in the 5 mg group and 2·83 (0·25–5·41, p=0·032) in the 10 mg group. Patients with functional constipation and IBS-C in the mizagliflozin 10 mg group also had significant increases in the mean number of complete spontaneous bowel movements per week at week 1 (appendix).

The analyses done with the per-protocol population for the primary endpoint showed similar results (data not shown). Furthermore, ANCOVA with baseline spontaneous bowel movements, complete spontaneous bowel movements, and BSFS score as covariates showed consistency with the primary analysis (data not shown). The spontaneous bowel movement and complete spontaneous bowel movement responder rates at week 1 for the intention-to-treat population were significantly higher in both mizagliflozin groups than those in the placebo group (appendix). The relative risk for spontaneous bowel movement responder rate was 1·44 (95% CI 1·13–1·82) in the mizagliflozin 5 mg group and 1·61 (1·29–2·01) in the mizagliflozin 10 mg group, and the number needed to treat was 4 (95% CI 3–11) in the 5 mg group and 3 (2–5) in the 10 mg group (table 2).

The number of patients with adverse events was 28 (33%) of 85 patients in the mizagliflozin 5 mg group, 28 (33%) of 86 in the 10 mg group, and 17 (20%) of 86 in the placebo group. The most frequently observed adverse events that were attributable to the study drugs were diarrhoea and abdominal distension (table 3). All adverse events were either mild or moderate and there were no deaths or other clinically significant events. One (1%) of 86 patients in the placebo group, three (4%) of 85 in the mizagliflozin 5 mg group, and six (7%) of 86 in the mizagliflozin 10 mg group were withdrawn from the study because of adverse events. Of these patients, one from the mizagliflozin 5 mg group and five from the mizagliflozin 10 mg group were withdrawn because of diarrhoea; other adverse events that caused patients to withdraw were lower abdominal pain, abnormal gastrointestinal sounds, and abdominal distension. No clinically significant changes or findings were observed in laboratory parameters, vital signs, bodyweight, or 12-lead electrocardiogram in any treatment group, according to physician's judgment.

	Placebo (n=86)	Mizagliflozin 5 mg (n=85)	Mizagliflozin 10 mg (n=86)
Nasopharyngitis	1 (1%)	7 (8%)	5 (6%)
Diarrhoea	0	4 (5%)	8 (9%)
Abdominal distension	3 (3%)	4 (5%)	7 (8%)
Nausea	1 (1%)	1 (1%)	3 (3%)
Frequent bowel movements	0	1 (1%)	3 (3%)
Abnormal gastrointestinal sounds	0	2 (2%)	2 (2%)
Flatulence	1 (1%)	1 (1%)	2 (2%)
Vomiting	0	0	2 (2%)
Abdominal pain	1 (1%)	2 (2%)	1 (1%)
Upper abdominal pain	1 (1%)	2 (2%)	1 (1%)
Blood in urine	0	1 (1%)	2 (2%)
Alanine aminotransferase concentrations increased	2 (2%)	2 (2%)	0
γ-glutamyl transferase concentrations increased	0	2 (2%)	0

Data are n (%). Increases in alanine aminotransferase and γ-glutamyl transferase concentrations were noted according to physician's judgment.

Table 3: **Adverse events reported in 2% or more of the safety population**

No signs, symptoms, or changes in blood glucose-related parameters suggesting hypoglycaemia were seen in this study. There were no clinically meaningful changes in glycoalbumin, or random blood glucose concentrations in the five patients who received antidiabetic drugs (three in the mizagliflozin 5 mg group and two in the 10 mg group). Glycosuria was also not observed. The relative risk for the incidence of adverse events was 1·67 (95% CI 0·99–2·81) with mizagliflozin 5 mg and 1·65 (0·98–2·78) with mizagliflozin 10 mg. The number needed to harm for the incidence of adverse events was 8 (95% CI 4–821) with mizagliflozin 5 mg and 8 (4–484) with mizagliflozin 10 mg.

Discussion

In this randomised placebo-controlled phase 2 trial, we showed the efficacy and tolerability of mizagliflozin for functional constipation. To our knowledge, this is the first report showing the efficacy and safety of SGLT1 inhibition for patients with functional constipation. The mechanism of action of mizagliflozin is novel: it selectively inhibits SGLT1 in the small intestine because it is poorly absorbed[15] and acts specifically on the intestinal epithelia.[12] The ability of mizagliflozin to retain water and glucose in the small intestine, especially after a meal, leads to increased water volume in the small intestine and colon, triggering propulsion of the gut by peristaltic reflex.[27] Our results with the BSFS score reflect this, showing a stool-softening effect of mizagliflozin. The safety of mizagliflozin and its effect on functional constipation probably result from this pharmacological action.

The results of this study suggest that SGLT1 inhibition can improve functional constipation without any changes in glucose-related parameters or hypoglycaemia-like symptoms. A clinical pharmacology study of mizagliflozin found that the effect of postprandial administration of mizagliflozin on plasma glucose concentrations in healthy people was negligible.[11] Because the number of patients with functional constipation and diabetes assessed in our study was small, the safety of mizagliflozin in these patients needed to be assessed in future studies. Additionally, the previous study showed that glucagon-like peptide-1 (GLP-1) secretion was enhanced by mizagliflozin.[11] The effect of mizagliflozin caused more glucose substrates to reach the distal portions of the ileum and colon, potentially augmenting the luminal glucose stimulus to enhance GLP-1 release from L cells in the distal gastrointestinal tract.[11] Serum GLP-1 was reported to inversely correlate with the severity and frequency of abdominal pain or discomfort in patients with IBS-C.[28] Furthermore, a clinical trial in patients with irritable bowel syndrome showed that a GLP-1 analogue was twice as effective as placebo in terms of total pain relief in patients with irritable bowel syndrome affected by pain.[29] The subgroup analysis in our study showed a significant increase in complete spontaneous bowel movements in patients with IBS-C treated with 10 mg of mizagliflozin. Because IBS-C is characterised by abdominal pain or discomfort and abnormal defecation, these findings suggest that mizagliflozin might also be beneficial for improving symptoms associated with IBS-C.[30]

Our study had several limitations. The treatment duration of this study was only 4 weeks, based on Rome III recommendations for treatment trials[19] and on phase 2 and phase 3 studies of lubiprostone in Japan,[20,21] which was the usual strategy at that time. Therefore, a long-term study for functional constipation according to more current recommended trial designs is warranted. The limitations of this study also included the absence of follow-up after treatment completion or discontinuation, small number of patients with IBS-C, and absence of positive effects for some of the secondary outcomes. However, the results of these secondary outcomes were similar to those of the lubiprostone study,[20] which showed an increase in the number of spontaneous bowel movements in a subgroup of patients with IBS-C. The global assessment of treatment efficacy in mizagliflozin groups was superior to that of placebo, even in this small number of patients. Therefore, the assessment of individual symptoms might show improvements when done in a larger-scale study. The potential efficacy of the drug on abdominal defecation, abdominal pain, discomfort, and bloating for patients with IBS-C will need to be evaluated with the specific endpoints recommended by the US Food and Drug Administration[30] in the future. Finally, the risk of hypoglycaemia should be further examined from a pharmacological perspective. This risk would be low after postprandial administration of mizagliflozin, because the area under the curve of plasma insulin after 10 mg of mizagliflozin was also reduced in a registered but unpublished study (NCT02343978), in line with the suppression of blood glucose increase.

Despite some limitations, this study supports the hypothesis that 5 mg and 10 mg of mizagliflozin are effective and safe treatments for patients with functional constipation. Further studies of SGLT1 inhibitors in patients with functional constipation or IBS-C are warranted.

Contributors

SF, MH, AN, and KK advised in the study design. Data collection was undertaken by YE, AN, TA, HK, TNakat, TNakaj, and KS. All authors contributed to data interpretation, writing, and final approval of the manuscript.

Declaration of interests

SF reports grants and personal fees from Kissei Pharmaceutical during the conduct of the study, personal fees from Dainippon Sumitomo Pharma, Scampo Pharma, Sanwa Chemical, Zeria Pharmaceutical, Glaxo-Smith-Kline, Mochida Pharmaceutical, and Shionogi, grants and personal fees from Abbott Japan, Astellas Pharma, AstraZeneca, Tsumuta, and Zespri International, grants from Ono Pharmaceutical, Smoking Research Foundation, and Kao, and personal fees and non-financial support from Miyarisan Pharmaceutical, outside the submitted work. YE reports grants from Kissei Pharmaceutical during the conduct of the study. MH reports personal fees from Kissei Pharmaceutical during the conduct of the study and personal fees from Astellas Pharma, Kenei, Sanwa Kagaku Kenkyusho, Sucampo Pharma, Danone Japan, and Mylan EPD, outside the submitted work. AN reports grants from Kissei Pharmaceutical during the conduct of the study, grants and personal fees from Kowa Pharmaceutical, Astellas Pharma, and Mylan EPD, and grants from Biofermin Pharmaceutical, Taisho Pharmaceutical, Danone Japan, Daiichi-Sankyo, Shionogi Pharmaceutical, Eisai, and Ono Pharmaceutical, outside the submitted work. TA, HK, TNakat, TNakaj, and KS report grants from Kissei Pharmaceutical during the conduct of the study. KK reports personal fees from Kissei Pharmaceutical during the conduct of the study, grants and personal fees from Boehringer Ingelheim, Taisho Toyama Pharmaceutical, Mitsubishi Tanabe Pharma, Astellas Pharma, and Takeda Pharmaceutical, grants from Daiichi Sankyo, and personal fees from AstraZeneca, Sumitomo Dainippon Pharma, Kissei Pharmaceutical, Kowa Pharmaceutical, Merck, Novartis, Ono Pharmaceutical, and Sanofi, outside the submitted work.

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