Safety and efficacy of elobixibat for chronic constipation: results from a randomised, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial

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Summary

Background A subset of patients with constipation has reduced colonic bile acid concentrations, which are associated with slow colonic transit. In a previous study, elobixibat, a locally acting ileal bile acid transporter inhibitor, accelerated colonic transit in Japanese patients with functional constipation. In this study, we aimed to determine the efficacy of elobixibat for short-term treatment of chronic constipation, and safety, patient satisfaction, and quality of life with long-term treatment.

Methods We did two phase 3 studies of patients aged 20–80 years in Japan with at least 6 months of chronic constipation, who satisfied Rome III criteria for functional constipation, including fewer than three spontaneous bowel movements per week. The first trial, including patients enrolled at 16 clinics, was a 2-week, randomised, double-blind, placebo-controlled study in which (after a 2-week run-in period) patients were randomly assigned (1:1) to either elobixibat 10 mg/day for 2 weeks or placebo. Randomisation was done with permuted block method (block size six) without stratification. Masking to treatment allocation was achieved with identical appearances of elobixibat and placebo, which were supplied in sealed, opaque containers. Group assignment was concealed from patients, investigators, and analysts. The second trial, including patients enrolled at 34 clinics or hospitals, was an open-label, 1-year study in which all patients received elobixibat; participants could titrate the dose to 5 mg/day or 15 mg/day, or maintain the 10 mg/day dose. In both studies, participants took the study drug as an oral tablet once per day before breakfast. The primary outcome of the 2-week randomised trial was the change from baseline (ie, last week of the 2-week run-in) in the frequency of spontaneous bowel movements during week 1 of treatment. The primary outcome of the 52-week open-label trial was safety (type, severity, and incidence of adverse drug reactions) at all times from treatment initiation. All efficacy analyses were based on the modified intention-to-treat (ITT) population without imputation for any missing data. Safety analyses included all patients who received at least one dose of study drug. These trials are registered with the Japan Pharmaceutical Information Center (numbers JapicCTI-153061 and JapicCTI-153062) and have been completed.

Findings Between Nov 4, 2015, and June 11, 2016, we assigned 133 patients to treatment in the 2-week randomised trial: 70 to elobixibat (69 included in the modified ITT and safety populations) and 63 to placebo. The frequency of spontaneous bowel movements per week during week 1 of treatment was greater with elobixibat (least-squares mean 6·4, 95% CI 5·3–7·6) than with placebo (1·7, 1·2–2·2), p<0·0001). Between Oct 31, 2015, and March 15, 2017, we allocated 341 patients to 52 weeks of elobixibat (340 included in the modified ITT and safety populations). 163 (48%) patients in the 52-week trial had an adverse drug reaction, the most common of which were mild gastrointestinal disorders (in 135 [40%] patients). Inguinal hernia was reported in one patient with elobixibat in the 52-week study as a moderate adverse drug reaction. The most common adverse drug reactions in both trials were mild abdominal pain (13 [19%] patients with elobixibat and one [2%] with placebo in the 2-week randomised trial, and 82 [24%] patients in the 52-week trial) and diarrhoea (nine [13%] patients with elobixibat and none with placebo in the 2-week randomised trial and 50 [15%] in the 52-week trial).

Interpretation Elobixibat resolved constipation in the short-term, and was well tolerated with both short-term and long-term treatment. The evidence supports the use of this novel approach to increase intracolonic concentrations of endogenous bile acid for the treatment of chronic constipation.

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Introduction

Self-reported constipation is reported by 27·2% of North American[1] and 28·4% of Japanese[2] adults, although the reported prevalences differ depending on the definition used for constipation. The symptoms of chronic constipation are infrequent bowel movements, straining, sensation of incomplete evacuation, and hard stools.[3] These negatively affect quality of life (QOL) and impose a socioeconomic burden.[4] In the absence of rectal evacuation disorders, most patients with constipation have normal

Research in context

Evidence before this study

A subset of patients with constipation has reduced colonic bile acid concentrations, and inhibition of ileal bile acid transport provides an approach to treating this condition by increasing both fluid secretion and stimulation of colonic transit. Elobixibat is a novel pharmaceutical drug that is restricted to the gut and is able to selectively inhibit the active reabsorption of bile acids in the distal ileum. We did a PubMed search of articles published from Jan 1, 2000, to Sept 30, 2017 (not limited to the English language), with the search terms "elobixibat", "A3309" (the former name of elobixibat), "constipation", "chronic constipation", and "functional constipation". We identified one phase 1b trial and three phase 2 clinical trials including patients with chronic constipation. The phase 1b trial and two of the three phase 2 trials were 14 days long; the other phase 2 trial lasted for 8 weeks (with 190 patients randomly assigned to one of three doses of elobixibat or placebo). However, two of the studies had small samples sizes (30 in the phase 1b trial, and 36 women in one of the phase 2 trials), there were few patients in each treatment group in the 8-week trial, the preferred dose for efficacy and tolerability was not fully determined, and an indirect measure was used as the primary endpoint in one trial (the biomarker scintigraphic colonic transit). Additionally, the greatest efficacy assessed by patient-reported outcomes related to constipation (eg, stool frequency, consistency, and degree of straining) occurred during the first 2 weeks of the 8-week study with no additional improvement between 3 and 8 weeks at any dose. Therefore, our search justified our phase 3 clinical trials to investigate efficacy of elobixibat for short-term (2-week) treatment of chronic constipation and assessment of safety, quality of life, and satisfaction over 12 months.

Added value of this study

In the 2-week, randomised double-blind trial, significant improvements from baseline to week 1 and week 2 occurred for all efficacy endpoints, including the number of spontaneous bowel movements, the proportion of responders, the proportion of patients who had a first spontaneous bowel movement or complete spontaneous bowel movement within 24 h, stool consistency, median time to first spontaneous bowel movement, and improvement in constipation severity. In the open-label, single-arm, 52-week trial, elobixibat was associated with good tolerability; additionally, there was sustained improvement in bowel functions, quality of life, and satisfaction throughout the 52-week treatment period.

Implications of all the available evidence

The phase 3 trials showed that elobixibat resolved constipation in the short-term compared with placebo and was well tolerated and improved bowel functions and satisfaction when administered for 1 year. The evidence supports the use of this novel approach to increase intracolonic concentrations of endogenous bile acid for the treatment of chronic constipation. Future studies will be needed to assess long-term efficacy.

colonic transit but a few have slow colonic transit[5] associated with reduced colonic propagated contractions.[6] Low levels of 48-h faecal excretion of total and secretory bile acids (deoxycholic and chenodeoxycholic acids) are associated with constipation.[7] Moreover, lower total faecal excretion of bile acids and fasting serum 7-α-hydroxy-cholesten-one (a surrogate of hepatic bile acid synthesis) have been associated with slower colonic transit in patients presenting with constipation than in healthy controls without constipation.[8]

Conventional therapies for constipation include osmotic laxatives such as polyethylene glycol 3350, or second-line therapies including prokinetics such as prucalopride[9] (a serotonin 5-HT_4 receptor agonist), or intestinal chloride secretagogues such as lubiprostone,[10] linaclotide,[11] and plecanatide.[12] Elobixibat is a novel, minimally absorbed inhibitor of ileal bile acid transporter (IBAT; also called apical sodium-dependent bile acid transporter), which is encoded by the gene *SLC10A2* expressed locally in enterocytes. An IBAT inhibitor interrupts the enterohepatic circulation of bile acids and upregulates hepatic bile acid synthesis.[13] Increased concentrations of bile acids in the colon enhance transit by dual actions: stimulating fluid and electrolyte secretion[14] and inducing high-amplitude propagated contractions based on the effects of intraluminal chenodeoxycholate in the human colon.[15]

Elobixibat significantly accelerated colonic transit and improved bowel functions in phase 2 clinical trials in the USA.[16,17] A 2-week, phase 2b trial[18] in Japanese patients with chronic constipation showed that 10 mg of elobixibat once per day was safe and effective; hence, 10 mg was selected for a short-term, phase 3 trial of safety and efficacy to confirm the findings from the phase 2b trial.[18] Longer-term use would be facilitated if patients could titrate the dose, depending on effectiveness or adverse drug reactions. The objective of our randomised controlled study was to assess the efficacy and safety of once-daily 10 mg elobixibat for 2 weeks in patients with chronic constipation, and in a second, long-term study we assessed safety and efficacy including QOL and satisfaction during 52 weeks of treatment with elobixibat.

Methods

Study design and participants

We did two phase 3 studies in Japan. The first was a randomised, 2-week, multicentre, placebo-controlled, double-blind trial (with an initial 2-week run-in period after screening, before treatment, during which baseline bowel function diaries were completed daily) with

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patients enrolled at 16 gastrointestinal or internal medicine specialised clinics by investigators at each study site. The second was a 52-week, open-label, single-arm study (also with an initial 2-week run-in period after screening, before treatment during which baseline bowel function diaries were completed daily) with patients enrolled at 34 gastrointestinal or internal medicine specialised clinics, or departments of gastroenterology, internal medicine, or surgery in hospitals. The trial protocols were approved by institutional review boards at each participating institution.

Eligible patients were Japanese men and non-pregnant women aged 20–80 years, with chronic constipation of at least 6 months' duration, diagnosed on the basis of standard symptom-based criteria of fewer than three spontaneous bowel movements per week (defined as bowel movements occurring spontaneously and independently of administration of rescue medication for at least 24 h), with at least one of the following symptoms during 25% or more of bowel movements: straining, lumpy or hard stools, and sensation of incomplete evacuation. These criteria satisfied Rome III criteria for functional constipation.[4] Patients with symptoms of constipation-predominant irritable bowel syndrome (IBS-C) were included in both trials, in view of the evidence suggesting that patients with IBS-C and functional constipation are similar in terms of symptomatology and pathophysiology,[19,20] and latent class analysis suggests that functional constipation and IBS-C differ mostly on severity of symptoms rather than the type of symptoms.[21]

Eligible patients were recruited by investigators at each study site. Patients were excluded if their chronic constipation was caused by: organic disorders of the intestine such as mechanical obstruction, or neurological, endocrine, or metabolic disorders; medications; or surgery of the intestine or rectum, except for simple appendectomy. Patients were excluded if they had more than five spontaneous bowel movements or mushy or liquid stools during the run-in period. Patients participating in the 2-week randomised trial were not permitted to enter the 52-week open-label trial. Patients provided written informed consent before any trial procedures.

Randomisation and masking

For the 2-week double-blind trial we randomly assigned patients (1:1) to either elobixibat 10 mg or placebo, both taken once per day for 2 weeks. Computer-generated randomisation sequences were prepared by an independent contract research organisation using a permuted block method (block size six) without stratification. The contract research organisation adjudicated the study outcomes based on the information collected and independently of the study sponsor. Study drugs (elobixibat or placebo with identical appearance) were supplied in sealed, opaque containers, and each container was labelled with a randomisation number. Masked study investigators at each participating clinic assigned participants to interventions. Group assignment was concealed from patients, investigators, sponsors, and data analysts. The database was locked until all electronic case reports had been completed.

Procedures

In both trials, eligible patients took the study drug as an oral tablet before breakfast once per day and were monitored in an outpatient setting at each study site. In the short, randomised trial, participants received either 10 mg elobixibat or placebo once per day for 2 weeks (single cycle). In the 52-week open-label trial, eligible patients received elobixibat oral tablets for 52 weeks at a dose of 10 mg/day for the first week; thereafter, patients were allowed to titrate the dose to 5 mg/day or 15 mg/day, or maintain the 10 mg/day dose, depending on any adverse drug reactions or the effectiveness of the drug. Participants were permitted to stop medication for any reason except that their bowel movements were improved; investigators discontinued participation of patients who stopped the drug for more than 2 consecutive weeks or omitted treatment for more than 2 days per week for 4 consecutive weeks.

For **protocols** see http://yciu-hepabiligi.jp/info/pub.html

Throughout the studies, participants filled daily paper diaries in the 2-week randomised study and electronic daily diaries in the 52-week study, recording the following assessments: time of bowel movements, stool consistency (scored with the seven-point Bristol Stool Form Scale [BSFS]),[22] and sensation of complete bowel emptying (yes or no). Severity of constipation (using the five-point adjectival scale: none, mild, moderate, severe, and very severe) was also recorded weekly in the 2-week randomised trial. Use of rescue medication (10 mg bisacodyl suppositories) was permitted if the patient had no bowel movement for 72 h or longer, and this was recorded in the diary for consideration in the efficacy analysis. Thus, a bowel movement was not recorded in the analysis of efficacy if it occurred within 24 h after the last administration of a rescue medication.

In the 52-week trial, health-related QOL was assessed on the day of allocation (baseline), and at weeks 4, 12, 24, 36, and 52, or at time of patient discontinuation. Satisfaction scores were assessed every 2 weeks. Health-related QOL was assessed based on a validated Japanese-translated version of Patient Assessment of Constipation Quality of Life Questionnaire (JPAC-QOL; 28 questions assessed on a five-point adjectival score from 0 to 4, where a lower score indicates improved QOL).[23] Satisfaction was scored on a four-point scale (unsatisfied, slightly satisfied, fairly satisfied, and satisfied).

We also assessed results of physical examinations, vital signs (pulse, blood pressure, and weight) at baseline and week 2 in the 2-week randomised study, and at baseline and weeks 2, 4, and every 4 weeks thereafter in the 52-week study. Standard laboratory tests for haematology, biochemistry blood tests, and urinalysis were done at baseline and week 2 in the 2-week study, and at baseline,

and weeks 4, 12, 24, 36, and 52, or at the time of discontinuation in the 52-week study. Specifically, although elobixibat partially inhibits reabsorption of bile acids only in the terminal ileum and faecal loss of bile acid is compensated by de-novo hepatic synthesis, we determined its potential effect on fat-soluble vitamins and nutrients. We measured lipid-soluble vitamins (vitamin A, vitamin D [25 (OH) D], and vitamin E), coagulation indices (prothrombin time and activated partial thromboplastin time, both surrogates for vitamin K absorption), and serum cholesterol (HDL and LDL cholesterols). Both vitamin and coagulation indices were measured at weeks 4, 12, 24, 36, and 52, or at the time of discontinuation in the 52-week trial. Serum cholesterol, which reflects the pharmacodynamic effects of elobixibat, was measured on the day of randomisation, and week 2 of treatment in the 2-week trial, and on the day of allocation, and weeks 4, 12, 24, 36, and 52, or on the time of discontinuation in the 52-week study using Clinical Analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan) by an independent contract research organisation.

Outcomes

The primary endpoint of the 2-week randomised study was the change from baseline (ie, the last week of the 2-week run-in period) in the frequency of spontaneous bowel movements per week during week 1 of treatment, centrally reviewed by the contract research organisation. Secondary endpoints were: change from baseline in the frequency of spontaneous bowel movements during week 2; changes in frequency of complete spontaneous bowel movements (complete spontaneous bowel movements were defined as spontaneous bowel movements associated with a sense of complete evacuation); proportion of spontaneous bowel movements or complete spontaneous bowel movement responders (defined as three or more spontaneous bowel movements or complete spontaneous bowel movements per week and an increase of at least one spontaneous bowel movement or complete spontaneous bowel movement per week from baseline); proportion of patients who had a spontaneous bowel movement within 24 h after the first dose of study drug; median time to first spontaneous bowel movement; stool consistency (using the BSFS);[22] and severity of constipation. The entire study took 4 weeks.

The primary outcome for the 52-week study was safety; safety outcome measurements were the type, severity, and incidence of adverse drug reactions, recorded at all times from treatment initiation. All adverse events were assessed by investigators at each study site at the visits of weeks 1 and 2 in the 2-week randomised study, and at the visits of weeks 2, 4, and every 4 weeks thereafter in the 52-week study. The secondary outcome in the 52-week study was efficacy assessment relative to baseline. The efficacy endpoint included health-related QOL, in addition to the bowel function-related assessments done in the 2-week randomised study.

Statistical analysis

We planned to include 60 patients in each group for the 2-week randomised study. This number was based on the difference of the primary endpoint (change in the frequency of spontaneous bowel movements from baseline during week 1) between groups (2·30 times per week) and SDs (placebo 2·90; elobixibat 4·24 spontaneous bowel movements per week) in the previous phase 2b published trial.[18] A sample size of 54 patients per treatment group was estimated to provide more than 90% power to test the hypothesis that there was a difference of the primary endpoint between the two groups, with a two-sided α of 0·05, based on a *t* test with unequal variances. Assuming withdrawals, we planned to include an additional 10% of patients in each treatment group.

Similarly, we planned to include a sample of 360 patients in the 52-week study to ensure 300 patients were available for analysis of outcomes at week 24 of treatment in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline E1.[24] This number of patients would be predicted to ensure that at least 100 patients were undergoing treatment at week 52, providing more than 95% power to assess that the true cumulative incidence of adverse drug reactions would be no greater than 3% if no serious reactions were observed throughout the test period.

All efficacy analyses were based on the modified intention-to-treat (ITT) population (ie, all patients who received at least one dose of study drug) without imputation for any missing data. Multiplicity of endpoints was not accounted for in the analysis. The significance between active and placebo drug for the primary endpoint in the 2-week study was based on ANCOVA using the baseline value as covariate and assuming unequal variances. At the week of discontinuation, if a patient had fewer than 5 days of diary entries regarding defecation during a week, that week was considered not to be assessable and was treated as a missing value. For the analysis of secondary endpoints, changes in the frequency of spontaneous bowel movements during week 2 and stool consistency (with the BSFS score) were also analysed using ANCOVA with unequal variances. We used Fisher's exact test for the comparison of proportion of patients in the spontaneous bowel movements and complete spontaneous bowel movements responder analyses and the proportion of patients who had spontaneous bowel movements within 24 h between treatment groups. We calculated 95% CIs with Wilson's score method. The median time to first spontaneous bowel movements was assessed using the Kaplan-Meier method, and a log-rank test was used for pair-wise comparisons. We analysed severity of constipation using the Wilcoxon rank sum test.

In the 52-week trial, we plotted total QOL and satisfaction scores to track trends over the treatment period, and included the baseline values for comparison. Additionally, statistical analyses using a *t* test compared

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with the baseline period were done at weeks 4, 12, 24, 36, and 52 rather than weekly to reduce the number of comparisons.

The safety analysis population included all patients who received at least one dose of study drug. The numbers and proportions of patients who had adverse drug reactions were summarised by treatment group. All reported p values were based on two-sided tests, and the significance level was set at 0·05.

Because of the differences in the primary endpoints required by the regulatory agencies of different countries for clinical trials (the Food and Drug Administration in the USA and the Pharmaceuticals and Medical Devices Agency [PMDA] in Japan), we did additional post-hoc analyses comparing the proportion of patients who had a complete spontaneous bowel movement within 24 h after the first dose and the median time to first complete spontaneous bowel movement in the 2-week study; and the proportion of complete spontaneous bowel movement responders for at least 9 weeks of the first 12-week treatment period in the 52-week study. The significance between treatment groups in the 2-week study was analysed with Fisher's exact test as for spontaneous bowel movements. We also assessed the statistical difference in LDL and HDL cholesterol concentrations between groups in the 2-week study and those changes from baseline in the 52-week study using a *t* test. All data were analysed using SAS 9.3 by an independent contract research organisation and the study funder. Both trials are registered as an international standard randomised controlled trial with Japan Pharmaceutical Information Center, numbers JapicCTI-153061 and JapicCTI-153062.

Role of the funding source

One of the funders of the study (EA Pharma) was responsible for trial oversight and data analyses according to a prespecified statistical analysis plan. EA Pharma had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The other funder of the study (Mochida Pharmaceutical) had no role in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Nov 4, 2015, and June 11, 2016, we assigned 133 patients to elobixibat (n=70) or placebo (n=63) in the 2-week randomised trial (figure 1). 132 patients (69 assigned to elobixibat and 63 assigned to placebo) received at least one dose of study drug and were included in the modified ITT and safety populations. Baseline demographic characteristics in both groups were similar and well balanced (table 1).

A greater increase in the primary endpoint of frequency of spontaneous bowel movements from baseline to week 1 occurred with elobixibat than with placebo (table 2, figure 2). Other endpoints, including change in frequency of spontaneous bowel movements from baseline to week 2, complete spontaneous bowel movements (figure 2), the proportion of responders, the proportion of patients who

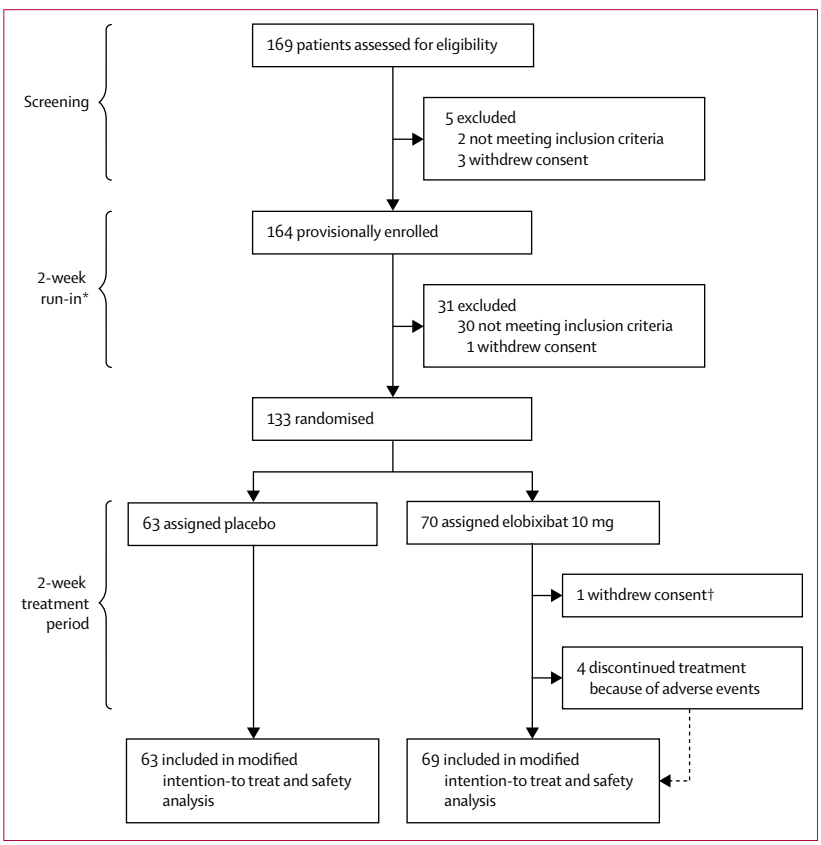

Figure 1: **Trial profile for randomised 2-week study**
*Baseline values were measured during week 2 of the run-in period. †Patient withdrew consent before taking study drug.

	2-week randomised trial		52-week open-label trial
	Placebo (n=63)	Elobixibat 10 mg (n=69)	Elobixibat 5–15 mg (n=340)
Age (years)*	43·8 (13·0)	43·0 (13·7)	43·9 (12·0)
Female sex	52 (83%)	57 (83%)	283 (83%)
Body-mass index (kg/m^2)	21·8 (2·7)	21·4 (2·6)	21·8 (3·1)
Fulfilled criteria for IBS-C	13 (21%)	22 (32%)	101 (30%)
SBMs per week†	1·7 (1·0)	1·8 (0·9)	1·5 (1·0)
CSBMs per week†	0·5 (0·8)	0·6 (0·8)	0·4 (0·7)
Stool consistency score†‡	2·1 (1·2)	2·5 (1·1)	2·2 (1·0)

Data are mean (SD) or n (%). IBS-C=constipation-predominant irritable bowel syndrome. SBM=spontaneous bowel movement. CSBM=complete spontaneous bowel movement. *Age was based on the date of informed consent. †Baseline value was based on the last week of run-in period (week 1). ‡Stool consistency was assessed with Bristol Stool Form Scale scores.

Table 1: **Demographic and baseline characteristics of modified intention-to-treat populations**

	Placebo (n=63)	Elobixibat 10 mg (n=69)	Difference between groups	p value
Primary endpoint				
Change in SBMs per week during week 1 compared with baseline (least-squares mean [SE], 95% CI)	1·7 (0·2), 1·2–2·2	6·4 (0·6), 5·3–7·6	4·7 (0·6), 3·4–5·9	<0·0001*
Secondary endpoints				
SBM				
Change in SBM per week during week 2 compared with baseline (least-squares mean [SE], 95% CI)	1·8 (0·2), 1·3–2·2	5·0 (0·4), 4·2–5·8	3·2 (0·5), 2·3–4·1	<0·0001*
Weekly responders at week 1 (% [n])	60% (38)	94% (63)†	34%	<0·0001‡
Weekly responders at week 2 (% [n])	63% (40)	92% (60)§	29%	<0·0001‡
Median (IQR) time to first SBM (h)¶	25·5 (4·0–50·5)	5·1 (2·3–9·5)	..	0·0001‖
SBM ≤24 h after first dose (% [n])	41% (26)	86% (59)	44%	<0·0001‡
Complete spontaneous bowel movements (CSBM)				
Weekly responders at week 1 (% [n])	17% (11)	52% (35)†	35%	<0·0001‡
Weekly responders at week 2 (% [n])	22% (14)	54% (35)§	32%	0·0003‡
Stool consistency score at week 1** (mean [SD])	2·6 (1·1)	4·3 (1·2)	1·7 (1·2)	<0·0001*
Stool consistency score at week 2** (mean [SD])	2·9 (1·4)	4·3 (1·2)	1·4 (1·3)	<0·0001*
Post-hoc analyses				
Median (IQR) time to first CSBM (h)††	81·6 (27·3–179·8)	9·0 (5·0–34·5)	..	<0·0001‖
CSBM ≤24 h after first dose (% [n])	13% (8)	46% (32)	34%	<0·0001‡
Serum cholesterol				
Change in LDL concentration from baseline to week 2 (mean [SD]; mg/dL)	1·5 (15·5)	14·2 (19·9)†	−15·7 (17·9)	<0·0001‡‡
Change in HDL concentration from baseline to week 2 (mean [SD]; mg/dL)	2·5 (8·8)	−0·2 (9·7)†	−2·7 (9·3)	0·0992‡‡

*Analysis of covariance. †n=67. ‡Fisher's exact test. §n=65. ¶Median obtained excluding one patient who did not have SBM for 2 weeks in the elobixibat group. ‖Log-rank test using the Kaplan-Meier method. **Stool consistency assessed with scores on the Bristol Stool Form Scale. ††Median value obtained excluding 22 patients who did not have CSBM for 2 weeks in the placebo group, and excluding 11 patients who did not have CSBM for 2 weeks and one patient who discontinued treatment in the elobixibat group. ‡‡ *t* test.

Table 2: **Efficacy in the 2-week randomised trial**

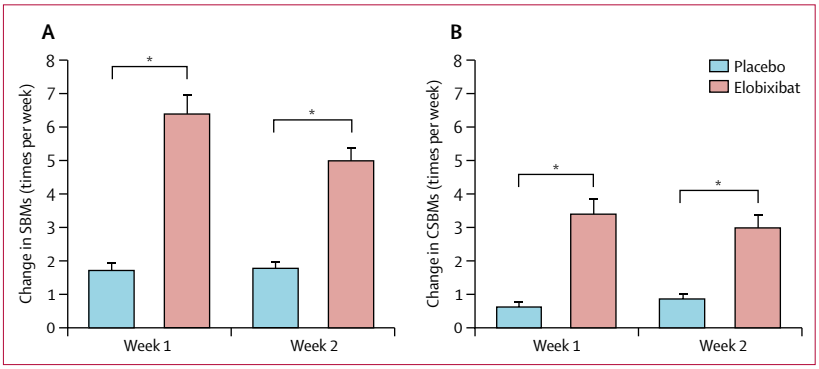

Figure 2: **Comparison of elobixibat and placebo on changes from baseline in the frequency of (A) SBM and (B) CSBM**

Data are least-squares mean (SE). Change in the frequency of spontaneous bowel movements (SBM) during week 1 of treatment was the primary endpoint. CSBM=complete spontaneous bowel movements. *p<0·0001.

had their first spontaneous or complete spontaneous bowel movement within 24 h, and stool consistency were also greater with elobixibat (table 2). Median time to first spontaneous bowel movement was shorter in the elobixibat group (table 2). The elobixibat group showed improvement in the severity of constipation compared with the placebo group (appendix p 1). At baseline, 12 (19%) patients assigned to placebo and ten (15%) patients assigned to elobixibat required rescue medication. At week 1, four (6%) patients in the placebo group required rescue medication, as did one (1%) in the elobixibat group. At week 2, seven (11%) patients in the placebo group and two (3%) in the elobixibat group require such treatment. The results of the primary endpoint in patients who fulfilled criteria for IBS-C were qualitatively similar to those of the entire group (appendix p 2).

Between Oct 31, 2015, and March 15, 2017, we allocated 341 patients to receive elobixibat 5–15 mg/day in the 52-week open-label trial (figure 3). 340 patients received at least one dose and were included in the modified ITT and safety populations (figure 3, table 1). All patients in the 52-week study of elobixibat started week 1 of treatment at the 10 mg dose. Mean duration of treatment was: at the 5 mg dose, 201·8 days (SD 137·7) in 145 (43%) patients; at the 10 mg dose, 132·9 days (142·0) in 340 (100%) patients; and at the 15 mg dose, 209·8 days (136·4) in 157 (46%) patients. Roughly 25% of patients titrated the dose up to 15 mg and around 25% titrated the dose down to 5 mg within 1 month after the first dose. During the last 4 weeks of the 52-week open-label trial, the proportions of patients who took the 5 mg, 10 mg, and 15 mg doses were approximately 33% each.

For the primary outcome of safety in the 52-week trial, 163 (48%) patients had an adverse drug reaction, the most common of which were mild gastrointestinal disorders (in 135 [40%] patients; table 3). During the 52-week trial, one patient was admitted to hospital for inguinal hernia repair, which was classed as a moderate adverse drug reaction possibly related to treatment. The mean numbers of weekly spontaneous bowel movements and complete spontaneous bowel movements numerically increased from baseline throughout the 52-week treatment period (figure 4). The proportion of weekly responders with a spontaneous or complete spontaneous bowel movement is shown in the appendix (p 2). The proportions of weekly responders of SBM or CSBM were sustained throughout the 52-week study period. Elobixibat numerically increased stool consistency scores from baseline throughout the 52-week study period (appendix p 4). Rescue medication was taken by 85 (25%) patients in the 2-week run-in, 25 (7%) patients in the first 2 weeks on treatment, and 12 (3%) patients over the next 50 weeks.

Mean overall JPAC-QOL scores were lower during the 52 weeks of treatment compared with baseline (1·63 [SD 0·60] at baseline *vs* 0·85 [0·55] at 52 weeks; scores at 4, 12, 24, 36, and 52 weeks were all significantly improved compared with baseline; figure 5). Satisfaction scores

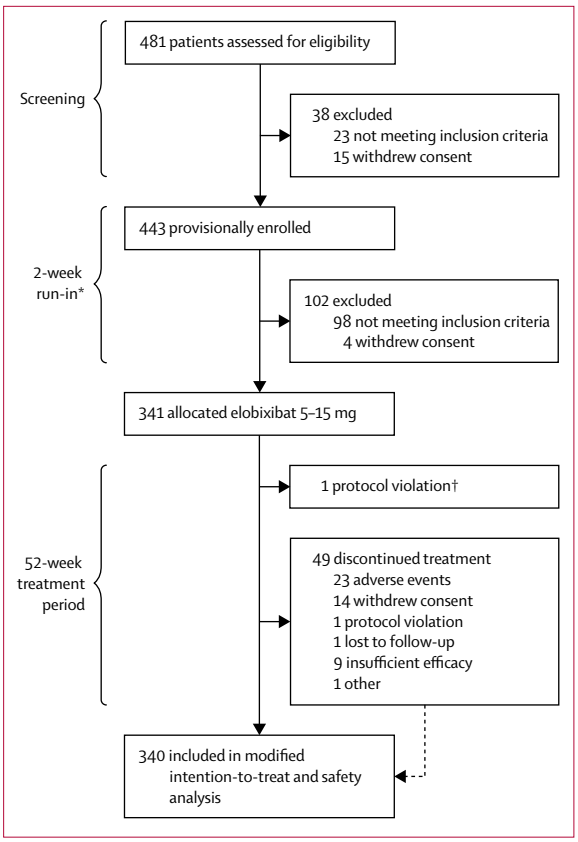

Figure 3: **Trial profile for open-label, 52-week study**
*Baseline values were measured during week 2 of the run-in period.
†Patient withdrew consent before taking study drug.

	2-week randomised trial		52-week open-label trial
	Placebo (n=63)	Elobixibat 10 mg (n=69)	Elobixibat 5–15 mg (n=340)
Total adverse drug reactions	5 (8%)	21 (30%)	163 (48%)
Adverse drug reactions leading to discontinuation	0	4 (6%)	18 (5%)
Adverse drug reactions for ≥2% of patients			
Gastrointestinal disorders	2 (3%)	19 (28%)	139 (41%)
Mild	2 (3%)	18 (26%)	135 (40%)
Moderate	0	1 (1%)	4 (1%)
Severe	0	0	0
Abdominal pain	1 (2%)	13 (19%)	82 (24%)
Diarrhoea	0	9 (13%)	50 (15%)
Abdominal pain lower	0	3 (4%)	17 (5%)
Abdominal distension	0	0	11 (3%)
Nausea	0	2 (3%)	10 (3%)
Abdominal discomfort	0	0	7 (2%)
Investigations*	3 (5%)	1 (1%)	27 (8%)
Liver function test abnormal	2 (3%)	1 (1%)	10 (3%)

Data are n (%) of patients. Categorisation of adverse drug reactions were based on the Medical Dictionary for Regulatory Activities versions 18.0 and 19.0. *Laboratory tests.

Table 3: **Adverse drug reactions possibly related to study drug in both trials**

increased from baseline (figure 5), such that more than 214 (63%) patients from week 6 onwards and more than 238 (70%) patients from week 14 onwards reported being fairly satisfied or satisfied. At 4, 12, 24, 36, and 52 weeks, satisfaction scores were significantly improved compared with baseline.

The most common adverse drug reactions in both trials were mild abdominal pain and diarrhoea; most of the adverse drug reactions were mild gastrointestinal disorders in both trials (table 3). No deaths or severe adverse drug reactions occurred in the two trials. Four (6%) patients discontinued treatment in the elobixibat group in the 2-week randomised trial because of adverse drug reactions (abdominal pain [n=4], diarrhoea [n=4], and nausea [n=1]); no patients in the placebo group discontinued treatment.

In the 52-week trial, 18 (5%) patients discontinued treatment because of adverse drug reactions, mainly abdominal pain (seven [2%] patients) or diarrhoea (six [2%] patients). In the 52-week trial, the median numbers of days to first onset of abdominal pain and diarrhoea were 2 (IQR 1–54) and 21 (2–86), respectively, and the median number of days for resolution of abdominal pain and diarrhoea were 15 (IQR 7–54) and 6 (2–34), respectively. The occurrence of abdominal pain was recorded 123 times (with individual patients recording the symptom multiple times). In 58 (47%) of the 123 instances, the abdominal pain resolved without changing elobixibat dose, and in 48 (39%) of the 123 reports, the abdominal pain resolved by titrating the dose down. Among the instances when diarrhoea was reported during the 52-week, open-label trial, 52 (61%) of 85 cases were resolved without changing dose, and 21 (25%) of 85 were resolved by titrating the dose down. In the 52-week open-label trial, one participant reported palpitations with elobixibat. No other cardiovascular adverse events were reported in either trial. Biochemical safety parameters showed no clinically relevant changes in vitamin A, vitamin D (25 [OH] D), or vitamin E, or in prothrombin time or activated partial thromboplastin time (appendix p 5).

In the post-hoc analysis, the proportion of responders in the 52-week open-label trial with a complete spontaneous bowel movement in the first 12 weeks of treatment (ie, ≥three times per week for at least 9 of the first 12 weeks) was 97 (29%) patients. There was a significant reduction of LDL cholesterol with elobixibat compared with placebo in the 2-week randomised trial, but no difference in HDL cholesterol (table 2).

See Online for appendix

Discussion

The findings from the 2-week phase 3 study showed that elobixibat, an ileal bile acid transporter inhibitor, is effective and well tolerated in the short-term treatment of chronic constipation, supporting results from a previous phase 2b, 2-week trial.[18] Elobixibat improved all efficacy endpoints compared with placebo.

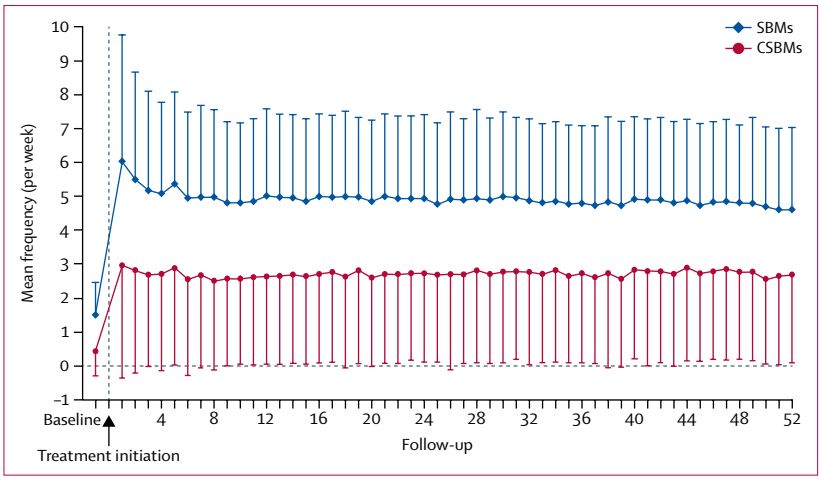

Figure 4: **Absolute mean (SD) SBMs and CSBMs per week during 52-week, open-label treatment with elobixibat**
SBM=spontaneous bowel movements. CSBM=complete spontaneous bowel movements.

In the long-term, 52-week study, aimed mainly to assess safety, patients also reported consistent improvements from baseline in spontaneous and complete spontaneous bowel movement frequency, stool consistency, and QOL. Additionally, the changes in spontaneous bowel movement frequency from baseline up to 8 weeks were similar to the results from an 8-week, phase 2b, randomised trial of elobixibat[17] in the USA.

In addition to the significant increase in the number of spontaneous bowel movements with elobixibat, the frequency of spontaneous bowel movements with treatment is clinically meaningful. The prespecified sample size provided sufficient power to detect clinically meaningful effects of elobixibat. Thus, a clinically important difference was a spontaneous bowel movement frequency of at least three times per week, and the 2-week randomised trial was powered to detect a change from baseline of 2·3 spontaneous bowel movements per week. Given that the average baseline stool frequency is typically at least once per week in patients with chronic constipation (also noted in our 2-week trial), the anticipated difference in spontaneous bowel movements in addition to the baseline frequency of at least one per week would result in at least three spontaneous bowel movements per week, consistent with a clinically accepted normal frequency.

In the 2-week randomised trial, elobixibat significantly shortened the time to the first spontaneous and complete spontaneous bowel movement compared with placebo, consistent with the known acceleration of colonic transit[16,25] and the dual biological effects of increased colonic bile acid concentrations on fluid secretion and motility. Because many patients take medications for constipation intermittently, the short median time to induce a bowel movement with elobixibat would be clinically beneficial. Elobixibat seems to be safe over both the short term and long term, and adverse drug reactions of abdominal pain and diarrhoea were resolved on average within 1–2 weeks.

The 52-week open-label study followed common clinical practice, allowing dose titration to reduce adverse drug reactions and increase efficacy within the 5–15 mg dose range. 18 patients discontinued treatment because of adverse drug reactions in the 52-week trial. Elobixibat did not alter lipid-soluble vitamins and coagulation indices during long-term treatment; conversely, there was a beneficial reduction in LDL cholesterol with no difference in HDL cholesterol. These findings are consistent with previous reports of the effects of elobixibat on lipid profiles.[26] Constipation relief has been reported with oral chenodeoxycholic acid,[27] but associated increased serum aminotransferases limited this as a therapeutic approach. In a previous study,[28] ileocolonic delivery of chenodeoxycholic acid stimulated colonic transit and resulted in looser stool consistency, increased stool frequency, and greater ease of passage in female patients with IBS-C. Elobixibat accelerated colonic transit and increased spontaneous bowel movements in phase 2a trial,[16] and increased endogenous hepatocyte synthesis of bile acids, thereby reducing serum cholesterol.[26] Elobixibat, similar to other medications for constipation assessed in clinical trials, was associated with a higher stool frequency in the first week of treatment; however, for all such studies there is the likelihood that the first week is associated with a flushing out of retained stool in the colon of patients with chronic constipation.

The ileal bile acid transporter inhibitor therapeutic approach is based on the rationale of decreased colonic bile acid concentrations in patients with constipation disorders and the dual stimulatory effect of bile acids on colonic motility and secretion, which are relevant given the lower amplitude and frequency of colonic contractions, including high-amplitude propagated contractions, in patients with slow transit constipation. Indeed, bile acids induce propulsive contractions in the human colon[15,29] and accelerate colonic transit.[28] The occurrence of abdominal pain in relation to the induction of a bowel movement is typically followed by relief of the pain. One study[15] showed that infusion of secretory bile acids, such as chenodeoxycholic acid, into the colon induced high-amplitude propagated contractions that might be associated with mass movements and induction of short-lived pain. Future studies need to document the timing of pain reported by patients in relation to the timing of bowel movements.

To fulfil the requirements for showing efficacy of chronic treatment according to regulatory guidance of some countries, including the European Medicines Agency,[30] longer placebo-controlled trials of 12 weeks' duration would be required. The open-label trial provided assessment of long-term safety and numerical evidence suggesting benefit, but it had limitations in assessing efficacy because it was undertaken as a single-arm, open-label study. The data presented were consistent with regulatory guidance on proof of short-term efficacy in Japan and the US Food and Drug Administration

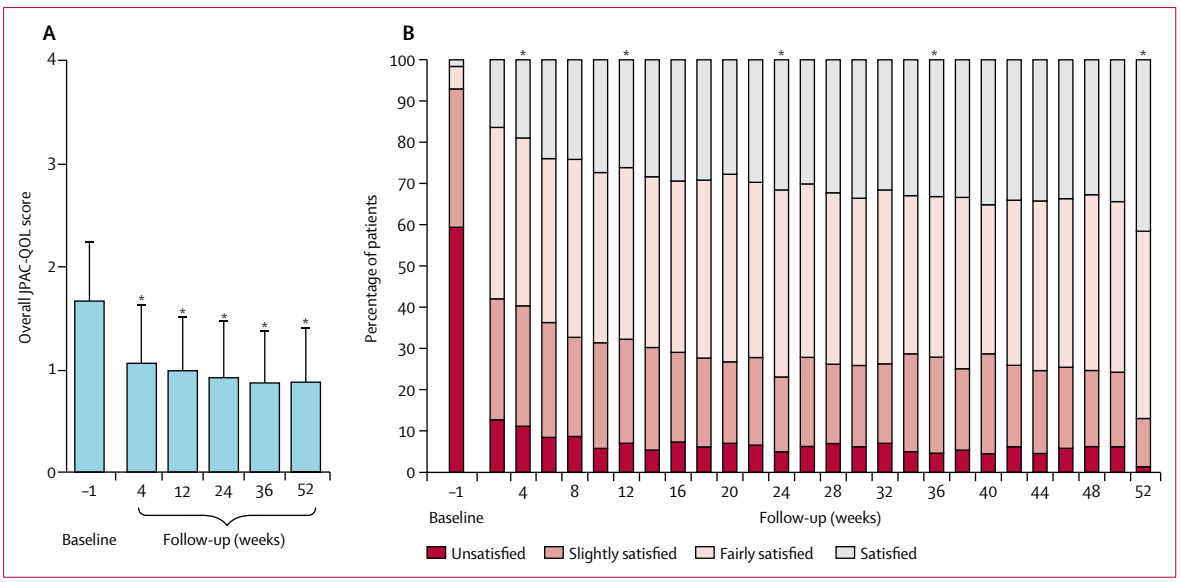

Figure 5: **Effect of 52-week, open-label treatment with elobixibat on quality of life and satisfaction**
(A) mean (SD) overall Japanese-translated version of Patient Assessment of Constipation Quality of Life Questionnaire (JPAC-QOL) scores. *p<0·0001 compared with baseline. (B) Satisfaction scores. *p<0·0001 at 4, 12, 24, 36, and 52 weeks compared with baseline.

guidelines on assessment of safety. Elobixibat was approved on Jan 19, 2018, by the Japanese PMDA on the basis of these results.

Data from the two trials are somewhat generalisable, based on the randomised controlled trial design of the 2-week study and the large number of participants in the 52-week, open-label study. Both populations were Japanese and the results need to be confirmed in non-Japanese populations for external validity and true generalisability; however, a phase 2 study[17] suggested that the drug was also efficacious in patients in the USA, of whom 77·9% were white and 21·6% were black or African-American. Other limitations of our studies include that the long-term efficacy, including effects on satisfaction and QOL, require formal study, given that the 52-week trial was designed to assess safety. Although anchored in an a-priori power calculation, there were relatively small numbers of patients in our 2-week randomised trial in comparison with other phase 3 studies of patients with chronic constipation with medications such as linaclotide,[11] plecanatide,[12] and prucalopride.[9] There was also some evidence of heterogeneity in the study population, which might have reduced the estimation of efficacy; the heterogeneity was manifest in the baseline stool frequency and stool consistency across the patient cohorts, as well as the concurrence of symptoms consistent with IBS-C in about 30% of the patients in the randomised, controlled trial. Last, the 2-week study was too short for an efficacy trial and will need replication in randomised controlled trials of longer duration, such as 12 or 26 weeks, in accordance with regulatory guidance in other countries.

In conclusion, elobixibat provided a novel approach, reversing a pathophysiological mechanism, to relieve chronic constipation in the short term. Additionally, elobixibat was well tolerated throughout a 52-week treatment period. The evidence supports the use of this novel approach to increase intracolonic concentrations of endogenous bile acid for the treatment of chronic constipation.

Contributors

AN and MS were involved in the design, conduct, and oversight of clinical trial. ST was involved in the design, data analysis, and interpretation of the clinical trial, and wrote a first draft and edited subsequent drafts of the manuscript. AO did the statistical analyses. P-GG and JPM were involved in the discovery and application of ileal bile acid transporters (IBAT) in therapeutics, and designing and interpretation of the clinical trial. MC showed the concept of bile acid deficiency in constipation (providing the rationale for use of an IBAT inhibitor) and was involved in the clinical trial design and extensive editing. AN, ST, and MC wrote the manuscript. All authors had full access to the study data and reviewed and approved the final draft of the manuscript for submission.

Declaration of interests

AN has served as a medical adviser to EA Pharma. MS, ST, and AO are employees of EA Pharma. P-GG and JPM are employees of Albireo AB. MC has served as a consultant to EA Pharma and Albireo AB with no personal financial remuneration, has his consulting fees paid to his employer, Mayo Clinic, and receives funding from the National Institutes of Health (R01-DK67071 and R01-DK115950).

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