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Rationale and design of a multicentre, 12-week, randomised, double-blind, placebo-controlled, parallel-group, investigator-initiated trial to investigate the efficacy and safety of elobixibat for chronic constipation

Kosuke Tanaka ,[1,2] Takaomi Kessoku,[1,2] Atsushi Yamamoto,[2] Kota Takahashi,[2] Yuki Kasai,[2] Anna Ozaki,[2] Michihiro Iwaki ,[1,2] Takashi Kobayashi,[2] Tsutomu Yoshihara,[2] Noboru Misawa,[2] Takayuki Kato,[3] Jun Arimoto,[4] Akiko Fuyuki,[1,2] Eiji Sakai,[5] Takuma Higurashi ,[2] Hideyuki Chiba,[4] Kunihiro Hosono,[2] Masato Yoneda,[2] Tomoyuki Iwasaki,[6] Takeo Kurihashi,[7] Machiko Nakatogawa,[8] Ayao Suzuki,[8] Masataka Taguri,[9] Shunsuke Oyamada,[10] Keisuke Ariyoshi,[11] Noritoshi Kobayashi,[12,13] Yasushi Ichikawa,[12,13] Atsushi Nakajima [2]

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For numbered affiliations see end of article.

Correspondence to
Dr Takaomi Kessoku;
kessoku-tho@umin.ac.jp

ABSTRACT

Introduction Chronic constipation (CC) is a functional disorder that negatively impacts the quality of life of patients. This is a protocol for a multicentre, 12-week, randomised, double-blind, placebo-controlled study to test the efficacy and safety of elobixibat (EXB) versus placebo in patients with CC.

Methods and analysis This will be a multicentre, double-blind, placebo-control, randomised controlled trial. A total of 100 adult patients with CC, diagnosed based on Rome IV criteria, who fulfil the inclusion/exclusion criteria will be enrolled. The patients will be randomly assigned to receive EXB (10 mg) or placebo treatment (n=50 per group). Blood tests and stool sampling will be performed 12 weeks following initiation of treatment and questionnaires will be issued to participants. The primary outcome will be the change in complete spontaneous bowel movements after 12 weeks of administration. The secondary outcomes will include the change in Japanese Patient Assessment of Constipation Quality of Life and absolute serum and faecal bile acid.

Ethics and dissemination Ethics approval has been obtained from Yokohama City University Certified Institutional Review Board before participant enrolment. The results of this study will be submitted for publication in international peer-reviewed journals and the key findings will be presented at international scientific conferences.

Protocol version V.3.0, 15 June 2021.

Trial registration number ClinicalTrials.gov (number NCT04784780).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised, double-blind, placebo-controlled trial to determine the efficacy and safety of elobixibat treatment for 12 weeks in patients with chronic constipation.
⇒ Previous double-blinded randomised controlled trials of elobixibat for chronic constipation have only lasted for up to 2 weeks.
⇒ Our research will not be limited to the patient's defecation status; we will also collect faecal and blood samples to measure intestinal bacteria, organic acids, amino acids and bile acids.
⇒ The primary outcome is set as complete spontaneous bowel movements, which is not simply the number of bowel movements, but the number of bowel movements with quality of life taken into account.
⇒ Limitations include the lack of active comparator laxatives and the inclusion of patients of a single ethnicity.

INTRODUCTION

Chronic constipation (CC) is a frequently occurring functional disorder encountered in daily clinical practice, with a prevalence of 2%–27% in Japan. It is more prevalent in women than in men, and the prevalence increases with age in both sexes. In addition, comorbid functional gastrointestinal diseases are common, and reduced quality of life (QOL) has also been reported.[1–3] It is

important to establish a 12-week effective treatment for CC because of the high frequency of concomitant ischaemic heart disease among the patients[4–6] and the poor prognosis of chronically constipated patients compared with that of non-constipated patients.[7]

Elobixibat (EXB) is an oral drug for CC that specifically inhibits ileal bile acid transporter/apical sodium-dependent bile acid transporter (IBAT/ASBT) (a transporter involved in bile acid reabsorption) in the terminal ileum.[8] EXB was approved for marketing in Japan in January 2018. EXB is able to inhibit IBAT, leading to inhibition of bile acid reabsorption and an increase in the amount of bile acid that reaches the large intestine; this promotes the secretion of water into the lumen of the large intestine, thereby improving gastrointestinal motility. A placebo (PBO)-controlled double-blind study confirmed that EXB improves various symptoms including the frequency of spontaneous bowel movements (SBMs), frequency of complete spontaneous bowel movements (CSBMs), time to first SBM and stool consistency in Japanese patients with CC. However, the duration of treatment in the aforementioned trial was only 2 weeks, and it was a single-arm study with confirmed safety and efficacy for 52 weeks. In addition, there was no control group.[9]

Recently, 12-week randomised controlled trials (RCTs) aimed at developing new drugs for CC have been conducted in Europe and the USA. In Japan, lubiprostone has been used as a comparator, and a clinical trial was conducted using the number of SBMs at 1 week as the primary endpoint.[10] Safety was also assessed in a 52-week open study. Therefore, 12-week RCTs have not been conducted in Japan, and the efficacy and safety of the 12-week administration of EXB should be verified with a double-blinded comparison.

This study aims to investigate the efficacy and safety of the 12-week administration of EXB or PBO for 12 weeks in patients with CC.

METHODS AND ANALYSIS

Trial design

The Standard Protocol Items: Recommendations for Interventional Trials statement and checklist were followed in preparing the study protocol. The trial is designed as a multicentre, randomised, double-blind, PBO-controlled, parallel-group, investigator-initiated study to evaluate the efficacy and safety of EXB and PBO treatments. All treatments will be administered orally once daily to patients with CC for 12 weeks. The experimental groups will be as follows (figure 1): the EXB group (10 mg EXB) and the PBO group. The study plan involves recruiting 100 adult patients with CC from seven institutions (the Yokohama City University Hospital, International University of Health and Welfare Atami Hospital, Omori Red Cross Hospital, Yokohama Sakae Kyosai Hospital, Iwasaki Naika Clinic, Kanagawa Dental University Yokohama Clinic and NamikiKoiso-medical clinic) cohort. The study protocol

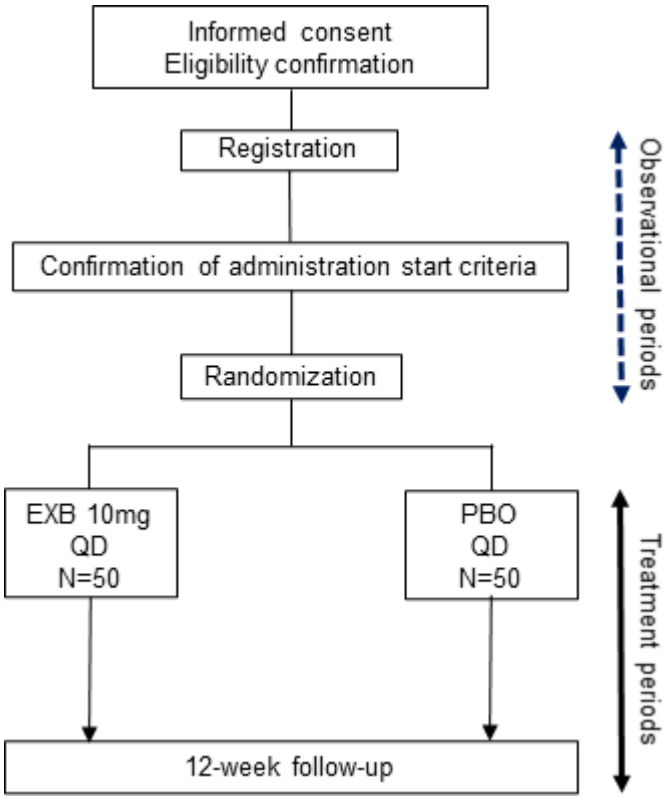

Figure 1 Flowchart of the study design. EXB, elobixibat; PBO, placebo.

and informed consent form are shown in online supplemental document 1, 2. This trial was registered with ClinicalTrials.gov (number NCT04784780) on 28 February 2021. The trial results will be reported in conformity with the Consolidated Standards of Reporting Trials 2010 guidelines.[11]

Rationale for treatment dose, mode and duration

A previous study used the primary endpoint of 'SBM',[9] whereas this study will use 'CSBM', which represents the frequency of bowel movements assessed for QOL; this has been recommended by the European Medical Agency (EMA) guidelines in recent years.[12] Previous studies had reported significant differences at week 2; however, CC is defined as unsatisfactory bowel movements for 3 months or longer. Therefore, efficacy after 2 weeks of administration does not necessarily indicate an improvement in CC. To demonstrate efficacy, the change in CSBMs after 12 weeks of administration has been set as our primary endpoint.[13]

Drug supply

Only the Patient Enrolment Centre will be aware of the treatment allocation, and double-blinding of the physicians and patients will be maintained throughout until all patients have completed the 12-week study and the database with all study data has been locked. EXB tablets (5 mg) and the corresponding reference PBO, which are indistinguishable in appearance, are manufactured and supplied by EA Pharma Co. (Tokyo, Japan). For the

study drugs prescribed, the physicians will enter the drug allocation number provided by the Patient Enrolment Centre on the prescription form. The drug manager will dispense the study drug to the patient based on the drug allocation number.

Sample size estimation and interim analysis

The target enrolment number will be 50 patients per group, for a total of 100 patients. A previous phase 3 study[9] showed that the change in CSBMs during week 2 of the observational period was 2.98±3.1 (mean±SD) in the EXB group (n=65) and 0.86±1.45 in the PBO-treated group (n=63).

Additionally, it was previously reported that the change in CSBMs at week 2 of the treatment period relative to week 2 of the observational period was calculated at 2.12 for the between-group difference and approximately 2.288 for the common-SD. Since the study period in this trial is longer than that of the previous study, it is assumed that the difference between the mean values of the groups will be small, whereas the variation in the difference between groups in the amount of change will be larger due to differences regarding the participating medical institutions in the previous study.

Therefore, in calculating the sample size for this study, it was assumed that the between-group differences and common-standard-deviations for the primary endpoint (CSBMs change relative to week 2 of the observational period at week 12 of the treatment period) will be 1.8 and 2.5, respectively. At this time, Student's t-test provides a 2-sided significance level of 5% and a power of 90% for 43 patients per group.

Since the study period is longer than that of the previous study, a dropout rate of approximately 10% was assumed, and a total of 100 patients (50 per group) was selected to ensure adequate power.

Eligibility

The physicians will enter legally capable patients into the Screening List, assign an identification code to each patient, and determine eligibility according to the inclusion and exclusion criteria (table 1). If no eligibility issues are identified, the investigator, subinvestigator or investigative staff will enter the necessary information into the Electronic Data Capture (EDC) system for enrolment. A patient enrolment number will then be assigned, and enrolment will be completed.

Randomisation, masking and keycode open

The patients will be randomised to each group (EXB and PBO) at a ratio of 1:1 using a computer-generated centrally administered procedure (permuted block method, no factor for stratification). The contract research organisation will create the list of study drug randomisation and link the appropriate study drug number. After the investigators confirm the eligibility of participants, the required information will be entered into the EDC system, and the drug number will be issued. Investigators and patients will be blinded to the details of the assignment to conceal the drug allocation number with the independent contract research organisation until the keycode is opened. All trial drugs will be packed identically and identified only by the number assigned. As noted above, the treatment assignments will be fully masked from the patients and physicians.

Keycode break

If the investigator or subinvestigator considers it urgently necessary to break the study keycode prematurely, they will contact the individual responsible for the study drug randomisation to file the request. This may occur due to a serious adverse event (SAE), the need to treat an adverse event (AE) or other similar situations.

Adverse reactions and AE monitoring

AEs are defined as any unfavourable or unintended sign (including laboratory parameters and abnormal vital signs), symptom or disease that may occur during the study period. AEs that are not directly related to the study drugs may develop. The investigator or subinvestigator will assess the severity of the AEs. Any AE that fulfils any of the following criteria will be considered an SAE: death, life-threatening situation, requirement for hospitalisation or prolonged hospitalisation for treatment, disability, threat of disability, other serious conditions, congenital disease or anomaly in offspring. If an SAE occurs, the investigator or subinvestigator will treat it appropriately, and the investigator will immediately report the details to the Hospital Director, Minister of Health, Labour and Welfare and the study drug supplier.

Study procedures

The investigator or subinvestigator will perform all observations, tests, investigations and evaluations according to the descriptions provided in table 2. After the initiation of treatment, drug returns and blood test results will be evaluated to monitor for adherence at each visit. Blood/stool samples will be collected and stored to assess the gut microbiota, bile acid, short-chain fatty acids and amino acids. When the study drug is distributed to the participants at each visit, the pharmacist will provide instructions on the dosage and administration. The pharmacist will request that participants return the unused study drug at their next visit and record the number of tablets (packages) that are returned. These strategies will improve adherence to the intervention protocol.

Concomitant treatment

The administration of the following medications and therapy is prohibited from the start of the observational period to the end of treatment: various laxatives (magnesium oxide preparations, sodium picosulfate, sennoside, etc), bile acid transporter inhibitors other than the study drugs, Chinese herbal medicines with indications for constipation (Daio-kanzoto, Dai-kanzo-to, Dai-ko-to, Dai-saiko-to, etc), irritable bowel syndrome medications, 5-HT_3 antiemetics, macrolide antibiotics, antidepressants

Table 1 Patient inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Time of registration	1. Patients with or suspected of having structural constipation
Patients who meet all of the following criteria (1–6)	2. Patients with or suspected of having functional ileus
1. Individuals diagnosed with chronic constipation according to the Rome IV criteria for chronic constipation	3. Patients with or suspected of having an inguinal hernia
2. Age: 20–85 years (at the time of informed consent)	4. Patients who have undergone laparotomy within 12 weeks before providing informed consent (excluding appendicitis resection)
3. Sex: any	5. Patients with a history of surgical or endoscopic procedures related to cholecystectomy and papillotomy
4. Outpatient	6. Patients with concomitant malignancies. However, patients who have undergone radical surgery or who have completed chemotherapy or radiotherapy can be enrolled.
5. Patients from whom written informed consent can be obtained	7. Pregnant women, breastfeeding women, women who are currently possibly pregnant, or patients who do not consent to contraceptive use during study participation
6. Patients who can record bowel movements in a patient diary	8. Patients with serious concomitant renal, hepatic or cardiac disease
	9. Patients allergic to the study drug
	10. Patients who meet contraindications for rescue medications (bisacodyl suppositories and Pursennid tablets). However, if either rescue drug is not contraindicated, registration is permitted.
	11. Patients participating in other clinical studies within 4 weeks before providing informed consent, excluding observational studies
	12. Other patients whose inclusion in the study is deemed inappropriate by the investigator or subinvestigator
At the time of allocation (baseline)	
Patients who fulfil all of the following criteria (1–3)	
1. Patients with ≤6 spontaneous bowel movements (SBMs)* during the 2-week observational period prior to the initiation of treatment.	
2. Patients who did not have loose or watery stools (Bristol Stool Form Scale 6 or 7) in SBMs** during the 2-week observational period prior to the start of treatment.	
3. Patients who do not use concomitant drugs or therapies during the observation period.	

*Bowel movements occurring without laxatives/enemas or disimpaction. **If laxatives or relief medications were used on the day before the start of the run-in period, bowel movements within one day after use will not be considered spontaneous.
SBMs, spontaneous bowel movements.

and anticholinergics, among others. The restricted concomitant medications are permitted only if the rescue medication prescribed for this study (bisacodyl suppository 10 mg/1 tablet once and Pursennid tablet 12 mg/2 tablets once) could only be used if defaecation is not observed for more than 2 consecutive days.

Criteria and procedure for withdrawal from the study

The investigator or subinvestigator will discontinue the enrolment of a patient in the study if they fulfil any of the following criteria: (1) the patient desires withdrawal; (2) the patient is found not to meet the inclusion criteria or to meet the exclusion criteria after enrolment; (3) if it is the opinion of the investigator or subinvestigator that having the patient continue in the study is inappropriate due to an AE; or (4) if the investigator or subinvestigator believes that having the patient continue in the study is not appropriate due to any other reason.

Criteria for reducing and increasing the dosage of medications

No criteria for reduction and escalation of the dose of EXB will be established in this study.

Table 2 Schedule of observations, tests and assessments

		Observational period	Treatment period			
		V1	V2/randomisation	V3	V4	V5/EOT
Study week		Registration	Randomisation	Week 4	Week 8	Week 12/ discontinuation
Visit window	Informed consent	–	2–4 weeks after registration	±7 days	±7 days	±7 days
Informed consent	○					
Inclusion/exclusion criteria		○				
Demographics		○				
Vital signs/height and weight*		○	○	○	○	○
Blood test		○				○
Registration		○				
Confirmation of administration start criteria/allocation			◎			
Blood and stool collection for exploratory research			●	●		●
Providing drugs			○	○	○	
Checking the medication status				○	○	○
Review concomitant medications		○	○	○	○	○
Review rescue drugs			○	○	○	○
Review adverse events		←	—	—	—	→
Questionnaire/ review patient diary†			○	○		○
Patient diary confirmation		←	—	—	—	→

○ To be performed.
◎ After confirming the treatment initiation criteria, the drugs will be allocated.
● Test stool collection kits will be provided mandatorily at the previous visit.
*The patient's vital signs, including blood pressure and pulse rate, will be recorded. Height and weight will be measured only at enrolment.
†Patient diaries will be provided on V1, and diary entries will be checked at each visit.

Evaluation of efficacy

The primary efficacy endpoint will be the change in the number of CSBMs at week 12 of the treatment period compared with those at week 2 of the observational period, from the baseline to 12 weeks after treatment initiation. CSBMs are defined as the number of defaecations not induced by rescue medication and not accompanied by a sense of incomplete evacuation. CSBMs will be evaluated by having patients note each bowel movement in their diary. The secondary endpoints are provided in table 3. According to the EMA guidelines, the number of CSBMs, the responder ratio of CSBMs, Japanese Patient Assessment of Constipation Quality of Life (JPAC-QOL) score, and the desire to defaecate will be assessed in this study to evaluate not only bowel movements but also defaecation-specific QOL.

Safety assessments

The following safety evaluations will be performed during each patient visit from week 2 of the observational period until the week 12 treatment period: incidence of AEs in the EXB group compared with that of the PBO group.

Table 3 Study endpoints

Primary endpoint	Secondary endpoints	
Efficacy endpoint	**Efficacy endpoints**	**Safety endpoint**
► Change in the number of complete spontaneous bowel movements* (CSBMs) at week 12 of the treatment period relative to week 2 of the observational period	► Change in the number of CSBMs* at weeks 1 through 11 of the treatment period relative to week 2 of the observational period	► Incidence of adverse events
	► Change in the number of SBMs for each week of the treatment period relative to week 2 of the observational period	
	► Percentage of responders † as seen in the number of SBMs and the number of CSBMs observed in each week of the treatment phase	
	► Percentage of responders ‡ as seen in the number of CSBMs during treatment (12 weeks)	
	► Percentage change in stool consistency based on the Bristol Stool Form Scale at each week of the treatment period relative to week 2 of the observational period	
	► Percentage change in the presence or absence of a sense of incomplete evacuation at each week of the treatment period relative to week 2 of the observational period	
	► Percentage change in the degree of straining at each week of the treatment period relative to week 2 of the observational period	
	► Percentage change in the presence or absence of defecation desire at each week of the treatment period relative to week 2 of the observational period	
	► Change in JPAC-QOL scores at week 4 and week 12 relative to baseline (V2)	
	► Changes in the following at week 4 and week 12 relative to baseline (V2) 1. Changes in the absolute faecal gut microbiota and percentages 2. Changes in the absolute values and percentages of blood and faecal bile acid 3. Changes in the absolute values and percentages of faecal organic acids 4. Changes in the absolute values and percentages of blood and faecal amino acids 5. Changes in blood C4	

All objectives will be compared between EXB 10 mg and placebo groups. C4, 7α-Hydroxy-4-cholesten-3-one.
*SBMs without a sense of incomplete evacuation.
†Responders are defined as subjects whose SBMs and CSBMs per week have increased by at least one relative to week 2 of the observational period, and a total of at least three times per week.
‡ Responder definition: at least three CSBMs per week and at least one CSBMs per week relative to baseline in 9 weeks of the entire treatment period (12 weeks), including at least 3 weeks during weeks 9–12 of the treatment period.
CSBMs, complete spontaneous bowel movements; JPAC-QOL, Japanese version of the patient assessment of constipation quality of life; SBMs, spontaneous bowel movements.

Analysis population

The set of participants to be analysed will be determined before locking the data of each patient and will be defined as follows. The modified intention-to-treat analysis, which is the full analysis set (FAS), and per-protocol set (PPS) will be used for the assessment of primary efficacy. The FAS will include all patients who are randomised, except those who meet any of the following criteria: (1) patients with serious violations of selection and exclusion criteria, (2) patients who have not received any dose of the study drugs and (3) patients who have no measurement of the efficacy

endpoint. A PPS will include patients without protocol deviations. The FAS will be the primary analysis set for efficacy. For the assessment of secondary efficacy, the FAS will be used. The safety analysis set (SAS) will be used for safety assessment and will include all patients who receive at least one dose of the study drug.

Statistical analysis

The multiplicity of endpoints will not be accounted for in the analysis. The significance between the active drug and PBO for the primary endpoint will be based on analysis of covariance (ANCOVA) using the baseline (week 2 of the observational period) value as the covariate. For the analysis of secondary endpoints, the change in the number of CSBMs and SBMs, and JPAC-QOL in the treatment groups at weeks 1–11 of the treatment period relative to week 2 of the observational period will be compared and analysed by ANCOVA using the baseline value. The changes in stool consistency using the Bristol Stool Form Scale (BSFS) score and degree of straining will be analysed using the Wilcoxon rank-sum test. We will use Fisher's exact test for comparison of the proportion of patients in the SBM and CSBM responder analyses and the proportion of patients with incomplete evacuation and loss of defaecation desire (LODD). Gut-microbiota, bile acid, organic acids and amino acids will be analysed using Student's t-test, while taking into account the false discovery rate in the EXB and PBO groups using the Benjamini-Hochberg method. We will assess the statistical difference in C4 concentrations between the groups in the 2-week study using Student's t-test.

The numbers and proportions of patients with adverse drug reactions will be summarised according to treatment group. All reported p values will be based on 2-sided tests and the significance level set at 0.05.

Statistical analyses will be performed using SAS, V.9.4 (SAS Institute).

Interim analysis

Not applicable.

Data management, central monitoring and audit

The investigators' sites will maintain individual records of each patient as source data, including a copy of the patient's written informed consent, medical records, laboratory data and other records or notes. All data will be collected by the independent data management centre. The data management centre will oversee the inter-study data sharing process. The clinical data entry, data management and central monitoring will be performed using the electric data capture VIEDOC 4 (PCG Solutions, Uppsala, Sweden). Furthermore, auditing will be planned and conducted by an external clinical research organisation.

Study flow and schedule of enrolment, interventions and assessments

A study flowchart is shown in figure 1. The study schedule is presented in table 2.

Patient and public involvement

In this RCT, patients will be involved in the recruitment and conduct of the study. The development of the research question and outcome measures will be based on patients' priorities, experience and preferences. The burden of intervention will be assessed by patients before commencement of the trial; patients' satisfaction with the treatment will be recorded as a part of the postintervention assessment.

ETHICS AND DISSEMINATION

The study protocol complies with the Declaration of Helsinki[14] and the Ethics Guidelines for Clinical Trial Act published by the Ministry of Health, Labor, and Welfare, Japan. We obtained approval for this study from the Yokohama City University Certified Institutional Review Board on 4 February 2021 (CRB20-023, study protocol; Online supplemental document 1). The protocol and informed consent form were approved by the Yokohama City University Certified Institutional Review Board. Written informed consent for participation in the study will be obtained from all participating patients. The results of this study will be disseminated by face to face to participants who indicate interest in obtaining the results. The results of this study will be submitted for publication in international peer-reviewed journals and the key findings will be presented at international scientific conferences.

DISCUSSION

This is the first study proposed to explore the 12-week effect of EXB in patients with CC, focused on bowel movements and defaecation-related QOL with CSBMs as the primary endpoint.

In Japan, it is common to administer laxative pharmacotherapy for CC when symptoms do not improve sufficiently even after patients have received diet, lifestyle and defaecation habit guidance. Two types of conventional laxatives, magnesium oxide (MgO) and stimulant laxatives, are widely used in clinical practice; MgO is the most commonly prescribed drug. Regular monitoring of serum magnesium levels is necessary if MgO is prescribed to patients with renal impairment, such as older individuals and patients with chronic kidney disease. Stimulant laxatives exhibit potent effects, but there are concerns about dependence and drug tolerance due to continuous use, and in principle, they should be used only occasionally. Therefore, MgO, the dosage of which can be finely adjusted and has demonstrated safety, is often chosen as a first-line drug. However, because there is a risk of hypermagnesaemia occurring not only in patients with renal impairment, as explained previously, but rarely in those with normal renal function, it is recommended that serum magnesium levels be monitored at 3–6 month intervals during 12-week high-dose administration of MgO.[15]

While stimulant laxatives are generally divided into two groups, anthraquinones (senna and rhubarb) and

diphenolics (bisacodyl, sodium picosulfate, etc), to date, most reported RCTs have involved diphenolic laxatives. Some RCTs and systematic reviews from Western countries have confirmed the efficacy of bisacodyl and sodium picosulfate.[16–18] In fact, a recent review has highly recommended bisacodyl, whose efficacy has been reported at a high level of evidence.[19] Regarding clinical trials of MgO, the most frequently prescribed drug for the treatment of chronic idiopathic constipation in Japan, Mori *et al* is the only reported study demonstrating that MgO significantly improves bowel movement and QOL compared with PBO.[20] Additionally, Morishita *et al* first conducted a randomised PBO-controlled comparative study involving PBO, MgO and senna over a period of 4 weeks, and demonstrated that senna and MgO significantly improved the frequency of bowel movements and QOL score and appear effective in the treatment of constipation.[21] There is an RCT of conventional laxatives (MgO and stimulant laxatives) for 4 weeks in patients with CC,[20 21] and a 12 week randomised PBO-controlled trial of linaclotide, a novel laxative.[13] However, no clinical trial has evaluated a constipation drug with a novel mechanism of action, such as EXB, for 12 weeks using CSBMs and defaecation-specific QOL as the primary endpoint.

A web-based questionnaire-based survey reported that patients with CC had a significantly higher rate of LODD than healthy adults, with about 60% of patients losing their defaecation desire (DD), leading to the decrease of defaecation QOL.[22] Bile acids are expected to have a restorative effect on DD because they have an effect to lower the rectal sensory threshold, which is an objective index of DD.[23 24] EXB inhibits IBAT/ASBT (a transporter involved in bile acid reabsorption) in the terminal ileum.[8] The IBAT inhibitory action of EXB increases the amount of bile acid reaching the colon by inhibiting bile acid reabsorption, thereby promoting water secretion into the lumen of the large intestine and gastrointestinal motility. In addition, we will assess a recovery ratio of LODD in the secondary endpoint.

In recent years, CSBMs have attracted attention in clinical trials as an indicator of the efficacy of therapeutic agents for constipation.[13] To increase CSBMs, which is SBMs accompanied by a sensation of complete evacuation, facilitating the passing of stool that is type IV on the BSFS is important. A recent study suggested that type IV stool form contributes significantly to the improvement of QOL compared with other stool forms.[25] Reports have revealed that patients with CC generally have low QOL.[26] Using Patient Assessment of Constipation QOL, this study examined constipation-related QOL before and after drug treatment. Therefore, our study uses the BSFS and JPAC-QOL to assess constipation-related QOL.

Our study has the following strengths: (1) assessment of CSBMs is the primary endpoint; (2) the 12-week duration; (3) BSFS and bowel movements related to defaecation-related QOL are also measured as secondary endpoints; and (4) the measurement of faecal bile acid, serum bile acid, C4, gut-microbiota, organic acids and amino acids. Nevertheless, our study also has the following limitations: (1) lack of comparison with other laxatives; and (2) a patient population of a single ethnicity.

Author affiliations
[1]Department of Palliative Medicine, Yokohama City University Hospital, Yokohama, Kanagawa, Japan
[2]Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan
[3]Department of Gastroenterology, International University of Health and Welfare Atami Hospital, Atami, Japan
[4]Department of Gastroenterology, Omori Red Cross Hospital, Ota-ku, Japan
[5]Department of Gastroenterology, Yokohama Sakae Kyosai Hospital, Yokohama, Japan
[6]Department of Internal Medicine, Iwasaki Naika Clinic, Yokohama, Japan
[7]Department of Internal Medicine, Kanagawa Dental University Yokohama Clinic, Yokohama, Japan
[8]Department of Internal Medicine, NamikiKoiso-Medical Clinic, Yokohama, Japan
[9]Department of Data Science, Yokohama City University Graduate School of Medicine, Yokohama, Japan
[10]Department of Biostatictics, JORTC Data Center, Arakawa-ku, Tokyo, Japan
[11]Department of Data Management, JORTC Data Center, Arakawa-ku, Tokyo, Japan
[12]Department of Oncology, Yokohama City University Hospital, Yokohama, Kanagawa, Japan
[13]Department of Oncology, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan

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Contributors KT, T.Kessoku and AN conceived the study. T.Kessoku conducted the feasibility phase work. Recruitment of participants and follow-up will be performed by AY, KT, YK, AO, MI, T.Kobayashi, TY, NM, T.Kato, JA, AF, ES, TH, HC, KH, MY, TI, TK, MN, AS and NK. Analysis and interpretation of data will be conducted by MT, SO, KA, YI and AN. MT, SO and KA will perform bioinformatic analysis. All authors have read and approved the final manuscript.

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ORCID iDs
Kosuke Tanaka http://orcid.org/0000-0002-5285-939X
Michihiro Iwaki http://orcid.org/0000-0002-7650-0699
Takuma Higurashi http://orcid.org/0000-0002-1815-4396
Atsushi Nakajima http://orcid.org/0000-0002-6263-1436

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